



Study Protocol

Quantitative Fibronectin to help Decision-making in women with Symptoms of Preterm Labour – Comparison with Partosure and Actim Partus

QUIDS 2

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COORDINATING CENTRE

<p>Chief Investigator</p> <p>Sarah J Stock Senior Clinical Lecturer Maternal and Fetal Health MRC Centre for Reproductive Health Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ Tel: 0131 242 6449 Email: sarah.stock@ed.ac.uk</p>	<p>Co-sponsor Representative</p> <p>Mr Chris Coner University of Edinburgh Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ Tel: 0131 242 9446 Fax: 0131 242 9447 Email: chris.coner@ed.ac.uk</p>
<p>Co-sponsor Representative</p> <p>Kenneth Scott The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ Tel: 0131 242 3325 Fax: 0131 242 3343 Email: accord@nhslothian.scot.nhs.uk</p>	<p>Trial Statistician</p> <p>Professor John Norrie Director; Chair of Medical Statistics and Trial Methodology Director of Edinburgh Clinical Trials Unit (ECTU) University of Edinburgh No. 9, Bioquarter Rm. 2.685 Medical School, Teviot Place Tel: 0131 651 7875 / 0131 650 9473 Email: j.norrie@ed.ac.uk</p>
<p>Trial Manager</p> <p>Lisa Wotherspoon The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ Tel: 0131 242 6603 Fax: 0131 242 6441 Email: Lisa.Wotherspoon@ed.ac.uk</p>	<p>Trial Administrator</p> <p>Angela Niven The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ Tel: 0131 242 2168 Fax: 0131 242 6441 Email: Angela.Niven@ed.ac.uk</p>

CO-INVESTIGATORS

<p>Dr Kathleen A Boyd Senior Lecturer (Health Economics) Institute of Health & Wellbeing Health Economics & Health Technology Assessment University of Glasgow 1 Lilybank Gardens Glasgow G12 8RZ Tel: +44(0)141 3302713 Fax: +44(0)141 3305018 Email: Kathleen.Boyd@glasgow.ac.uk</p>	<p>Dr Jon Dorling Clinical Associate Professor (Neonatology) Room E/E1720 Queens Medical Centre Queen's Medical Centre Nottingham NG7 2UH UK Tel: 0115 8230635 Email: Jon.Dorling@nottingham.ac.uk</p>
<p>Professor Jane Norman Professor of Maternal and Fetal Health University of Edinburgh MRC Centre for Reproductive Health Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TY Tel: + 44 131 242 2694 E-mail: jane.norman@ed.ac.uk</p>	<p>Professor Richard Riley Professor of Biostatistics DJW 0.62 Arthritis Research UK Primary Care Centre Primary Care Sciences Keele University Staffordshire, ST5 5BG Tel: +44 (0) 1782 733920 Email: r.riley@keele.ac.uk</p>
<p>Dr Lesley Jackson Consultant Neonatal Medicine and Honorary Senior Lecturer University of Glasgow Neonatal Unit Royal Hospital for Children Glasgow G51 4TF 0141 232 7921 Email: Lesley.Jackson@ggc.scot.nhs.uk</p>	<p>Professor Ben Mol Professor Obstetrics and Gynaecology University of Adelaide Women's & Children's Hospital 72 King William Rd North Adelaide SA 5006 Australia Tel: +61 4 3412 2170 Email: ben.mol@adelaide.edu.au</p>

<p>Dr Asma Khalil Consultant Obstetrician Fetal Medicine Unit Blackshaw Rd, Tooting, London SW17 0QT Tel: 020 8725 0071 Email: asmakhalil79@googlemail.com</p>	<p>Professor Andrew Shennan Professor of Obstetrics/Consultant Obstetrician 10th Floor, North Wing St Thomas's Hospital Westminster Bridge Road London SE1 7EH Tel: +44 (0) 20 7188 3639 Email: andrew.shennan@kcl.ac.uk</p>
<p>Professor Dame Tina Lavender Professor of Midwifery University of Manchester School of Nursing Midwifery & Social Work Jean McFarlane Building University Place Oxford Road Manchester M13 9PL Tel: +44 (0)161 306 7744 Email: Tina.Lavender@manchester.ac.uk</p>	<p>Dr Rachel K Morris Senior Clinical Lecturer Maternal and Fetal Medicine Birmingham Women's Hospital Metchley Park Road Edgbaston Birmingham B15 2TG Tel: +44 (0)121 623 6652 Email: r.k.morris@bham.ac.uk</p>
<p>Prof Khalid Khan Professor of Women's Health and Clinical Epidemiology Centre for Primary Care and Public Health Barts and The London School of Medicine and Dentistry Yvonne Carter Building 58 Turner Street Whitechapel London E1 2AB Tel: +44 20 7882 2525 Email: k.s.khan@qmul.ac.uk; t.d.holtham@qmul.ac.uk</p>	<p>Dr Manju Chandiramani Consultant Obstetrician Honorary Senior Clinical Lecturer Department of Surgery & Cancer Parturition Research Group, 3rd Floor IRDB Imperial College London Hammersmith Hospital Campus Du Cane Road London W12 0NN Tel: +44 (0)20 7594 2137 Email: m.chandiramani@imperial.ac.uk</p>
<p>Susan Harper-Clarke PPI representative Email: su_clarke@hotmail.com</p>	

PROTOCOL REVISIONS

PROTOCOL VERSION	DATE	REASON FOR UPDATE	AMENDMENT NUMBER	SUMMARY OF CHANGES
2	31 st May 2017	Primary Aim Updated Recruitment timelines and sample size Concealment of results from sample testing	SA01	The primary aim of the study has been updated to reflect the QUIDS2 study as a separate research topic from QUIDS. IPD meta analysis updated Recruitment timelines and sample size updated Updates around sample testing with regards to concealment of results
3	26 th January 2018	Update to Justification for sample size and recruitment timelines	MA01	Justification for sample size and increase in recruitment phase
4	27 th September 2018	Update to Study end date	MA04	Extension to Study end date
5	23 rd October 2018	Update to sample size	SA02	Sample size increased

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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
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.

Currently being evaluated in the QUIDS study (REC ref: 16/WS/0068), 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.

In addition to fetal Fibronectin, there are two further pre-term birth marker tests available for use in the NHS; Actim Partus and Partosure. Actim Partus involves the measurement of pHIGFBP-1 (phosphorylated insulin-like growth factor binding protein) in swab taken from the cervix at a speculum examination. The amount of pHIGFBP-1 is measured via a dipstick test and results are provided in 5 minutes giving a positive or negative result. The Partosure test measures placental alpha microglobulin-1 (PAMG-1) in a low vaginal swab taken without a speculum. The amount of PAMG-1 is measured with a dipstick test and results provided in around 5 minutes, also giving a positive or negative result.

The main aim of this research is to compare the prognostic values of each of the three tests of preterm labour (quantitative fFN; Actim Partus and Partosure) for prediction of preterm birth within seven days of testing. We will firstly, perform Individual Patient Data Level (IPD) meta-analysis of existing data sets to develop a prognostic model using clinical risk factors and 1. Actim Partus and 2. Partosure. We will validate (+/- refine) the prognostic models using data collected in a prospective cohort study in at least 20 UK sites. An economic analysis will be undertaken from an NHS perspective to assess potential cost-effectiveness of the Actim Partus and Partosure prognostic models, in comparison to the qfFN prognostic model developed in the related QUIDS study.

This work will be complimentary to, and carried out alongside QUIDS. It will be carried out over 16 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.

SCIENTIFIC SUMMARY

RESEARCH QUESTION

In women with symptoms suggestive of preterm labour which test of preterm labour (qfFN, Actim Partus or Partosure) has the best prognostic value and is most cost effective for prediction of preterm birth within seven days?

AIM

The primary aim of the QUIDS 2 study is to determine whether the use of Actim Partus and or Partosure in the QUIDS prognostic model will have additional decision benefit over qfFN.

DESIGN

We will perform an IPD meta-analysis of existing data sets from existing efficacy studies to evaluate the prognostic ability of Actim Partus and Partosure and other clinical risk factors, for the prediction of preterm birth within seven days of testing. We will validate (+/- refine) the prognostic model using data collected in a prospective cohort study in at least 20 UK sites (approximately 500 participants). We will compare model performance of the two tests with each other, and with a prognostic model for qfFN developed as part of the linked QUIDS study. An economic analysis will be undertaken from an NHS perspective to assess potential cost-effectiveness of the model.

SETTING

IPD meta-analysis: Published and ongoing studies of women with symptoms of preterm labour and either Actim Partus or Partosure will be evaluated.

Prospective cohort study: At least 20 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

Actim Partus and Partosure.

MEASUREMENT OF COSTS AND OUTCOMES

The primary outcome will be ability of the prognostic models to rule out spontaneous preterm birth within 7 days. Other endpoints of the model may include delivery within 48 hours of testing and delivery <34 weeks gestation or delivery <37 weeks gestation. IPD meta-analysis of existing data sets from existing efficacy studies will evaluate the prognostic ability of Actim Partus and Partosure as risk factors, in addition to other important clinical risk factors, and evaluate the added value of Actim Partus and Partosure in the performance of the prognostic models. The prognostic models 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 Actim Partus and Partosure prognostic models, and compared to that of the qfFN prognostic model developed in the related QUIDS study. Decision analytic models 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: This will depend on the number of ongoing prospective cohort studies of Actim Partus and Partosure in women with symptoms of preterm labour eligible for inclusion.

Prospective Cohort Study: 568 women with estimated 10 - 20 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

June 2017 - January 2019

The prospective cohort study will commence in September 2017 and run for up to 14 months. Our estimated recruitment rate is based on the current recruitment rate in the QUIDS study. Full delivery details of participants will be available 20 weeks after recruitment ends to enable full data collection for all participants.

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.

Research has been conducted using Actim Partus for the past 16 years. Much of the research compares Actim Partus with qualitative fFN as a predictor of pre-term birth. Of the recent studies, Cooper^[6], found that the Negative Predictive Value between Actim Partus and fFN did not differ for delivery before 37 weeks and neither test improves on pretest probability of delivery before 37 weeks. Bruijn^[7] also stated that

(in combination with cervical length) Actim Partus could be used as an alternative to fFN to identify women who will not deliver within seven days after presentation. However, it has also been shown that Actim Partus was a more reliable predictor of preterm delivery than the equivalent fFN test for delivery before 34 weeks and within 7 days of testing. ^[12].

Partosure is a new pre-term birth bedside test only available since December 2015 in the UK. There is currently limited research into the effectiveness as a pre-term birth predictor test in women showing signs of threatened pre-term labour. Previous studies have been small cohorts, the largest of these being n=203 in the Nikolova study (2015) ^[13]. It states that in settings where Cervical Length by TVU is not utilised at initial screening, Partosure is the single most accurate test when compared to qualitative fFN and CL for the prediction of imminent spontaneous delivery in patients presenting with signs and symptoms, or complaints suggestive of PTL. Therefore, Partosure should be considered as the first-line test for any patient presenting with threatened pre-term labour between 20 – 27 weeks gestation. It should be noted that this study was done with Quick-check fFN which only yields a qualitative value and not qfFN which is being observed in the QUIDS study. Indeed, in 5 of the further studies listed by Partosure in their marketing literature ^[14, 15, 16, 17, 18] all state that Partosure has a high Positive Predictive Value (PPV). Heverhagen even states that PAMG-1 has a higher PPV compared to other commercially available bedside tests for preterm birth such as fFN or IGFBP-1 ^[14].

These tests have 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].

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.

Further research is required into comparing all available bedside tests for the prediction of pre-term birth. This evaluation needs to come not only from a predictive value of the test but also cost effectiveness for the NHS. The data collected within QUIDS 2 will be used to compare with the qfFN data in QUIDS so an accurate comparison can be made.

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 either Partosure, Actim Partus or qfFN.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

Primary Objective

The primary aim of the QUIDS 2 study is to determine whether the use of Actim Partus and or Partosure in the QUIDS prognostic model have additional decision benefit over qfFN

Specific objectives relating to this are to:

- i) Perform an IPD meta-analysis of existing data sets from existing efficacy studies to evaluate the prognostic ability of Actim Partus and Partosure using the model developed in the QUIDS Study.

ii) Externally validate and, if necessary, refine the prognostic models using data collected in a prospective cohort study of women presenting with symptoms suggestive of preterm labour in UK hospitals and compare performance of the models with each other, and with a prognostic model based on qfFN (developed as part of QUIDS)

iii) An economic analysis will be undertaken from an NHS perspective to assess potential cost-effectiveness of the Actim Partus and Partosure prognostic models, and compared to that of the qfFN prognostic model developed in the related QUIDS study.

iv) The best model will be converted to a web based or mobile app presented format at the end of the study.

2.2 ENDPOINTS

Primary Endpoint

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

Secondary Endpoints

Secondary endpoints 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. These endpoints will depend on number of events (e.g. number of deliveries within 48 hour of test) and/or test performance at 7 days.

3 STUDY DESIGN

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

Health technologies being assessed

The study will evaluate the Actim Partus test (Medix Biochemica, Espoo, Finland) and Partosure test (Parsagen Diagnostics Inc. Distributor: AGH, Gravesend Kent).

The Actim Partus test is a visually interpreted, qualitative immunochromatographic dipstick test for detecting the presence of phosphorylated IGFBP-1 (insulin-like growth factor binding protein-1) in cervical secretions during pregnancy. It gives a qualitative (positive or negative) result within 5 minutes.

The lowest detectable amount of phIGFBP-1 in the extracted sample is approximately 10µg/l. Samples will be taken using the Actim Partus test kit as per the manufactures instructions. The test kit comprises Actim Partus dipstick in aluminium foil pouch with desiccant, sterile polyester swab and tube of Specimen Extraction Solution (0.5ml; bovine serum albumin, protase inhibitors and preservatives). The sample is collected using the sterile polyester swab from the cervix during a speculum examination. The swab should be left in the cervix for 10-15 seconds to allow it to absorb the secretions. The sample is then placed into the provided Specimen Extraction Solution and swirled vigorously for 10 seconds. The swab is then pressed against the wall of the tube to remove any remaining liquid from the swab before it is discarded. It is at this point that the sample will be stored appropriately. The samples will be tested by the Research team/nominated site staff that are not involved in direct clinical care of the woman so the results can be concealed (please see section 5.3 for further details)

The test involves two monoclonal antibodies to human IGFBP-1. One is bound to the blue latex particles (the detecting label). The other is immobilized on a carrier membrane to catch the complex of antigen and latex-labeled antibody and indicate a positive result. When placed in the sample, the dipstick absorbs the liquid, which starts to flow up the dipstick. If the sample contains phIGFBP-1 it binds to the antibody labeled with latex particles. The particles are then carried by the liquid flow and, if IGFBP-1 is bound to them, they bind to the catching antibody. A blue line (test line) will appear in the result area if the concentration of phIGFBP-1 in the sample exceeds the detection limit of the test. A second blue line (control line) confirms correct performance of the test. The yellow dip area of the dipstick is placed into the extracted sample and held until the liquid is seen to enter the result area. The dipstick is then removed and placed on a horizontal surface. Test results will be reported as either Positive/Negative or Invalid. The presence of 2 lines (test line and control) indicates a positive result, however strong the line is. A negative result is shown by only one line, the control line and Invalid result is no lines present or only the sample line and no control line present.

The Actim Partus test is designed to be a point of care test, and clinical staff can easily perform analysis. All reagents for Actim Partus can be stored at room temperature and specimen collection kits and vials can be kept in clinical areas where women with symptoms of preterm labour are assessed so they can be conveniently accessed. In

QUIDS2 the test strips will be kept separately and only accessible by the Research team /nominated staff who will be doing the testing of the samples.

The Partosure test provides a qualitative result (positive or negative) within 5 minutes. It is a rapid, non-instrumented, qualitative immunochromatographic test for the in vitro detection of placental alpha macroglobulin-1 (PAMG-1) in vaginal secretions of pregnant women. The test employs monoclonal antibodies sufficiently sensitive to detect 1 ng/ml of PAMG-1. Samples will be taken using the Partosure test kit as per the manufactures instructions. The test kit comprises Partosure test strip in foil pouch with desiccant, sterile flocked vaginal swab and plastic vial with solvent solution (0.9% Sodium Chloride, 0.05% Sodium azide, 0.01% Triton x100). The swab is inserted into the vagina (no more than 5-7cm) without speculum and withdrawn after 30 seconds. The sample is then placed into the provided solvent vial and rinsed by rotating for 30 seconds. The swab is then removed and discarded. It is at this point the sample will be stored appropriately and tested by the Research team/nominated site staff that are not involved in direct clinical care of the woman so the results can be concealed (please see section 5.3 for further details).

For testing of the sample, the sample flows from an absorbent pad to a nitrocellulose membrane passing through a reactive area containing monoclonal anti-PAMG-1 antibodies conjugated to a gold particle. The antigen-antibody complex flows to the test region where it is immobilised by a second anti-PAMG-1 antibody. This event leads to the appearance of the test line. Unbound antigen-antibody complexes continue to flow along the test strip and are immobilized by a second antibody. This leads to the appearance of the internal control line. The test strip is inserted into the sample and held there until there is either two lines present or 5 minutes has elapsed. The strip should then be placed on a horizontal, flat surface to read the results. Test results will be reported as either Positive/Negative or Invalid. The presence of 2 lines (test line and control) indicates a positive result, however strong the line is. A negative result is shown by only one line, the control line and Invalid result is no lines present or only the sample line and no control line present.

Like the Actim Parts test, the Partosure test is designed to be a point of care test, and clinical staff can easily perform analysis. All reagents for Partosure testing can be stored at room temperature and specimen collection kits, and vials can be kept in clinical areas where women with symptoms of preterm labour are assessed so they can be conveniently accessed. In QUIDS2 the test strips will be kept separately and

only accessible by the Research team/nominated staff who will be doing the testing of the samples.

Target population

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

Design and theoretical/conceptual framework

The primary aim of the QUIDS 2 study is to determine whether the use of Actim Partus and or Partosure in the QUIDS prognostic model have additional decision benefit over qfFN

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.

1. Perform an IPD meta-analysis of existing data sets from existing efficacy studies to evaluate the prognostic ability of Actim Partus and Partosure using the model developed in the QUIDS Study..We will include an economic analysis to provide an economic rationale for the prognostic model.
2. Data on Actim Partus and Partosure will be collected as part of a prospective cohort study (running alongside the already established QUIDS study) in at least 20 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.

At the end of the study the best test of preterm labour for NHS use will be determined, based on prognostic model performance and cost effectiveness. The prognostic model will be developed into a web based or mobile app format.

4 PART 1: DEVELOPMENT OF PROGNOSTIC MODEL AND DECISION ANALYSIS MODEL

4.1 IPD META-ANALYSIS

STUDY POPULATION

Utilising the prognostic model developed in the QUIDS Study, we will perform an IPD meta-analysis of existing data sets from existing efficacy studies to evaluate the prognostic ability of Actim Partus and Partosure. Existing datasets will be identified by literature searching, preterm birth and study networks, and notification from the manufacturers of the tests.

The primary outcome of the models 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 considered if feasible to do so within the constraints of the data available for model development, and dependent on the test performance for delivery within 7 days.

We will include an economic analysis from an early stage to provide an economic rationale for the prognostic models and the value of the information included in it prior to its validation in the prospective cohort study.

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 July 2017; which include Actim Partus (IGFB and/or Partosure results and pregnancy outcome data; and the Principal Investigator of which has agreed to collaborate and provide data.

EXCLUSION CRITERIA

Studies where pHIGFBP-1 (Actim Partus) or PAMG-1 (Partosure) are measured by ELISA. Studies of women with Preterm Prelabour Rupture of Membranes. Studies where IPD is not available for meta-analysis.

CO-ENROLMENT

Not applicable

PARTICIPANT SELECTION AND ENROLLEMENT

IDENTIFYING TRIALS FOR INCLUSION

We will perform a literature review and search clinical trial databases and registries for completed and ongoing cohort studies of Actim Partus and Partosure, and consult preterm birth researchers and networks and the manufacturers of Actim Partus (Medix Biochemica) and Parosure (Parsogen) to ensure capture of all relevant studies. We will contact PIs of the studies and invite them to collaborate.

CONSENTING PARTICIPANTS

All women in the included studies will have provided informed consent for participation in studies and for their data to be used in subsequent analyses.

SCREENING FOR ELIGIBILITY

Studies for inclusion will be screened by at least two of the investigators to ensure they fulfil eligibility criteria.

STATISTICS AND DATA ANALYSIS

SAMPLE SIZE CALCULATION

The size of the IPD meta-analysis will be limited by the number of studies with data available. 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]

PROPOSED ANALYSES

The following factors which have been shown to influence risk of preterm labour, will be considered for inclusion as covariates in each prognostic model: test result (positive/negative), singleton/multiple pregnancy, previous spontaneous preterm labour, gestation at 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 test result (positive/negative), 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 Actim Partus and Partosure 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 be 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 shrunk 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 TESTS

The added value of Actim Partus and Partosure 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).

4.2 HEALTH ECONOMIC DECISION ANALYSIS MODEL

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 Actim Partus and Partosure. 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.

5 PART II: PROSPECTIVE COHORT STUDY

A prospective cohort study will be performed in at least 20 UK hospitals with different settings (rural/urban) and different levels of neonatal care facilities to collect data on the efficacy of Actim Partus and Partosure in predicting pre-term birth. It will run alongside the already established QUIDS study. Women who have provide consent for QUIDS will be offered participation in QUIDS 2. The data will be used to externally

validate, and if necessary refine, the prognostic models developed in IPD-Meta Analysis.

We will also assess the potential cost-effectiveness of the final prognostic models 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.

5.1 STUDY POPULATION

NUMBER OF PARTICIPANTS

The study will include women with signs and symptoms of preterm labour at 22⁺⁰ to 34⁺⁶ weeks gestation in whom admission, transfer or treatment is being considered. Our recruitment target is 568 women with estimated 10 -25 events of preterm delivery within 7 days of testing. These will be recruited from at least 16 sites with a mix of rural/urban settings, and have different levels of neonatal care facilities. The recruitment period is anticipated to last up to 14 months.

INCLUSION CRITERIA

The following inclusion criteria apply at screening assessment (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.
- 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.

The following inclusion criteria apply on speculum examination:

- Cervical dilation \leq 3cm
- Intact membranes
- No significant vaginal bleeding, as judged by the clinician.

The potential participant must meet all criteria at screening and speculum examination to be able to be fully enrolled on the study. Participants that sign the consent but are not eligible upon internal examination will still be enrolled and have outcome data collected.

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.

CO-ENROLEMENT

This trial involves the comparison of different pre-term birth marker tests currently 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. We anticipate that the majority, if not all, of participants in QUIDS 2 will be participants in QUIDS. Participation in QUIDS 2 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.

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 to explain the test we are evaluating and the procedures for the two vaginal swabs. The participant and the consentor 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 pre-term birth marker tests are usually taken at this point. Potential participants in the QUIDS 2 study will be identified after the initial assessment and provided with information about the study. Informed consent will take place before speculum examination and the swabs will be taken at the same time as the fFN swab for QUIDS. This approach means that samples are collected at routine speculum examination and participants avoid an additional vaginal examination. Swabs for qfFN and Actim Partus will be taken during the speculum examination. The swab for fFN (taken from the posterior fornix) will be taken first (as per the QUIDS study if the woman is participating), then the swab for Actim Partus (taken from the cervical os). The swab for Partosure (Low Vaginal Swab) will be taken when the speculum is removed (as per manufacturer's instructions).

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 not be eligible for the swabs to be taken after consent is given. These women will still be enrolled and delivery outcomes collected. The decision whether to use this data for analysis will be the decision of the Chief Investigator and Statisticians.

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

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 a 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 Consent Form. This will be done before the speculum examination and the swabs taken. It is at this point, if required, the woman will undergo the speculum examination. The clinician will then decide whether the swabs can be taken for the tests to 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 swabs cannot be taken, the participant will be provided with a letter explaining while they cannot be fully enrolled, we will still be collecting their delivery outcomes 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. Since this study is linked to the QUIDS study the only additional data that is to be collected will be the results of the swabs and the method of collection (speculum, doctor/midwife or self-collection by participant). 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.

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 as for QUIDS. 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.

ACTIM PARTUS/PARTOSURE RESULTS

The sites involved in QUIDS and QUIDS2 use fFN as per local hospital practice for the diagnosis of preterm birth. QUIDS2 samples will be tested after the clinical pathway of that woman has been decided and implemented, and QUIDS2 test results will not be revealed to the woman or her care team. One or other of the following methods will be used:

1) QUIDS2 samples will be stored until the clinical pathway of the participant has been decided and implemented. A member of the research team will test the samples out with the immediate clinical area (test strips will be stored away from clinical areas, and only be accessible by a researcher/nominated staff), document results on a paper cRF and place in a sealed envelope. Results will be sent to the Edinburgh trial office via recorded delivery.

2) QUIDS2 samples will be sent to the local NHS Biochemistry Service who will perform testing. A results report will be sent to the trial team in Edinburgh via secure email or post. Results will not be recorded in patient records or disclosed to clinicians.

In both cases results will be entered onto the study eCRF by the trial team in Edinburgh and will be the only ones who have access to these pages in the database.

STUDY ASSESSMENTS

	Attendance with signs and symptoms preterm labour		
Visit	Screening and Recruitment	After Decision made on Clinical Pathway	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		
Endocervical Vaginal Swab and Low Vaginal Swab taken	X		
Testing of swabs with Actim Partus and Partosure tests		X	
Delivery details			X
Neonatal outcomes			X
Finalise eCRF data			X

SAFETY ASSESSMENTS

Both Partosure and Actim Partus tests utilise the use of an internal control line. In the Partosure test the antigen-antibody complex flows to the test region where it is immobilised by a second anti-PAMG-1 antibody. This event leads to the appearance of the test line. Unbound antigen-antibody complexes continue to flow along the test strip and are immobilized by a second antibody. This leads to the appearance of the internal control line. The test strip should be read after 5 minutes sharp. Results should not be read or interpreted after 10 minutes have passed.

With Actim Partus, the blue latex particles are carried by the liquid flow and, if IGFBP-1 is bound to them, they bind to the catching antibody. A blue line (test line) will appear in the result area if the concentration of pHIGFBP-1 in the sample exceeds the detection limit of the test. A second blue line (control line) confirms correct performance of the test. The result can be interpreted as positive as soon as two blue lines become visible in the result area. The negative result should be read after 5 minutes and no later. No attention should be paid to lines appearing later than 5 minutes. As with both tests, if no control line is present, the test is invalid.

5.4 DATA COLLECTION

DATA FOR PROGNOSTIC MODEL VALIDATION

In the prospective cohort we will utilise the database currently set up for QUIDS to avoid duplication of data collection. We plan to use our current sites participating in QUIDS for recruitment to QUIDS 2. Since this study aims to compare the three available test of preterm labour - Actim Partus, Partosure and qfFN, it is likely that women who participate in QUIDS will also participate in QUIDS 2. 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 Actim Partus and Partosure testing will be collected on paper based CRFs and research midwives 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.

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

There is uncertainty in the recruitment rate and event rate within this add on study to QUIDS. We aim to recruit approximately 500 women in the prospective cohort study and have 10 - 25 events (pre-term labour within 7 days).

A table with the 95% confidence interval for various sensitivities (75% to 95% in steps of 5%, and 99%) for various prevalences (3.0%, 3.5%, and 4.0%), for various achieved sample sizes (N=350, 400, 450, 500) is given below.

An example would be, if we achieve in QUIDS2 the current observed prevalence of 3.5% within the QUIDS study and with a projected sample size in QUIDS2 of n=450 we would expect 16 events. If the true sensitivity of a test was 95%, the 95% confidence interval around this would be expected to be $\pm 10.8\%$. i.e. (84.2% to 100%) (see table below).

Table – The half-width of the 95% confidence interval for various sensitivities (75% to 95% in steps of 5%, and 99%) for various prevalences (3.0%, 3.5%, and 4.0%), for various achieved sample sizes (N=350, 400, 450, 500).

Sensitivity	Prevalence	N=350	N=400	N=450	N=500
75%	3.0%	26.2	24.5	23.1	21.9
	3.5%	24.2	22.7	21.3	20.3
	4.0%	22.7	21.2	20.0	19.0
80%	3.0%	24.2	22.6	21.3	20.2
	3.5%	22.4	21.0	19.8	18.7
	4.0%	21.0	19.6	18.5	17.5
85%	3.0%	21.6	20.2	19.1	18.1
	3.5%	20.0	18.7	17.6	16.7
	4.0%	18.7	17.5	16.5	15.6
90%	3.0%	18.1	17.0	16.0	15.2
	3.5%	16.8	15.7	14.8	14.1
	4.0%	15.7	14.7	13.9	13.1
95%	3.0%	13.2	12.3	11.6	11.0
	3.5%	12.2	11.4	10.8	10.2
	4.0%	11.4	10.7	10.1	9.6
99%	3.0%	6.0	5.6	5.3	5.0
	3.5%	5.6	5.2	4.9	4.7
	4.0%	5.2	4.9	4.6	4.4

PROPOSED ANALYSES

VALIDATION OF PROGNOSTIC MODELS

The prognostic model 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 models 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).

ECONOMIC ANALYSIS

The economic models 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].

COMPARISON OF TEST PERFORMANCE

The best test and model for use in the NHS will be determined by 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). Based on the findings, a final models and its implementation strategy will then be recommended for use.

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 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) Edinburgh statistician	Richard Riley John Norrie
Build validation model at 8 sites, 1600 patients	Edinburgh statistician	Richard Riley John Norrie
Refine prognostic model (allow site specific intercepts)	Edinburgh statistician	Richard Riley John Norrie
Final HTA Report – monograph	Edinburgh 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.
- The remaining members include the trial clinicians and scientists and participating centres will have responsibilities for the conduct of the trial in their hospital.

6.3 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.

6.4 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.

6.5 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 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 procedure for taking endocervical and low vaginal swabs, 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 swabs 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.

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 (qa@accord.scot) 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.

8.3 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 3 years and then review according to current guidance at that time.

8.4 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.

8.5 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.

PEER REVIEW

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

9.3 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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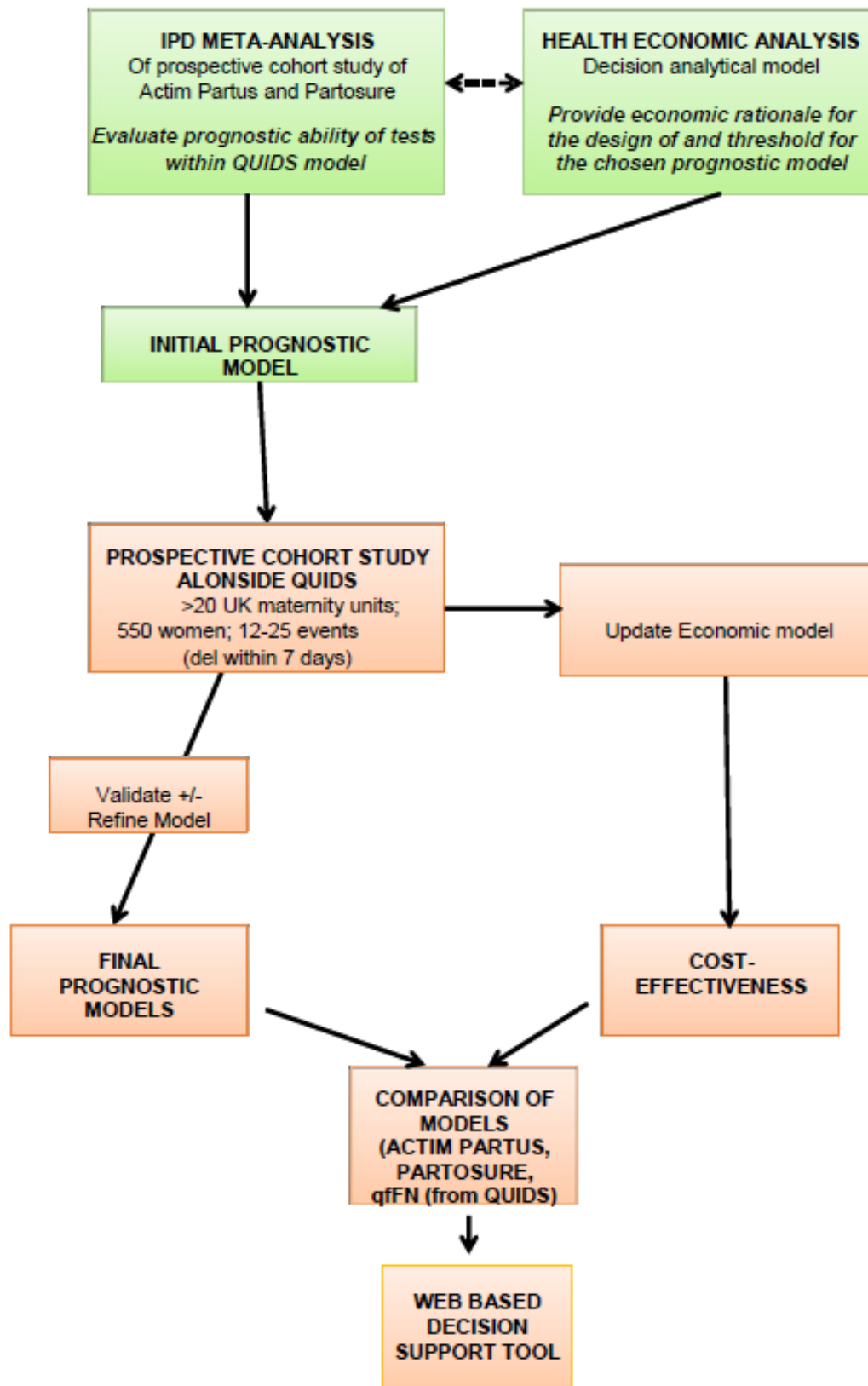
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10.1 APPENDIX 1: FLOWCHART



10.2 APPENDIX 2: Details of TSC/DMEC

INDEPENDENT MEMBERS:

TSC Independent Chair:
Professor Philip Bennett

Director, Institute for Reproductive and
Developmental Biology
Imperial College London
Faculty of Medicine
Institute for Reproductive and Developmental
Biology
Hammersmith Hospital Campus
Du Cane Road
London W12 0NN
Tel: +44 (0)20 7594 2176
Email: pbennett@imperial.ac.uk

TSC Independent Member:
Dr Peter Blair

Reader in Medical Statistics
St Michael's Hospital Level D
St Michael's Hospital
Southwell Street
Bristol
BS8 1TQ

Email: P.S.Blair@bristol.ac.uk

TSC Independent Member:
Dr Melissa Whitworth

Consultant Obstetrician
Department of Obstetrics,
St Mary's Hospital
Central Manchester and Manchester
Children's University Hospitals NHS
Foundation Trust
Hathersage Road
Manchester
M13 9WL

Email: Melissa.Whitworth@cmft.nhs.uk

TSC Independent Member
Public Member

TSC Independent Member
Public Member

NON- INDEPENDENT MEMBERS:

TSC Non- Independent Member:
Professor Olivia Wu

Professor of Health Technology Assessment
Health Economics and Health Technology
Assessment (HEHTA) Research Group
Institute of Health and Wellbeing
University of Glasgow
1 Lilybank Gardens
Glasgow
G12 8RZ

Email: Olivia.Wu@glasgow.ac.uk

Chief Investigator
Dr Sarah Stock

The Queens Medical Research Institute
47 Little France Crescent
Edinburgh
EH16 4TJ

Tel: 0131 242 6449

Email: Sarah.Stock@ed.ac.uk

Representative of the Sponsor
Mr Chris Coner (Non – Voting)

The Queens Medical Research Institute
47 Little France Crescent
Edinburgh
EH16 4TJ

Tel: 0131 242 9446

Email: chris.coner@ed.ac.uk

The Facilitator (Non - Voting)
Angela Niven
Trial Administrator

The Queens Medical Research Institute
47 Little France Crescent
Edinburgh
EH16 4TJ

Tel: 0131 242 2168

Email: Angela.Niven@ed.ac.uk

Members of the Project Management Group (PMG) who may be invited to attend as non-voting members:

Trial Manager
Lisa Wotherspoon

The Queens Medical Research Institute
47 Little France Crescent
Edinburgh
EH16 4TJ

Tel: 0131 242 6603

Email: lisa.wotherspoon@ed.ac.uk

Trial Statistician
Professor John Norrie

Director; Chair of Medical Statistics and Trial
Methodology

Director of Edinburgh Clinical Trials Unit
(ECTU)

University of Edinburgh

No. 9, Bioquarter

Rm. 2.685 Medical School, Teviot Place

Tel: 0131 651 7875 / 0131 650 9473

Email: j.norrie@ed.ac.uk