Threatened preterm labour: a prospective cohort study for the development of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management.

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ABSTRACT

Background: Preterm birth (PTB) is a major cause of infant morbidity and mortality, and accurate assessment of women in threatened preterm labour (TPTL) is vital for identifying need for appropriate intervention. Risk assessment in TPTL is challenging, however, due to its complex and multifactoral nature. In many women, TPTL symptoms do not progress to spontaneous PTB (sPTB) so assessment that reassures quickly, often through use of tests, e.g. fetal fibronectin (fFN) and cervical length (CL), may reduce unnecessary intervention and decrease anxiety. **Aims**: This PhD project had two main objectives: first to improve TPTL risk assessment by further developing the clinical decision support tool, the "QUIPP" mobile phone application, which simplifies risk assessment by calculating individual % risk of sPTB based on risk status, fFN and CL results. The second objective was to understand TPTL from the women's perspective in order to inform future improvements in care. **Method**: The study comprised three components: 1) a prospective cohort study, collecting data on risk factors, test results and interventions. Predictive utility of fFN and CL were investigated, as well as generation and validation of risk prediction algorithms for the second version of QUIPP; 2) a qualitative study of women's experience of TPTL through one-to-one semi-structured interviews; 3) a qualitative study of clinicians using the first version of QUIPP. **Results**: *Cohort study*: 1186 women were recruited at 11 UK hospitals between March 2015 and October 2017, with data available for analysis on 1037. Prevalence of sPTB was 3.9% (40/1037) and 12.1% (125/1037) at <34 and <37 weeks' gestation, respectively. Validation of QUIPP algorithms, using risk factors and fFN results alone, demonstrated good prediction of sPTB <30 weeks' gestation (AUC 0.96, 95% CI 0.94-0.99) and at <1 week of testing (AUC 0.91, 95% CI 0.87-0.96). *Qualitative study*: Four themes emerged following interviews with 19 women: i) coping with uncertainty; ii) dealing with conflicts; iii) aspects of care and iv) interactions with professionals. *QUIPP users' study*: 10 clinicians expressed predominantly positive views and suggested improvements. **Conclusion**: All components of this project informed development of QUIPP v.2 (algorithms and design), which appears superior in predicting sPTB compared to previously reported predictive utility of fFN, CL and QUIPP v.1 algorithms. The qualitative study was the first exploring women's experience of TPTL in a UK hospital with a specialist preterm service, and findings further support the need for women of all risk groups to have timely access to advice and information, and continuity of care.

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADU	Antenatal Day Assessment Unit
AFP	Alphafetoprotein
App	Mobile phone application
APS	Antiphospholipid syndrome
AUC	Area under the ROC curve
BMI	Body mass index
CL	Cervical length
CRF	Case report form
CRP	C-reactive protein
FDA	Food and Drugs Administration
FDCS	Full dilatation caesarean section
fFN	Fetal fibronectin
GSTfT	Guy's & St Thomas' NHS Foundation Trust
IMD	Index of Multiple Deprivation
IPDAS	International Patient Decision Aids Standards Collaboration
IUT	*In utero* transfer
MHRA	Medicines and Healthcare Products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNU	Neonatal unit
PPI	Patient and Public Involvement
PPROM	Prelabour preterm ruptured membranes
PTB	Preterm birth
PTL	Preterm labour
qfFN	Qualitative fetal fibronectin
REC	Research Ethics Committee
ROC	Receiver Operating Characteristic
SD	Standard Deviation
sPTB	Spontaneous preterm birth
TPTL	Threatened preterm labour
TVS	Transvaginal scan
TVS CL	Transvaginal ultrasound scan measurement of cervical length
UKPCN	UK Preterm Clinical Network
UTI	Urinary tract infection

PAPERS AND ABSTRACTS RELATING TO PRETERM BIRTH PUBLISHED DURING THE COURSE OF THIS PHD THESIS

Abbott, D.S., Hezelgrave, N.L., Seed, P.T., Seed, P.T., Norman, J.E., David, A.L., Bennett, P.R., Girling, J.C., Chandirimani, M., Stock, S.J., Carter, J., Cate, R., Kurtzman, J., Tribe, R.M. & Shennan, A.H. 2015, "Quantitative Fetal Fibronectin to Predict Preterm Birth in Asymptomatic Women at High Risk." *Obstetrics & Gynecology,* vol. 125, no. 5, pp. 1168-1176.

Cargill, Z., Shennan, A., Carter, J. and Seed, P., 2014. "A prospective case-control study looking at the effect of domestic violence on women at a high risk of spontaneous preterm birth." *BJOG: An International Journal of Obstetrics and Gynaecology*. 121(7), p.e2.

Carlisle, N., Carter, J., Radford, S. & Shennan, A. 2018, "Women's experiences of tests and procedures carried out at a preterm birth surveillance clinic." *British Journal of Midwifery,* vol. 26, no. 1, pp. 31-34.

Carter, J., Chandiramani, M., Seed, P., Shennan, A.H. & The MAVRIC Consortium 2015, "MAVRIC: Multicentre Abdominal vs Vaginal Randomised Investigation of Cerclage." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 122, pp. 1-7.

Carter, J., Gibson, S., Hezelgrave, N. & Shennan, A. 2014, "Full dilatation caesarean section and risk of subsequent preterm birth: a case series." *Archives of Disease in Childhood - Fetal and Neonatal Edition,* vol. 99, no. Suppl 1, pp. A168-A168.

Carter, J., Hezelgrave, N., Seed, P., Tribe, R., David, A., Lachelin, G., Shennan, A. & Poston, L. 2014, "Combined Fetal Fibronectin and Saliva Progesterone Measurement for Prediction of Spontaneous Preterm Birth." *Archives of Disease in Childhood - Fetal and Neonatal Edition,* vol. 99, no. Suppl 1, pp. A12-A12.

Carter, J., Seed, P.T., Tribe, R.M., David, A., Lachelin, G., Shennan, A.H. & Poston, L. 2017, "Saliva Progesterone for Prediction of Spontaneous Preterm Birth: the POPPY study." Poster presentation. British Maternal & Fetal Medicine Society Conference, Amsterdam", *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 124, pp. 122-154.

Carter, J., Tribe, R.M., Sandall, J. & Shennan, A.H. 2017, "Preterm Clinical Network Database: progress since launch and future plans." Oral presentation, *3rd Annual Preterm Birth Conference. Leeds.* Sept 2017.

Carter, J., Tribe, R.M. & Shennan, A.H. 2016, "The UKPCN database: a standardised and systematic data collection method for preterm clinics." Poster presentation,

BMFMS conference 2016, Birmingham. *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 123, pp. 40-63.

Carter, J., Tribe, R.M., Shennan, A.H. & Sandall, J. 2017, "Threatened preterm labour: women's experiences of risk assessment and management." Oral presentation, *ICM (International Confederation of Midwives) Congress, Toronto, Canada*, June 2017.

Carter, J., Tribe, R.M., Shennan, A.H. & Sandall, J. 2017, "Threatened preterm labour: women's experiences of risk assessment and management." Oral presentation, *3rd Annual Preterm Birth Conference, Leeds.* Sept 2017.

Carter, J., Tribe, R.M., Watson, H. & Shennan, A.H. 2016, "Threatened preterm labour management: results of a Delphi consensus on best practice." Poster presentation, BMFMS 2016, Birmingham. *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 123, pp. 88-106.

Carter, J., Tribe, R.M., Sandall, J. & Shennan, A.H. 2018, "The Preterm Clinical Network (PCN) Database: a web-based systematic method of collecting data on the care of women at risk of preterm birth." *BMC Pregnancy and Childbirth,* vol. 18, no. 1, pp. 335.

Carter, J., Tribe, R.M., Shennan, A.H. & Sandall, J. 2018, "Threatened preterm labour: women's experiences of risk and care management: a qualitative study." *Midwifery,* vol. 64 pp.85-92.

Carter, J., Tribe, R.M., Shennan, A.H. & Sandall, J. 2017, "Threatened preterm labour: women's experiences of risk assessment and management. Poster Presentation. British Maternal & Fetal Medicine Society Conference. Amsterdam." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 124, pp. 50-81.

Hall, M., Vousden, N., Carter, J., Hezelgrave, N. & Shennan, A.H. 2015, "Prevention of mid-trimester loss following full dilatation caesarean section: A potential role for transabdominal cervical cerclage." *Journal of Obstetrics & Gynaecology,* vol. 35, no. 1, pp. 98-99.

Kuhrt, K., Smout, E., Hezelgrave, N., Seed, P.T., Carter, J. & Shennan, A.H. 2016, "Development and validation of a tool incorporating cervical length and quantitative fetal fibronectin to predict spontaneous preterm birth in asymptomatic high-risk women." *Ultrasound in Obstetrics & Gynecology,* vol. 47, no. 1, pp. 104-109.

Ridout, A., Carter, J. & Shennan, A. 2016, "Clinical utility of quantitative fetal fibronectin in preterm labour." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 123, no.12, pp.1972.

Teoh, P.J., Ridout, A., Carter, J. & Shennan, A.H. 2018, "Mullerian tract anomalies and urinary tract infections." *Acta Obstetricia et Gynecologica Scandinavica,* vol. 97, no. 3, pp.357.

Toolan, M., Carter, J., Hezelgrave, N. & Shennan, A. 2014, "PPO.53 Ethnic differences in women attending preterm clinics." *Archives of Disease in Childhood - Fetal and Neonatal Edition,* vol. 99, no. Suppl 1, pp. A167-A167.

Vandermolen, B.I., Hezelgrave, N.L., Carter, J. & Shennan, A.H. 2016, "Successful vaginal delivery following an abdominal cerclage, predicted by serial vaginal cervical ultrasound." *Journal of Obstetrics and Gynaecology: the journal of the Institute of Obstetrics and Gynaecology,* vol. 36, no. 5, pp. 674-675.

Vousden, N.J., Carter, J., Seed, P.T. & Shennan, A.H. 2017, "What is the impact of preconception abdominal cerclage on fertility: evidence from a randomized-controlled trial." *Acta Obstetricia et Gynecologica Scandinavica,* vol. 96, no. 5, pp.543-546.

Vousden, N., Hezelgrave, N., Carter, J., Seed, P.T. & Shennan, A.H. 2015, "Prior ultrasound-indicated cerclage: how should we manage the next pregnancy?" *European Journal of Obstetrics & Gynecology and Reproductive Biology,* vol. 188, pp. 129-132.

Watson, H.A., Carter, J., David, A.L., Seed, P.T. & Shennan, A.H. 2017, "Full dilation cesarean section: a risk factor for recurrent second-trimester loss and preterm birth." *Acta Obstetricia et Gynecologica Scandinavica,* vol. 96, no. 9, pp.1100-1105.

Watson, H.A., Carter, J., Seed, P.T., Tribe, R.M. & Shennan, A.H. 2017, "The QUIPP app: a safe alternative to a treat-all strategy for threatened preterm labour." *Ultrasound in Obstetrics & Gynecology,* vol. 50, no. 3, pp. 342-346.

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1. Background

This PhD project focusses on threatened preterm labour (TPTL) risk assessment and management, and the experience of women with symptoms. The project has two major elements, the first being the development of a clinical decision support tool that predicts risk of preterm birth for individual women based on their background risk factors and test results. The second element is a qualitative study exploring women's experience of TPTL and identification of aspects of care that could be improved. Both elements together were designed to inform future changes to TPTL management that could result in a more positive experience for women. This chapter outlines current assessment and treatment options for women with symptoms of TPTL, and then moves on to discuss the broad concept of risk assessment in maternity care along with some of its challenges. It provides insights into how decision aids can be utilized to support both the communication of risk and decision making. The chapter concludes with the argument that this area of maternity care has potential for improvement.

1.1. What is preterm birth and threatened preterm labour?

Preterm birth (PTB), defined as birth before 37 weeks' gestation, is a major cause of infant death, as well as physical, developmental, emotional and financial problems for families, and health and social care systems (Marlow *et al.,* 2014). The incidence of preterm birth appears to be increasing globally (Blencowe *et al.,* 2013), currently affects around 7% of births in the UK (Office for National Statistics, 2015; Information Services Division, 2017) and it has been estimated to cost the NHS £2.9 billion every

year (Mangham *et al.,* 2009). Efforts to reduce the incidence and consequences of preterm birth are therefore of paramount importance.

Approximately two thirds of preterm births are associated with preterm labour and/or prelabour preterm ruptured membranes (PPROM) (Blencowe *et al*., 2013); the rest being medically indicated, or iatrogenic PTB. Preterm labour is the initiation of regular and painful contractions with dilatation of the cervix, before 37 weeks' gestation. If pregnant women present with symptoms of abdominal pain and/or uterine tightenings, but established labour is not diagnosed on speculum or digital examination, it is unknown whether, or not, they are indeed in the early stages of "true" labour, and they are described as having symptoms of threatened preterm labour (TPTL) (McPheeters *et al*., 2005).

1.2. What are the causes of threatened preterm labour?

The physiological mechanisms driving the onset of preterm labour remain unclear, but evidence suggests that it can be caused by inflammation or infection, uterine ischemia or haemorrhage, uterine over distension, cervical insufficiency and stress, by way of activation of the maternal/fetal hypothalamic-pituitary-adrenal axis (Goldenberg *et al.,* 2008; Romero *et al.,* 2006; Duthie and Reynolds, 2013) (Figure 1).

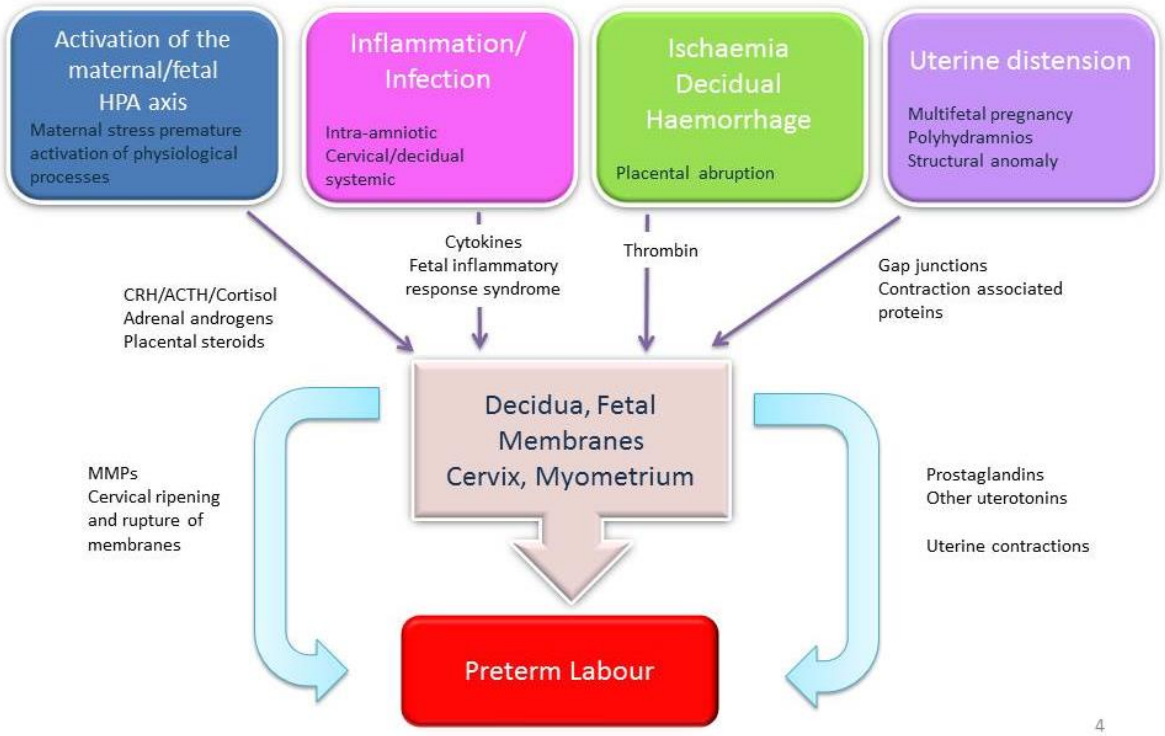


Figure 1. Causes of preterm labour. HPA=hypothalamic pituitary adrenal; CRH=Corticotropin-releasing hormone; ACTH= adrenocorticotropic hormone; MMPs=matrix metalloproteinases (Tribe, unpublished).

Abdominal pain associated with TPTL may not, however, be the onset of "true labour" as it may have other causes, such as urinary tract infection (UTI), fibroid and ligament distention.

1.3. Who is at risk of threatened preterm labour?

Many factors affect a woman's risk of preterm labour and birth. These include demographic factors, including age, ethnicity, weight and socioeconomic status (Di Renzo *et al.,* 2011a; Ferrero *et al.,* 2016). Lifestyle factors such as smoking, recreational drugs and environmental factors such as air pollution have also been associated with increased risk (Dew *et al*., 2007; Bertin *et al*., 2015). A woman's risk is

also influenced by previous medical and obstetric history, e.g. cervical surgery, uterine anomaly, previous preterm birth or late miscarriages, previous full dilatation caesarean section and factors specific to this pregnancy, for example multiple pregnancy, or conditions such as polyhydramnios or obstetric cholestasis (Berretta *et al.,* 2013; Epstein *et al.,* 1998; Fisk and Storey*,* 1988; Goldenberg *et al.,* 2008; Grimbizis *et al.,* 2001; Watson *et al*., 2017a). However, many women who have no known risk factors, particularly those experiencing their first pregnancy, will have preterm labour and/or birth (Mercer *et al.,* 1996).

The implications of preterm birth are widely known, so the development of symptoms or problems that may indicate premature birth can cause considerable stress and anxiety. This state is not only unpleasant, but may even increase the risk of preterm birth. A large body of literature suggests an association between stress and preterm birth and plausible aetiologies, such as the interaction between stress hormones and the inflammatory response, have been suggested (Christian, 2012; Latendresse, 2009; Rich-Edwards and Grizzard, 2005; Ruiz *et al.,* 2003; Wadhwa *et al.,* 2001). The form of stress may also be important. Lobel *et al.,* (2008) in their study of state anxiety, perceived stress, life events, pregnancy-specific stress, and health behaviours in 279 pregnant women, found that pregnancy-specific stress, i.e. stress resulting from factors relating directly to their pregnancy, which includes concerns about the baby's health, may be an even more important contributor to adverse birth outcomes than general stress.

1.4. Current methods of TPTL assessment

When a woman first presents with symptoms of threatened preterm labour, her clinician will review her maternity notes and take a history. This is in order to establish the woman's current condition and assess her risk of delivering early. Clinical signs and symptoms are noted, and a speculum examination is carried out in order to visually assess whether the cervix is dilating. If still unclear, the clinician may undertake a digital vaginal examination (NICE, 2015). If the diagnosis of preterm labour is uncertain, which is often the case in early labour, other tests may be performed. Methods of assessment vary around the UK but can also include transvaginal ultrasound scan measurement of cervical length (TVS CL) and various biochemical vaginal swab tests (Stock *et al.,* 2015). The first NICE guideline related to preterm birth was published in 2015 (NICE, 2015). A summary of the recommendations for care of women with symptoms suggestive of preterm labour with intact membranes are shown in Figure 2. It is not currently known how many hospitals are strictly using the guideline in practice, however, findings from a Delphi consensus of preterm specialists in the UK, undertaken separately from this PhD, indicated that they were not fully supportive of implementation, and they were particularly concerned about the recommended "treat-all" strategy for women at less than 30 weeks' gestation (Carter *et al*., 2016).

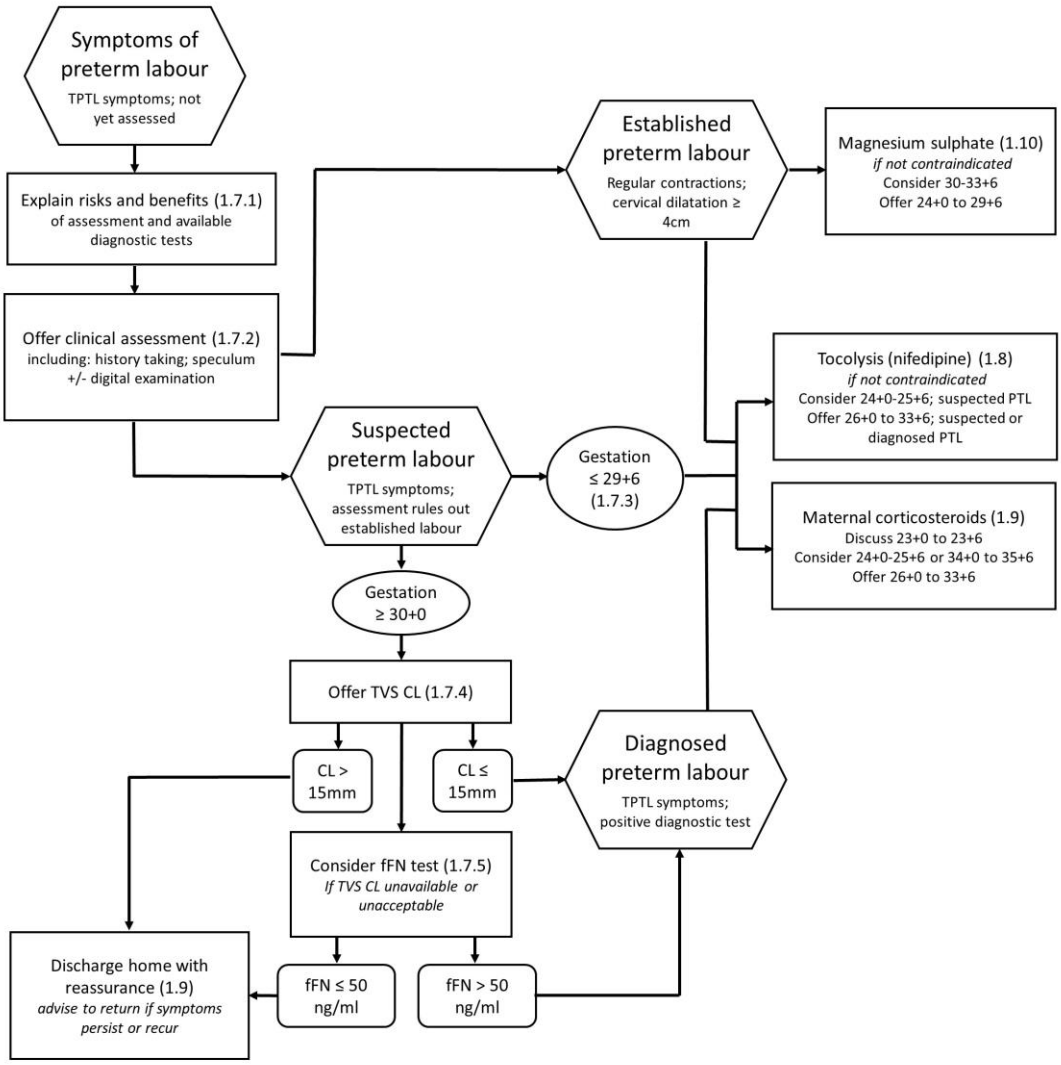


Figure 2. Summary of NICE (2015) Preterm Labour and Birth Guideline (NG25) recommendations for women with intact membranes with definitions and guideline section numbers. TPTL=threatened preterm labour; PTL=preterm labour; TVS=transvaginal ultrasound scan; CL=cervical length; fFN=fetal fibronectin.

1.4.1. Transvaginal ultrasound scan measurement of cervical length

Transvaginal ultrasound scan measurement of cervical length (TVS CL) has been shown to be useful in the risk assessment of women with symptoms of TPTL (Fuchs *et al.,* 2004; Iams *et al.,* 1996; Leitich *et al.,* 1999a; Owen *et al.,* 2003, Sotiriadis *et al.,* 2010). It is more accurate than digital examination because measurement can be made of the full length of the cervical canal including the internal os, and the presence or absence of cervical "funneling", where the cervix begins to open from the inside, can be determined (Crane *et al.,* 1997). A cervical measurement of 25 mm or less is generally considered short (Lim *et al.,* 2011). Risk of PTB is increased if cervical length is between 15 and 25 mm, and is significantly increased if less than 15 mm (Heath *et al.,* 1998; Tsoi *et al.,* 2005; Berghella *et al.,* 2009). Although recognised as a useful predictor of preterm birth in women with symptoms of TPTL, it is not currently widely performed in the UK, possibly due to a paucity of staff adequately trained in ultrasound scanning, and the availability of suitable equipment in relevant clinical areas. This was recognised by the National Institute for Health and Care Excellence (NICE) who proposed that the Royal College of Obstetricians and Gynaecologists (RCOG) should extend their obstetric trainees ultrasound module to include TVS CL (NICE, 2015).

In addition to its role in risk assessment, clinician knowledge of cervical length also might even prevent preterm birth. Berghella and colleagues' (2017) systematic review

and meta-analysis identified three trials, where a total of 287 participants with TPTL symptoms were randomised to CL screening with knowledge of the cervical length (n=145) or no knowledge (n=142). The known CL group had a significantly lower rate of preterm birth at less than 37 weeks than the control group (22.1% vs 34.5%; RR, 0.64 (95% CI 0.44-0.94)) and a later gestational age at delivery (mean difference 0.64 (95% CI 0.03-1.24)). The biological impact of TVS CL on PTB is unknown, however the authors suggest that knowledge of the result may reduce the need for repeated digital vaginal examinations.

1.4.2. Fetal fibronectin

Fetal Fibronectin (fFN) is an extracellular glycoprotein found in amniotic fluid, placenta tissue and in the decidua basilis. It is believed to be released following mechanical or inflammatory damage to the membranes and its potential as a predictive marker for preterm birth, particularly its high negative predictive value, has been established for several years (Abbott *et al.,* 2013; Honest *et al*., 2002; Leitich *et al.,* 1999b; Lockwood *et al*., 1991; Matsuura *et al*., 1988; Peaceman *et al.,* 1997). Originally, analysis was carried out by ELISA laboratory test. More recently bedside test analysers have been manufactured and are marketed by a US company, Hologic Inc. (Massachusetts, USA).

In the UK, test results for fFN were, until relatively recently, presented as dichotomous (i.e. positive or negative), based on a threshold of 50 ng/ml. Newer analysers can now provide results as concentrations in ng/ml, and it has been suggested that using alternative thresholds, i.e. <10 ng/ml and >200 ng/ml, rather than a cut off of 50

ng/ml, may improve positive prediction of the test and further aid clinical management (Abbott *et al.,* 2013; Foster and Shennan, 2014).

How beneficial fFN testing is in directing management or reducing negative outcomes remains unclear, however, as studies evaluating such effects report varying findings. A systematic review and health economic analysis, undertaken on behalf of the NIHR Health Technology Assessment (Deshpande *et al.,* 2013) concluded that use of fFN in the assessment of women with symptoms of TPTL is likely to reduce health care costs without adversely effecting outcomes, providing women with negative results are managed appropriately. Basak and Babbur (2012) undertook an audit of *in utero* transfers (IUT) over three years in their UK district general hospital, and found that the introduction of fFN testing reduced the proportion of IUTs for TPTL from 60% to 26.7%. More recently, however, a systematic review and meta-analysis of randomised controlled trials found no difference in the incidence of preterm birth at any gestation, in the management of women with TPTL or in neonatal outcomes, although they did find a slight increase in healthcare cost (Berghella and Saccone, 2016). As management, which included interventions such as the administration of tocolysis or steroids for fetal lung maturation, was similar in both groups, it is not surprising that there was no difference in rate of preterm birth or neonatal outcomes. The authors suggest that, based on their findings, routine use of fFN in women with TPTL is not justified. However, this conclusion must be viewed with caution. Four of the six included trials were published in or before 2004, one was available only in abstract form, and in two of the four where time frame was indicated, data were collected between the years 2000 and 2002. At this time, fFN was a relatively new test,

providing only dichotomous results, and it is possible that clinicians may not have been so confident in allowing the results to influence their management.

1.4.3. Other biomarkers

Since the establishment of fFN as a recognised predictor of preterm birth the detection of other proteins, such as insulin-like growth factor binding protein-1 (ILGF-1) and placental alpha microglobulin-1 (PAMG-1) have been the basis of newer bedside prediction tests. Although findings of some small studies suggest they may have a role in TPTL assessment (Ehsanipoor *et al*., 2016; Nikolova *et al*., 2014; Wing *et al*., 2017) the body of evidence supporting their efficacy is currently substantially smaller than that relating to fFN (Di Renzo *et al.,* 2011b).

Other potentially useful biomarkers for the prediction of preterm birth have been suggested, and these include albumin and vitamin D-binding protein in cervico-vaginal fluid (Liong *et al*., 2014) and cell-free RNA (cfRNA) transcripts in maternal blood samples (Ngo *et al*., 2018). Lucaroni and colleagues (2018) undertook a review of 14 systematic reviews of biomarkers for predicting spontaneous PTB (sPTB) and concluded that, after fFN, which had the strongest association with sPTB, maternal serum alpha fetoprotein (AFP), C-reactive protein (CRP) and the cytokine, interleukin-6 also had potential roles in prediction of sPTB. AFP was associated with an OR of 4 and 3 for sPTB <34 and < 37 weeks, respectively; CRP had odds ratios for sPTB of 2 (95% CI 1–2) and 8 (95% CI 4–16) in maternal plasma and amniotic fluid, respectively, and interleukin-6, had an odds ratio of 2 and a positive likelihood ratio of 12.

1.4.4. Combining biomarkers

Whether combining biomarkers can increase accuracy of prediction is contentious issue. Some commentators suggest that taking the two most strongly established predictors of preterm birth, combining fFN and TVS CL is likely to lead to better risk assessment (Bolt *et al.*, 2011; Bruijn *et al.*, 2016; DeFranco *et al.,* 2013; Gomez *et al*., 2005; Ness *et al*., 2007) and significant reduction in healthcare costs (van Baaren *et al.,* 2013). Others, however, disagree. Levine and colleagues (2018) found that combining fFN and CL did not improve prediction over using either test alone in a cohort of 537 USA women with symptoms of TPTL. In another prospective cohort study, carried out in four UK and two South African hospitals, where test results were blinded to attending clinicians (n=195), Tsoi and colleagues (2006) concluded that the addition of fFN result to TVS CL did not improve prediction of preterm birth within seven days.

1.5. Interventions to reduce risks associated with TPTL

Following examination and assessment, if a woman is considered to be at risk of delivering prematurely, she may be offered a number of interventions that have been shown to reduce the risks of neonatal morbidity and mortality associated with preterm birth. These include administration of antenatal corticosteroids for fetal lung maturation, drugs to reduce or stop uterine contractions (tocolytics), magnesium sulphate for fetal neuroprotection, and hospital admission with IUT, if necessary, to ensure the availability of appropriate neonatal intensive care. As with all interventions, however, the risks must be considered alongside the benefits.

Administration of steroids, usually in the form of dexamethasone or betamethasone, substantially improves outcomes in babies born preterm (Royal College of Obstetricians and Gynaecologists, 2010), and is recommended for all women at significant risk of delivery between 24 weeks' (or earlier, if the fetus is considered viable) and 34 weeks' gestation. A full course consists of two doses 24 hours apart, and the optimal clinical effect is seen between 24 hours and seven days (Norberg *et al*., 2017). This can, of course, be difficult to judge and evidence suggests that many women may be receiving them at inappropriate times. In a retrospective cohort study of 630 women who had had preterm birth between 24 and 34 weeks, Levin and colleagues (2016) found that although 93% (589/630) had received steroids, only 40% (238/589) received them between 24 hours and 7 days. If the birth does not take place within the optimal window and the women has a further episode of TPTL, repeated administration of steroids may occur. There is evidence, however, that multiple courses of steroids may be harmful and lead to growth restriction and possible longer term cardiovascular effects in the baby (Asztalos *et al.,* 2014; Murphy *et al.,* 2008; Norberg *et al.,* 2013). Although the balance of risk indicates administration of steroids should be repeated if preterm birth remains likely after the time of maximum effect (McKinlay *et al.,* 2012), this should be avoided if possible, and so appropriate timing of the first course is of great importance. Additionally, although not appearing to have lasting adverse effects on the woman, the administration of steroids can substantially affect blood sugar levels and those with impaired glucose tolerance or diabetes require extra monitoring (Royal College of Obstetricians and Gynaecologists, 2010).

Tocolytic drugs are designed to stop uterine contractions. A range of drugs have be used for this purpose and these include ritodrine, terbutaline, indomethacin, nifedipine, atosiban and magnesium sulphate (Gyetvai *et al.,* 1999). Evidence suggests that they can delay delivery for up to seven days, but with no proven reduction in neonatal morbidity (Gyetvai *et al.,* 1999; Haas *et al.,* 2009; Smith *et al*., 2009). Currently, the main rationale for tocolytic use is to delay the birth for at least 48 hours to allow completing of a course of steroids, and for IUT, if necessary, to a hospital with an appropriate level of specialist neonatal care (Haram *et al*., 2015). Many tocolytics have unpleasant and potentially dangerous side effects, including nausea, vomiting, palpitations and hypotension, and if offered, must be used with caution (NICE, 2015). Tocolytics most offered in UK currently include nifedipine and atosiban.

Evidence suggests that administration of antenatal magnesium sulphate substantially reduces the risk of cerebral palsy in children of women at risk of preterm birth (Constantine *et al.,* 2009; Crowther *et al.,* 2014). However, magnesium sulphate overdose can lead to loss of deep tendon reflexes and respiratory depression and both the woman and fetus require careful monitoring.

Women may be admitted to hospital for observation and to ensure neonatal facilities are available should their symptoms progress quickly to established labour, as this can substantially improve the outcomes of preterm babies (Marlow *et al.,* 2014). They may also be advised to stay in for “bed rest”. There is, however, no evidence to support the use of bed rest for women at risk of PTB (Sosa *et al.,* 2015) and there may be other potential adverse effects such as weight gain and risk of deep vein thrombosis

due to lack of mobility. Despite the lack of evidence bed rest is still frequently advised (Sciscione, 2010). Hospitalisation is costly, both for the NHS, and for the woman, and can mean loss of income, difficulties with childcare and work, as well as isolation and increased anxiety (Lowenkron, 1999; Mackinnon, 2006). In contrast, for women with a history of preterm birth, hospital admission may be reassuring. Although the mechanism is unclear, as discussed in more detail in Section 11.2.2, anxiety and depression are known to increase the risk of spontaneous preterm birth (Dole *et al.,* 2003) and a reduction in anxiety may help these high risk women (O'Brien *et al.,* 2010). The very process of being monitored carefully, or perceptions of additional support, may have a protective effect. Indeed, Sandall and colleagues' systematic review found a reduction of preterm birth in women who had received midwifery-led continuity models of care compared to those with "shared-care" models (Sandall *et al.,* 2016). The biological pathways for this effect remain to be clarified.

If a woman in TPTL is admitted to a hospital that does not have adequate neonatal facilities for her gestation, she may be transferred to another, which could be located at a significant distance from home. As well as practical and financial difficulties, the emotional impact on women is likely to be significant, with increased anxiety as a result of being in an unfamiliar environment and feelings of isolation and separation anxiety (Porcellato *et al.,* 2015). IUT can be a complicated and costly procedure for the doctors organising the transfer (Gale *et al.,* 2012), and if the woman does not subsequently deliver preterm, it could result in an antenatal bed and neonatal cot being unnecessarily "blocked", potentially leaving a woman living closer to the receiving hospital requiring IUT elsewhere, or her baby being transferred postnatally,

which is more dangerous (Watson *et al*., 2017b). Currently, there are no data available to estimate the number of seemingly unnecessary transfers in the UK, but Badgery-Parker and colleague's (2012) large Australian retrospective cohort study of women admitted to hospital at 20 to 36 weeks' between 2001 and 2008 (n=110,439) found that of women transferred for suspected TPTL only 38% delivered prematurely.

1.6. Challenges in providing appropriate care in TPTL

Although advances in care have led to more, and earlier, babies surviving preterm birth, it remains hard to accurately predict, even when a women presents with symptoms of threatened preterm labour (TPTL). If cervical dilation is not evident on speculum or digital examination it is difficult to know whether labour has indeed started and will progress to preterm birth, and whether the woman should be admitted and receive clinical care, or be discharged.

Symptoms of TPTL (e.g. abdominal pain and/or uterine contractions) are not accurate predictors of preterm birth (Copper *et al.,* 1990, Iams *et al.,* 2002) but because the consequences of not treating women in "true" preterm labour could be devastating, many receive unnecessary interventions. Overtreatment of women with symptoms of TPTL is a problem because of the danger of adverse effects of the interventions, as detailed in Section 1.5, as well as significant, and potentially unnecessary, healthcare expenditure (Lucovnik *et al.,* 2013; Mozurkewich *et al.,* 2000; van Baaren *et al.,* 2013).

The extent of this problem is significant. At least half of women with symptoms of TPTL will deliver at term (Kiefer and Vintzileos, 2008; McPheeters *et al.,* 2005). One study

reported as many as 82% of women with preterm labour symptoms eventually being discharged home with a diagnosis of false preterm labour (Chao *et al.,* 2011), while in Iams and colleagues' (1995) study of the utility of fFN in TPTL, using a threshold of 50 ng/ml, only 32% of women delivered preterm. Boesveld *et al.,* (2014) found that in their retrospective cohort study of 984 women receiving antenatal corticosteroids for fetal lung maturation, only 40.1% of those with suspected preterm labour delivered within 7 days, the time within which the drug has its optimum effect.

1.7. Risk assessment in maternity care

The purpose of antenatal care is to prevent and/or treat conditions that threaten the life or health of pregnant women and their babies, as well as to help women to "approach pregnancy and birth as positive experiences" (Banta, 2003, p.4). A fundamental element of maternity care is risk assessment which aims to identify those in need of extra surveillance or intervention. This is important because, while healthcare interventions are designed to prevent or mitigate poor outcomes they need to be appropriately targeted, both to avoid iatrogenic adverse effects and to protect finite health resources (Hoffman and Cooper, 2012; Pathirana *et al.,* 2017). Risk assessment in healthcare involves clinicians taking note of the patient's history and current symptoms, and applying their knowledge and experience of previous cases with known outcome. This assessment is then used as a basis for shared decision making, when the clinician and patient come to a conclusion on the best course of action (Godolphin, 2009).

1.7.1. Uncertainty in risk assessment

Whilst it is a fundamental part of healthcare, the process of risk assessment is not always straightforward. An individual's risk is often calculated based on a statistical probability that an event, or hazard, will occur. These probabilities are based on frequencies observed in past studies of heterogeneous populations. So, whilst they can provide some assistance in approximating the risk and informing decision making, they cannot eliminate the inherent uncertainty of future events (Dhawale *et al*., 2017). Although maternal and neonatal mortality rates have decreased dramatically in high income countries since the first half of the 20th century, pregnancy outcomes for individual women remain impossible to predict with certainty.

The issue of uncertainty resonates in all areas of healthcare, where the best course of action is often unclear and there has to be a trade-off between potential benefits and possible harms (Politi, 2015). The communication of uncertainty can also be very challenging. Han (2013) describes a number of difficulties that include the reliability of the probability information it is based upon, the lack of evidence on the best methods for communicating it and the ethical issue of whether the communication of uncertainty can affect patient autonomy to the extent that it does more harm than good. Politi and colleagues (2011) found that the communication of uncertainty can lead to lower patient satisfaction, although the authors argue that this is a necessary part of shared decision making. A later review of the literature concluded that uncertainty must at least be acknowledged and that clinicians should aim to help patients through "the emotionally laden process of grappling with unknowns." (Politi 2015, p.4):

> "Acknowledging uncertainty and collaborating with patients through the unknowns of medical care is not easy, but can have long-lasting benefits for both patient care and the patient-clinician relationship." (p.4).

Although now recognised as an important element of informed decision making (David and Akintomide, 2016), evidence remains lacking on the most effective methods of communicating uncertainty (Ahmed *et al.,* 2012; Politi *et al.,* 2007; Royal College of Obstetricians and Gynaecologists, 2008). In the absence of this evidence, the Royal College of Obstetricians and Gynaecologists has published guidelines and general principles, which advise the clinician to:

> *"accept and involve patients as a partner by informing them of the risk; plan what you will say and be appropriately informed about the patient's medical, social and educational circumstances; ensure that your advice is up to date and in line with your departmental practice; evaluate the patient's understanding of what you have discussed; listen to their concerns; maintain trust and credibility by being honest, frank and open."* (Royal College of Obstetricians and Gynaecologists, 2008, p.5).

Another issue with communication of uncertainty and risk probabilities is a lack of numerical understanding in both patients and clinicians (Lipkus *et al.,* 2001; Lloyd *et al.,* 2001). Recognising a particular need to address the lack of numerical literacy of patients which results in difficulties in understanding probability statistics, Fagerlin and colleagues (2011) made 10 recommendations on how best to communicate complex information on risk (Figure 3).

1	Use plain language to make written and verbal materials more understandable.
2	Present data using absolute risks.
3	Present information in pictographs if you are going to include graphs.
4	Present data using frequencies.
5	Use an incremental risk format to highlight how treatment changes risks from pre-existing baseline levels.
6	Be aware that the order in which risks and benefits are presented can affect risk perceptions.
7	Consider using summary tables that include all of the risks and benefits for each treatment option.
8	Recognize that comparative risk information (e.g., what the average person's risk is) is persuasive and not just informative.
9	Consider presenting only the information that is most critical to the patients' decision making, even at the expense of completeness.
10	Repeatedly draw patients' attention to the time interval over which a risk occurs.

Figure 3. Summary of recommendations for risk communication to patients, adapted from Fagerlin *et al.,* 2011, (p.1437).

Even when an individual's probability of risk has been reliably calculated, how that risk is perceived, what it means to the patient as an individual and how it influences their decision can be very varied, and not necessarily in line with that of their clinician (Brewer *et al.,* 2007; Herxheimer, 2005; Lee *et al.,* 2012). This risk perception can be influenced by the way the risk is communicated. Simply the way the risk is framed, that is, whether it is presented as a gain or a loss, e.g.: "you have a 5% chance of your baby being born early" as opposed to "you have a 95% chance of your baby being born at term", can have a profound effect on an individual's perception of risk (Paling, 2003). Gigerenzer and Edwards (2003) warn that care should be taken that risk is not presented in such a way as to serve the best interests of the institution, rather than that of the patient, for example, a screening programme aiming to increase uptake.

1.7.2. Decision support tools

Decision support tools, or decision aids, can help both patients and clinicians to evaluate the often vast and complex information required before they can come to an informed decision. These tools come in various forms, including booklets, questionnaires that help a patient to consider what is most important to them, videos, or interactive computerised tools. Use of decision aids in clinical practice has grown substantially over the last two decades, but recognition of the important influence they can have on patient decisions, and the variability of their quality, inspired the establishment of the International Patient Decision Aids Standards (IPDAS) Collaboration (Elwyn *et al.,* 2006). This collaboration developed a set of internationally recognised standards that could be used as a checklist by developers and evaluators for improving the quality of decision aids and the reporting of their evaluations.

Despite publication of these standards, and while the quantity of available patient decision aids increased, quality was not always assured. A systematic review of papers, published in 2013, describing development and evaluation of patient decision aids using an adapted framework based on an earlier set of criteria, the Ottawa Patient Decision Aids Framework (O'Connor *et al.,* 1999), and IPDAS criteria found that: "Only about half [patient decision aids] appear to have been field tested with patients, and even fewer had been reviewed or tested by clinicians not involved in the development process" (Coulter *et al.,* 2013, p.4).

More recent evidence appears to support the use of patient decision aids. A Cochrane Systematic Review (Stacey *et al.,* 2017) found good quality evidence that using decision aids can improve accuracy of risk perceptions (accuracy of risk perceptions (relative risk 2.10; 95% CI 1.66 to 2.66)) and reduce decisional conflict (mean difference in decisional conflict score (DCS) −9.28/100; 95% CI −12.20 to −6.36). Nilsson *et al.,* (2015), in their systematic review, also found a decrease in decisional conflict in women using decision aids when considering vaginal birth after caesarean section.

The popularity and acceptance of decision aids in healthcare appears to now be well embedded in the UK. The NHS Rightcare initiative makes available a number of evidence-based patient decision aids through their website. However, the number of aids is currently limited, with only one related to maternity care: "Birth options after previous caesarean section decision aid" (NHS England, 2018).

1.7.3. Improving the presentation of risk information

The way the information is presented in a decision support tool can have a major influence on decision making. This is particularly important with the presentation of risk information (Ahmed *et al.,* 2012). As described earlier, numerical literacy can affect the ways people interpret risk, so ratios and percentages may be more helpfully reported as frequencies, e.g. 1 in 100 people (David and Akintomide, 2016).

Personalised risk estimates have also been shown to increase informed choice. Of the three good quality studies included in Edward *et al.,*'s (2013) Cochrane Systematic Review, 45.2% (592/1309) of participants receiving personalised risk information made

informed choices, compared to 20.2% (229/1135) who received generic risk information.

In an attempt to identify best practice in risk communication used in decision aids, Trevana *et al.,* (2013) developed an evidence summary by expert consensus and proposed a set of guiding principles that should be considered when including numerical estimates in decision aids. These are shown in Figure 4.

1	The inclusion of numeric estimates with PtDAs [patient decision aids) improves patient's accuracy of risk comprehension.
2	Consider the cognitive tasks required of DA [decision aid] users and choose the appropriate format for presenting the information (e.g. comparing the chance of two independent events at a defined point in time).
3	Define a relevant reference class (i.e. denominator) for your target audience and try to keep this consistent throughout the DA. In defining the reference class, take time into consideration.
4	Try to use a consistent format throughout the DA.
5	Avoid using 1 in x formats with variable denominators.
6	Consider your target group's graph literacy and numeracy and include appropriate formats.
7	Consider the magnitude of the numbers you are presenting and the possibility of format bias. This may be reduced through concurrent use of appropriate visual formats.

Figure 4. Guiding principles for including numeric estimates in decision aids. Adapted from Trevana *et al.,* 2013.

Graphical representations, such as icon arrays, can be used to illustrate risk visually, and may even save time during consultations (Edwards *et al.,* 1999). Galesic and colleagues' (2009) study of older adults and university students found using icon arrays increased accuracy in understanding risk reduction in both groups. Icon arrays display a number of dots, or other figures representing people, and highlighting is used to depict those affected by the risk within the context of the population.

A relatively recent example of an icon array can be found in a decision aid for women choosing place of birth (Coxon, 2014, Figure 5). This visually demonstrates the differences in neonatal outcome - as defined in the Birthplace Study (Hollowell *et al.,* 2011) – by planned place of birth, and is designed to help women compare these risks as they make this important decision. Although the use of these icon arrays in this decision aid booklet aims at simplifying risk in different scenarios, some women, particularly those with limited literacy, may need assistance in interpretation.

Figure 5. Icon array displaying risk of poor neonatal outcome by planned place of birth. From Coxon (2014).

1.7.4. Mobile technology in healthcare

The use of digital technology in healthcare has been recent and rapid and the advantages of mHealth, i.e. digital health technologies that utilize mobile phones, is seen as a natural progression (Perera, 2012). Mobile technology has been found to be useful for data collection, provision of health information and communications, particularly in lower and middle income countries, where mobile phones are very common (Amoakoh-Coleman *et al.,* 2016; Kay *et al.,* 2011; Sondaal *et al.,* 2016). An increasing body of evidence suggests mHealth interventions can improve outcomes and health service utilization (Bush *et al.,* 2017; Chen *et al.,* 2018; Sondaal *et al.,* 2016). One of the particular advantages of mobile phone applications is that they can be updated regularly, ensuring information is based on current evidence, and they are so readily accessible (Arbour and Stec, 2018). Clinical decision support tools that incorporate an element of personalised risk calculation may be most suited to a computer-based programme which calculates an individual's risk based on inputted risk factors and variables such as age. Complex tools such as these are sometimes referred to as Computerized Decision Support Systems (CDSSs) (Liberati *et al.,* 2017).

Mobile phone health applications are widely used by clinicians as well as patients. A survey of UK medical students (n=257) and junior doctors (n=131) carried out in 2011 found a high level of smart phone ownership (79%, 203/257 and 75%, 98/131, respectively) and mobile application usage (76%, 155/203 and 72%, 71/98, respectively) with both groups expressing an interest in the development of additional apps to enhance their education and professional practice (Payne *et al*., 2012). As

technology has moved on in recent years, this is likely to have increased. A more recent survey of 197 Californian obstetrics and gynaecology doctors found that 95% used mobile apps in the clinical setting (Perry *et al.,* 2017).

There are concerns, however, that without official validation and regulation some medical apps may produce erroneous results and lead to incorrect, inappropriate or even dangerous decisions (Bierbrier *et al*., 2014). In 2015, in recognition of the growing number of medical apps in use, the USA's regulatory body the Food and Drugs Administration (FDA) issued guidance (FDA, 2015). This guidance stipulates that if a mobile app is defined as a medical device it will be regulated in the same way as other medical devices. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) also considers and regulates medical mobile apps providing they meet the regulatory body's definition of a medical device (MHRA, 2018).

1.8. Relationship of this PhD project with the QUIPP app.

One of the objectives of this PhD project, as explained in detail in Chapter 4, was to inform development of a risk assessment tool that had already been created by the King's College, London (KCL) Department of Women and Children's Health Preterm Birth Group (Abbott *et al*., 2011; Kurht *et al*., 2016a, 2016b). This section explains the relationship between my PhD project to the ongoing development of the tool.

1.8.1. Creation of the preterm birth risk assessment tool

The risk assessment tool was first manifest as a Microsoft Excel spreadsheet (Figure 6), where risk factors, gestation and test results were entered in defined cells (highlighted in mauve in Figure 6) and a probability of preterm delivery was generated and shown in other cells (highlighted in green, Figure 6). The algorithms used in generating the risk prediction scores were developed using data collected during the EQUIPP study (REC Ref. 10/H0806/68) and are reported in Kuhrt *et al.,* (2016a) and Kuhrt *et al.,* (2016b).

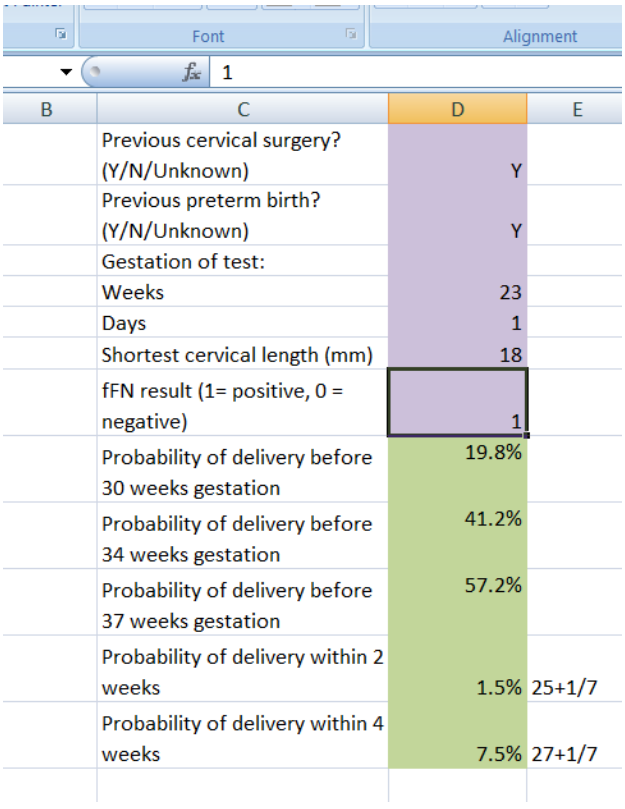


Figure 6. Excel spreadsheet showing first version of the KCL Department of Women and Children's Health preterm birth risk assessment tool.

1.8.2. First version of the risk assessment tool as an iPhone App.

Before commencement of the recruitment phase of this PhD project, an independent mobile phone app designer (James Appatta) was engaged to develop the risk assessment tool into an iPhone app, QUIPP version 1 (Figure 7). This app utilized the same prediction algorithms into a more user-friendly format, which was then used in the Preterm Surveillance Clinic at Guy's and St Thomas' NHS Foundation Trust (GSTfT) and by other members of the UK Preterm Clinical Network (UKPCN), a body of clinicians running specialist clinics for women at high risk of preterm birth.

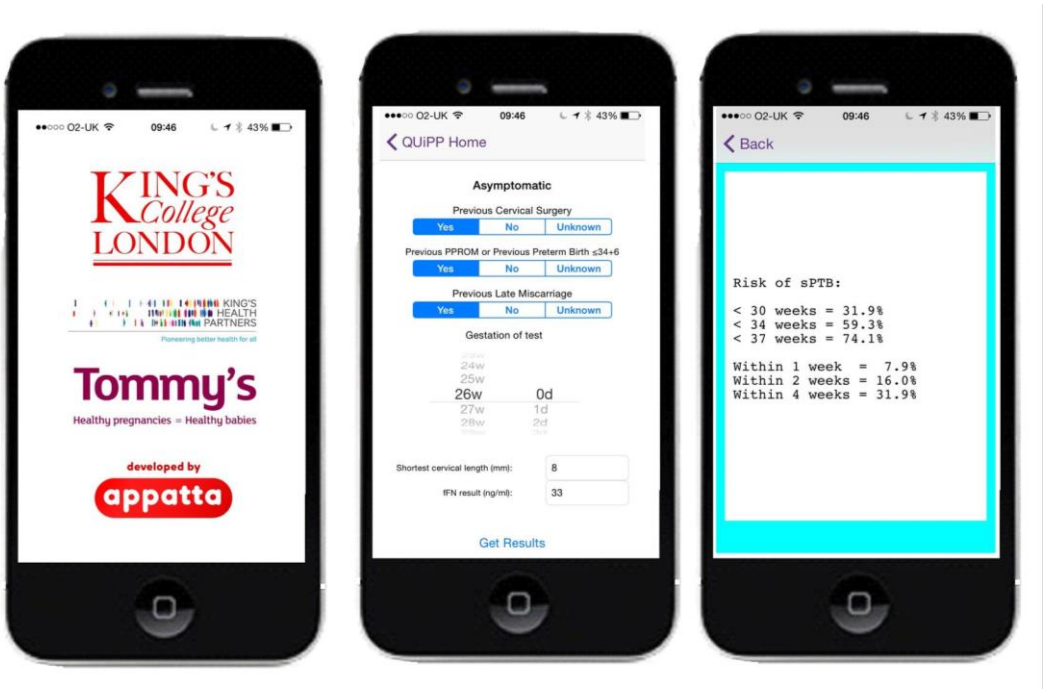


Figure 7. Risk assessment tool for high risk asymptomatic women – QUIPP App version 1.

1.8.3. Developments occurring during PhD project

The next phase of development was planned to commence after the completion of this PhD project. However, before the participant recruitment phase was complete, a

funding application to evaluate the QUIPP app in practice was successful (EQUIPTT, REC Ref. 17/LO/1802, funded by Guy's and St Thomas' Charity, Registered Charity No. 1160316; ISRCTN trial registry number ISRCTN17846337). The opportunity was taken to proceed with developing the second version of the app and to ensure the prediction algorithms were as up-to-date as possible before commencement of that study. A decision was taken by the Preterm Birth Research group, of which I am a member, to update the predictive algorithms prior to completion of PETRA using data already gathered (as at the end of May 2017) along with relevant participant data from earlier studies that I had been closely involved in (EQUIPP REC Ref. 10/H0806/68 and POPPY REC Ref. 09/H0802/97). My involvement at that stage had been to prepare the data set used in creation of the new algorithms. These were tested by calibration before being applied in the new version of the QUIPP app. Formal validation was carried out, by myself and the department statistician, Mr Paul Seed, after completion of the PETRA study and is presented in Section 8.7 as part of the final results of this thesis.

Data obtained from the qualitative components of the PhD project were also used to inform developments in usability and visual illustration of risk. These will be explained in more detail in later relevant chapters.

1.9. Summary and justification for thesis

In summary, for those women whose symptoms develop into preterm labour and birth, accurate risk assessment and diagnosis is vital so interventions that minimize the associated risks can be instigated quickly. What is also very important, however, is the fact that many women who experience symptoms of TPTL will not subsequently

deliver early, so clinical assessment and test results that can reassure as quickly as possible are likely to be beneficial by both reducing unnecessary intervention and decreasing anxiety.

Risk assessment in TPTL remains complex, partly because clinicians need to make judgements based on the woman's history as well as at least three other continuous variables, i.e. pregnancy gestation, fFN result and cervical length. A simple-to-use, accurate tool, which combines risk factors and test results into one % risk score, was proposed to improve the process of decision making (Abbott *et al.,* 2011; Kuhrt *et al.,* 2015). Because data from symptomatic women was limited, in the first version of QUIPP, prediction algorithms for use in TPTL were limited to singleton pregnancies and qfFN test results. This study would address this by gathering data, including TVS CL, from a large prospective cohort.

Other aspects of a woman's clinical care may also affect her experience of TPTL in positive and negative ways. Levels of anxiety, as discussed earlier in Section 1.3 may also independently influence risk of preterm birth. A deeper understanding of the experience from the woman's perspective may highlight areas for potential improvement in TPTL care that could be subsequently incorporated into clinical guidelines.

This PhD project sought to address these two issues: i) the need for improved risk assessment and ii) the identification of how TPTL care could be improved. This was achieved through developing a clinical decision support tool that predicts individual risk of preterm delivery and undertaking a qualitative study exploring women's

experience. Prior to addressing these questions experimentally, two literature reviews were undertaken to determine the current knowledge pertaining to the use of mobile apps in pregnancy and to establish what is currently known about women's experience of TPTL.

2. Literature Review 1: Mobile Apps for Clinical Decision Support in Pregnancy

2.1. Introduction to literature review

Despite the apparent extensive use of medical mobile phone applications (apps) by both clinicians and patients, there appears to be a paucity of peer-reviewed professional journal publications, particularly in relation to preterm birth. A review of the Cochrane Pregnancy and Childbirth Group's Trials Register (Davey *et al.,* 2015), found no trials of risk-scoring systems, of any kind, for predicting preterm birth with the aim of reducing associated adverse outcomes.

As development of a TPTL risk assessment tool was a core element of this PhD project, the main purpose of this literature review was to explore use of mobile phone apps for clinical decision support or risk assessment, and to identify papers that could provide insights that could be used to inform further development of the QUIPP app. An initial scoping exercise undertaken for this thesis identified only one paper reporting any sort of evaluation of a mobile app for decision support specifically related to preterm birth (Watson *et al.,* 2017b). This paper, in fact, relates to the first version QUIPP app developed by our research team, as outlined in section 1.8, and it reports results of a study using retrospectively collected data on 355 women with symptoms of threatened preterm labour to evaluate the predictive accuracy of the app. Watson *et al*., (2017b) modelled the effect of a "treat all" strategy for 188 women presenting in TPTL under 30 weeks' gestation, as per the contemporary NICE Preterm guideline (NICE, 2015). The findings of this exercise suggested that 89% (n=169) of hospital

admissions could have been safely avoided if a threshold of 5% risk of delivery within the next seven days had been used to guide clinical practice. However, whilst the paper reports an evaluation of reliability of the statistical algorithms used in the risk prediction calculations, no other aspects of the QUIPP app, such as usability or acceptability by clinicians or women are reported.

In view of the paucity of relevant literature relating to preterm birth, the scope of the review was expanded to include evaluations of any mobile phone applications used by clinicians for decision support or risk assessment in any area of pregnancy care. Specific objectives were to:

1. Determine the current landscape of mobile phone apps use for decision support or risk assessment by clinicians in pregnancy care.
2. Identify perceived benefits and potential hazards of use in clinical practice.
3. Identify facilitators and barriers to implementation of these apps into clinical practice.

2.2. Search Strategy

Inclusion and exclusion criteria for the review were decided upon prior to initiating a database search and are listed in Table 1.

Table 1. Inclusion and exclusion criteria for the literature review "Mobile apps for clinical decision support in pregnancy".

Inclusion	**Exclusion**
Mobile phone applications (apps) for decision support or risk assessment in pregnancy	Decision aids not utilizing mobile app technology, e.g. clinical guidelines/models/decision trees Apps for data collection or delivery of information/health promotion Statistical prediction models
Primary research or report of app development and evaluation published in peer reviewed journals	Literature review Study protocols Commentaries or editorials
App for use by clinicians or both clinicians and pregnant women	App for use by pregnant women only

The research databases used in the search included: Medline, Embase, PsychoInfo and the Cochrane Database of Systematic Review, with search terms and limits used for each database listed in Table 2. Reference lists and citing articles were also reviewed for other potentially relevant papers. In addition to these research databases, the online journals JMIR MHealth and UHealth, which have a specific focus on digital health, were also searched for papers reporting on pregnancy, labour or birth.

Table 2. Search terms and limits for the literature review "Mobile apps for clinical decision support in pregnancy".

	Search term		**Search term**	**Limit**
Medline (n=598)	Pregnancy OR Exp Labour, Obstetric OR Labour OR Premature Birth OR Obstetric Labor, Premature OR preterm.mp	AND	mHealth.mp OR mobile application.mp OR Exp Mobile Applications OR smart phone.mp OR Exp Smartphone OR Decision aid$.mp OR Risk assessment tool$.mp OR Predictive model.mp OR App.mp	Papers published since 2007 (when the iPhone and first mobile apps were available); Humans
Embase (n=187)	Pregnancy OR Exp Labour, Obstetric OR Labour OR Premature Birth OR Obstetric Labor, Premature OR preterm.mp	AND	mHealth.mp OR mobile application.mp OR Exp Mobile Applications OR smart phone.mp OR Exp Smartphone OR Decision aid$.mp OR Risk assessment tool$.mp OR Predictive model.mp OR App.mp	Papers published since 2007 (when the iPhone and first mobile apps were available); Humans; Full text (as large number, n=479, of abstract only references were returned)
PsychInfo (n=61)	Pregnancy OR Exp Labour, Obstetric OR Labour OR Premature Birth OR Obstetric Labor, Premature OR preterm.mp	AND	mHealth.mp OR mobile application.mp OR Exp Mobile Applications OR smart phone.mp OR Exp Smartphone OR Decision aid$.mp OR Risk assessment tool$.mp OR Predictive model.mp OR App.mp	Papers published since 2007 (when the iPhone and first mobile apps were available); Humans
Cochrane Database of Systematic Reviews (n=46)	Pregnancy: tl,ab,kw (including word variations)	AND	mHealth OR decision aid OR risk assessment tool OR smart phone OR mobile phone	No limits
JMIR MHealth and UHealth (n=43)	Pregnancy OR Labour OR Labor OR Birth	AND	Risk OR Decision	No limits

2.3. Results of search strategy

After removal of duplicates, the database and JMIR journals search produced a total of 909 articles for screening. Review of the titles and abstracts identified 774 of these to be ineligible based on the inclusion criteria, leaving 135 papers for full text review. Of these, only 13 were eligible for inclusion, with 122 being excluded for the reasons shown in the PRISMA flow diagram (Figure 8).

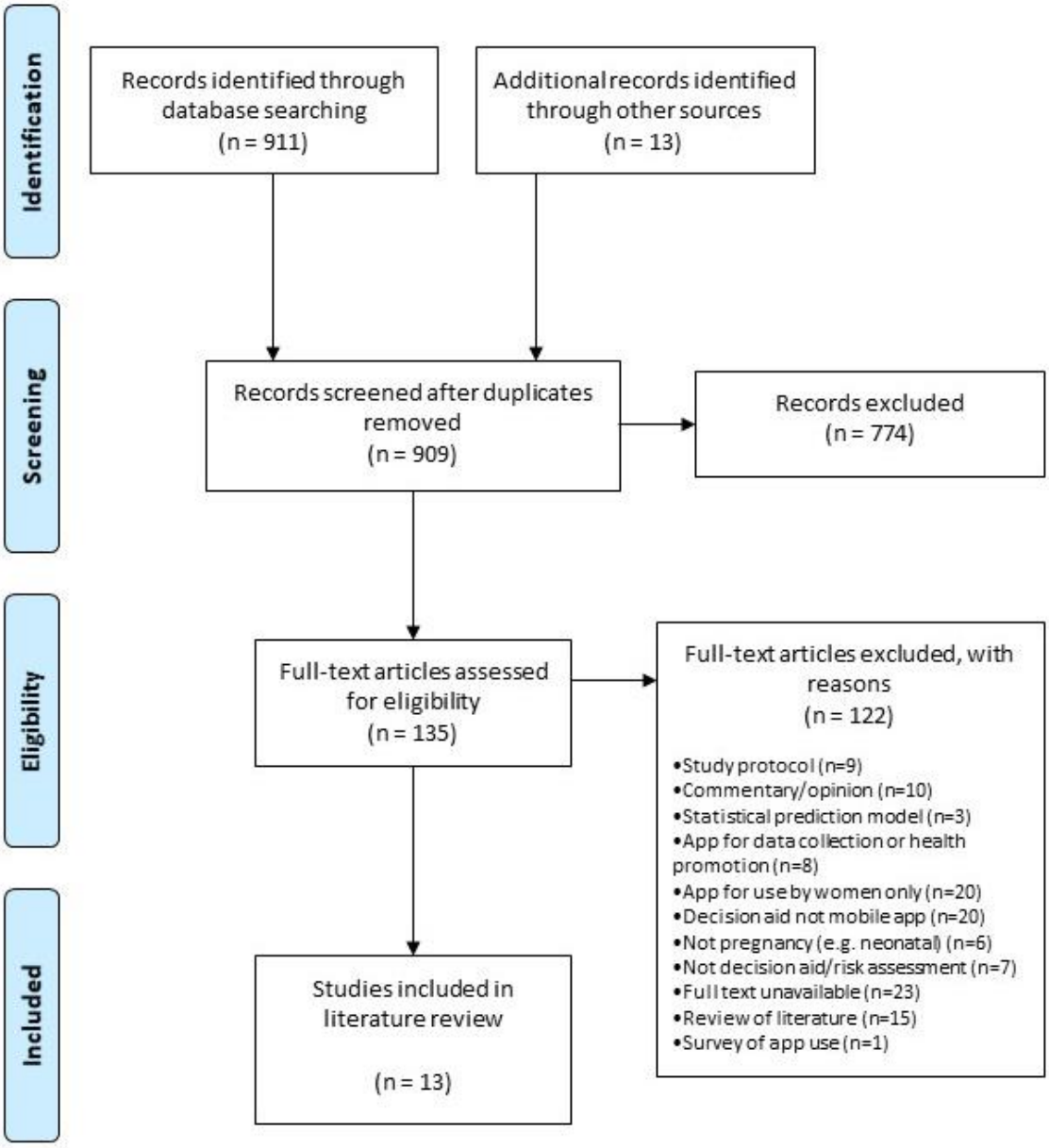


Figure 8. PRISMA 2009 Flow Diagram of results of literature search for "Mobile apps for clinical decision support in pregnancy".

2.4. Characteristics of the papers included in the review

Details of the 13 included papers are shown in Table 3. A formal review of quality was not undertaken because this was not a rigorous attempt at establishing the efficacy of an intervention. Instead, the aim was a broad exploration of the use of mobile apps, with the added objective of gaining helpful insights into the development process gleaned from reports published by their developers. Of the included papers, the majority (n=10) described early development of the mobile application with results of feasibility, usability studies and/or satisfaction studies (Dunsmuir *et al.,* 2014; Jeon *et al.,* 2016; Jonas *et al.,* 2016; Lim *et al.,* 2015; Mackillop *et al.,* 2014; Marko *et al.,* 2016; Peleg *et al.,* 2017; Stroux *et al.,* 2016; Tsai *et al.,* 2014; von Dadelszen *et al.,* 2015). Two reported results of studies evaluating maternity care projects in which the app was a central component of care delivery (Battle *et al.,* 2015; Vélez *et al.,* 2014) and one (Watson *et al.,* 2017b) reported a study testing the reliability of the risk prediction scores created by the QUIPP app, as noted above.

Seven papers reported on studies or projects based in low and middle income countries, including Africa and Guatemala (Battle *et al.,* 2015; Dunsmuir *et al.,* 2014; Lim *et al.,* 2015; Stroux *et al.,* 2016; Tsai *et al.,* 2014; Vélez *et al.,* 2014; von Dadelszen *et al.,* 2015). Two were based in the UK (Mackillop *et al.,* 2014; Watson *et al.,* 2017b), one in Spain and Italy (Peleg *et al.,* 2017) and one in USA (Marko *et al.,* 2016). In two papers the location of the project was unclear, however one of the corresponding authors was based in Korea (Jeon *et al.,* 2016) and the other in Germany (Jonas *et al.,* 2016). All were published between 2014 and 2017: four in 2014; three in 2015; four in 2016 and two in 2017.

Four papers reported on apps focusing on preeclampsia (Dunsmuir *et al.,* 2014; Jonas *et al.,* 2016; Lim *et al.,* 2015; von Dadelszen *et al.,* 2015). Three of these, however, all referred to the same project, Pre-eclampsia Integrated Estimate of Risk (PIERS) (Dunsmuir *et al.,* 2014; Lim *et al.,* 2015; von Dadelszen *et al.,* 2015). Gestational diabetes was the focus for two papers (Mackillop *et al.,* 2014; Peleg *et al.,* 2017). The aims of the maternity care projects were to increase the number of births in a health facility in Zanzibar (Battle *et al.,* 2015) and to improve access to maternity care for women in Ghana (Vélez *et al.,* 2014). The pregnancy focus of each of the remaining five papers were: metabolic syndrome (Jeon *et al.,* 2016); weight and blood pressure monitoring (Marko *et al.,* 2016); identification of fetal compromise (Stroux *et al.,* 2016); antenatal depression (Tsai *et al.,* 2014) and preterm birth (Watson *et al.,* 2017b).

Table 3. Characteristics of papers included in literature review "Mobile apps for clinical decision support in pregnancy".

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
1. Battle *et al.,* (2015)	Mixed methods evaluation of program using app. Report of findings from a mixed methods study qualitative and quantitative data evaluation the "mHealth for Safer Deliveries" program - an integrated mobile health intervention on maternal care utilization. The program was designed to address each of the "three delays" to receiving skilled care at delivery: (1) the decision to seek care; (2) reaching skilled care; and (3) the provision of adequate care once at the health facility.	Zanzibar, Africa January 2013 to December 2014. Qualitative interviews were conducted during September-October 2014 in all districts using semi-structured interviews (women, n=27; CHWs, n=25; health facility workers, n=12) Quantitative data were collected as part of the intervention between January 2013 and December 2014 (n=13,231).	Encourage facility birth	YES	YES	YES		"The program supported community health workers (CHWs) who were trained to use a phone with a user-friendly decision-support application. This enabled the CHWs to: 1. Counsel the mother and family on healthy behaviours and recognizing danger signs. 2. Record permissions from husband and family members agreeing to a facility-based delivery. 3. Screen women (and their babies) for complications from pregnancy up to a week after delivery and refer them as needed to the health facility. 4. Use mobile banking to pay for transportation to the health facility when the woman is referred, paying for transport without ever touching cash. 5. Use text or voice communication to notify a health facility that a woman is in transit."	"The qualitative interviews identified perceptions of the program, including both reasons for success and barriers to facility delivery. One of the themes that emerged from many of the CHW participants was the positive effect of the phone in increasing their confidence in referring women to the health facility. CHWs felt a greater sense of self-efficacy due to a broadening of their knowledge. CHWs and mothers cited the portability of the phone (with client record) and the ability to send and receive calls and SMS messages critical for their communication with clients, health facilities, and drivers at all times of the day. For mothers, the ability to easily reach their designated CHW also created a sense of security and trust between them. Overall the sense of feeling safe, supported, and secure was a strong theme and a primary reason for women getting to the facilities. The ease of arranging and paying for transport in case of a complication or for labour was cited as critical in all three informant groups. Transport was cited by most health worker informants from delivery facilities as a reason for the increase in facility delivery. The actual decision to seek care was often attributed to CHWs' counselling messages and the general support they provided during the mother's pregnancy, delivery, and the postnatal period, even over the availability of free transport. Many health workers stated that a CHW present at the point of referral was a positive impact on the health worker preparedness. Health workers from delivery centres almost universally attributed the increase in deliveries at their facilities to the program. Some women reported concerns about facility care and costs. Of the 13,231 women who delivered in the program, 75% did so at a facility and 78% under skilled care compared to a baseline of 35%. The majority of CHWs discussed the positive relationships that emerged between themselves and the facility worker due to their frequent communication. Some mothers also mentioned the cost associated facility deliveries being a deterrent to themselves or their husbands/families, despite national policy declaring services to be free."

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
2. Dunsmuir *et al.,* (2014)	Describes development of app and results of usability study. This paper describes the development process, including challenges and solutions, of the PIERS on the Move (POTM) is a low cost, easy-to-use, mobile health (mHealth) application for accurately predicting the risk of adverse outcomes associated with pre-eclampsia in pregnant women.	Cape Town, South Africa. November 2011 to January 2013 At the time of publication, 202 women had been assessed with the POTM application. A total of 37 nurses and midwives evaluated the user interface through three usability studies	Pre-eclampsia	YES	YES			"The clinical data collected in women with pre-eclampsia are used as the inputs to a predictive model providing a risk score for the development of adverse outcomes. App calculates a risk score using clinical findings (including measurements by pulse oximeter connected to a smartphone). Based on the risk score, the application provides recommendations on treatment, referral, and reassessment."	"Smartphones are rapidly becoming available in many low resource settings and their small size and weight facilitate their use during home visits. The developed Phone Oximeter applications can run on existing smartphones, already owned or used by health care providers. Smartphones can also serve as communication devices to facilitate escalation of care. GPS functionality can also be used to track data collection locations. Mobile devices can be used to perform data validation and inform the user of any errors. The application selectively requires the performance of additional investigations. E.g. if the woman is hypertensive, the application will suggest the need for a dipstick proteinuria measurement and ask about the symptoms the woman is experiencing. Multiple language support was required. Translations in the necessary languages are stored. The first usability study revealed that entering patient contact details was the most time-consuming task due to user inexperience with a small onscreen keypad. The keypad size was expanded for the next usability study. Many potential users had not had prior experience with smartphones. To address this problem, the amount of information on one screen was kept to a minimum and if scrolling is necessary, the application auto-advances the scrolling as the user enters data. The interface now avoids the use of dropdown lists, and instead shows all options simultaneously with checkboxes or radio buttons. Security is a challenge when data are collected on mobile devices during home visits. Therefore, the data stored are encrypted. Additionally, to deter the theft of devices, all devices are marked as being used for medical research purposes. The app uses GPS-based location information and includes an audit trail of each user's modifications to the data on the device. The task of user control is delegated to local data managers. Datasets are stored on Research Electronic Data Capture (REDCap) and synchronised with mobile devices of the care team. Cultural differences were identified and led to modified application versions for each country. In addition to different pictograms and languages, some of the data fields and recommendations for treatment were specific to users and locations. Achieving the acceptance of the mobile application by investigators in the countries involved in the trial has been an ongoing process. The effort involves introducing new processes and new technology to users with very little relevant technology experience. The users required significant amounts of training, but they also provided valuable feedback that led to new ideas on how to simplify the information presented in the application. Above all, the application must be developed with input from users. This is necessary to design a flexible application that considers the users training and limitations and anticipates possible scenarios that will be encountered."

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
3. Jeon *et al.,* (2016)	Describes development of app and results of evaluation study. Paper reporting the development and evaluation of four mobile applications that provide tailored nursing recommendations for metabolic syndrome management in pregnancy. Evaluation included the algorithm proficiency and efficiency, user interface, usability, and effectiveness. Usability evaluated using different tools for each condition.	Unclear setting (corresponding author based in Korea). Paper reports "evaluations by experts and users." But does not specify any detail or numbers involved.	Metabolic syndrome in pregnancy, incl. obesity, diabetes, hyper-tension, and hyperlipida emia.	YES				"Mobile applications provide tailored nursing recommendations for metabolic syndrome management, e.g. "when a patient intakes more calories than needed, the alert function can alert the patient by sending a message based on the daily calorie intake that the diary function has helped the patient to track."p.512" No further detail or examples reported.	"Proficiency of the algorithms ranged from 88.2 to 100.0 and their efficiency ranged from 69.0 to 100.0. The obesity app had the lowest proficiency and efficiency. For the GDM and hypertension apps, all recommendations made by the evaluators concurred with recommendations derived from the apps. In the heuristics evaluations, 13 and 10 problems were flagged for the obesity and hypertension apps, respectively. All of these heuristics problems were resolved before the apps were used. Usability scored 3.5 out of 5 for the obesity app and 3.5 out of 5 for the GDM app. User satisfaction scored 3.6 out of 5 for the hypertension app. The hypertension app increased medication adherence from 4.2 to 5.2 out of 6 (p=0.001) for the hypertensive patients." Paper reports only results of usability scores but no detail on specific areas for improvement.
4. Jonas *et al.,* (2016)	Describes development of app and results of evaluation study. Paper describes the development and evaluation of a smartphone-based imaging and automated analytical tool which incorporates the Congo Red Dot (CRD) test. This test assesses the presence of misfolded proteins in urine, and shows promise as a diagnostic and prognostic tool for preeclampsia. Stage 1: evaluation of a preliminary version of image processing software tool using stored images. Stage 2: testing improvements in real-time on newly prepared standardized CRD arrays and analysed the results for agreement. Stage 3: Analysis of test results across four operators, including untrained personnel (n=1) who did not receive any instruction or prior knowledge of the system.	Setting and time period not explicit. Corresponding author based in Germany. No patient participants.	Pre-eclampsia	YES			YES	"Smartphone application guides the user through seven easy steps, and that can be used successfully by non-specialized personnel, through test image acquisition to interpretation of result. This approach provides an inexpensive molecular test and automated smart phone based readout that can be performed as a batched laboratory test by modestly trained personnel in almost any environment, from an urban medical centre to a lightly staffed field clinic."	"Eliminates the need for a separate handheld imaging device or other hardware. Smartphone-based diagnostic tool that is independent of communication data rate, quality of service, and data transfer security. An objective element to the clinical work-up for preeclampsia which especially in low resource settings relies heavily on subjective interpretation of signs and symptoms by healthcare providers. Due to its simplicity and the low cost of required materials, the CRD test has the potential to fill this gap for diagnosing preeclampsia in resource-poor settings."

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
5. Lim *et al.,* (2015)	Describes development of app and results of 2 usability and feasibility studies. Paper reports findings of study assessing the usability and feasibility of PIERS on the Move, an mHealth App for pre-eclampsia triage, with mid-level health workers, for iteratively refining the system. Two usability studies were performed with the potential end-users. Each step in the development process used the findings of the previous, thus iteratively improving on the design and features available in the app:	Usability study 1: evaluation by advanced midwifery students at Tygerberg Hospital (Cape Town, South Africa), (n=15). Usability study 2: evaluation of the next iteration by maternal nursing staff at Frere Maternity Hospital (East London, South Africa), (n=22). Nov 2012 to Dec 2013.	Pre-eclampsia	YES	YES		YES	"Pre-eclampsia Integrated Estimate of RiSk (PIERS) on the Move (PotM) is a low cost, easy-to-use, mobile health (mHealth) platform that has been created to aid health workers in making decisions around the management of hypertensive pregnant women. The app combines two previously successful innovations into a mHealth app: the miniPIERS risk assessment model and the Phone Oximeter."	"Study 1: major issues in the functionality of the touch-screen keyboard and date scroll wheels were identified (total errors n=212). Study 2: major improvements in navigation of the app were suggested (total errors n=144). Overall, users felt the app was usable using the Computer Systems Usability Questionnaire; median (range) values for Study 1 = 2 (1-6) and Study 2 = 1 (1-7). Usability problems were often related to mobile phone features (e.g., scroll wheels, touch screen use). To demonstrate feasibility, PotM was used by one research nurse for the pilot clinical study. In total, more than 500 evaluations were performed on more than 200 patients. The median (interquartile range) time to complete an evaluation was 4 min 55 sec (3 min 25 sec to 6 min 56 sec)." Authors emphasise the importance of using target end-users in the design and evaluation and that is will result in easier integration into health care settings.
6. Mackillop *et al.,* (2014)	Describes development of app and results of evaluation study. Paper describes development of a prototype software application for the management of women with or at high risk of Gestational Diabetes. A custom website was built for clinician review of the data transmitted by the smartphone. After system refinement, further evaluation was undertaken for usability and reliability in a 48-patient service development project.	UK Seven women participated in the beta testing phase and 50 of the 104 women approached volunteered to test the system in the service development phase.	Gestational Diabetes	YES	YES	YES	YES	"Functional objectives included the ability to: 1. Allow women to accurately and easily record blood glucose measurements, which are then automatically uploaded to a website. 2. Allow health care professionals to access these measurements remotely and respond quickly to them, thus potentially improving glycaemic control without the need for more intensive face-to-face contact. 3. Allow 2-way communication between women and health care professionals. 4. Promote user participation (empowerment) of pregnant women in their medical management."	"The interactivity of the application has been extended with patients being able to add a comment to each reading-often using this to explain a high reading or to record what they have just eaten. To remind patients to perform a BG reading after their meal, an optional alert was implemented. The displays were changed to show BG readings in both graphical and tabular formats. To make the application more intuitive to navigate, illustrations have been added to on-screen buttons to illustrate key functions. User instructions are embedded in the application in the form of videos that automatically run to illustrate specific actions. Members of the clinical team were given the facility to add a note on the website, for example, to record a medication change or dietary advice intervention, when the management of patients is shared between several members of the clinical team. Alerts were added to help prioritize and highlight patients who required an intervention. A "strip" counter was added to help the midwife know when more blood glucose measurement strips needed to be sent to a patient. Patients are also able to place a request for strips from the midwife using either the free-text comment or phone-request functionalities. Findings demonstrate high usage and excellent compliance with the system, with 85% of women recording the minimum required number of BG readings each week."

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
7. Marko *et al.,* (2016)	Prospective observational study assessing feasibility, efficacy and satisfaction. Paper reports findings of a prospective observational pilot study to determine the feasibility of monitoring patients remotely in prenatal care using a mobile phone app and connected digital devices. As measures of the feasibility of the system, participants were studied for engagement with the app, accuracy of remote data, efficacy of alert system, and patient satisfaction. Patient satisfaction was measured using a 12-question survey that was completed by participants after 20 weeks of platform usage.	Department of Obstetrics & Gynecology at the George Washington University Hospital, USA. July 2014 to January 2015. n=8 women with low risk pregnancy in the first trimester.	Weight and blood pressure monitoring in pregnancy	YES	YES	YES	YES	Mobile phone app with a connected digital weight scale and blood pressure cuff for at-home data collection for the duration of pregnancy. At-home data was assessed for abnormal values of blood pressure or weight to generate clinical alerts to the patient and provider.	"Patient engagement with the mobile app averaged 5.5 times per week over the 6-month study period. Weight data collection and blood pressure data collection averaged 1.5 times and 1.1 times per week, respectively. At-home measurements of weight and blood pressure were highly accurate compared to in-office measurements. Automatic clinical alerts identified two episodes of abnormal weight gain with no false triggers. After reviewing data sets of all clinical variables and all organized alerts, no incidences of inappropriate alerts or unaddressed alerts were discovered. All 6 participants who completed the survey felt comfortable with the concept and technical aspects of remote monitoring, were able to easily access provider resources. Most (83%, 5/6) of the participants felt that the app assisted with healthy pregnancy-related behaviours, were satisfied with prenatal care, felt more connected with their provider, and felt more knowledgeable about their pregnancy. Patients demonstrated high satisfaction with the system. The described monitoring system has the ability to collect data more frequently than office visits alone, allowing for the potential to develop predictive models to screen normal pregnancies and identify pregnancy risk earlier. "

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
8. Peleg *et al.,* (2017)	Mixed methods study of compliance, satisfaction and quality of life. The MobiGuide project aimed to establish a user-friendly, patient-centred mobile decision-support system for patients and for their care providers, based on the continuous application of clinical guidelines and on semantically integrated electronic health records. The objective of this paper was to evaluate whether the initial deployment of the MobiGuide system, for two different clinical domains - atrial fibrillation (AF) and gestational diabetes (GDM) - had achieved three main outcomes: (a) high patients' and care providers' compliance to clinical-guideline based monitoring reminders and recommendations, (b) high patients and care providers' satisfaction, and (c) increased patients' quality of life.	Italy and Spain April to December 2015. The study involved ten AF patients from IRCCS Foundation "Sal-vatore Maugeri", Pavia, Italy and twenty gestational GDM patients from Parc Tauli Sabadell University Hospital, Sabadell, Spain. As a control group for GDM, researchers referred to data from a historical group of 247 patients, similar in characteristics, who had been followed up during 2010-2013 at the same GDM clinic.	Gestational diabetes	YES	YES	YES	YES	"MobiGuide is a remote chronic-patient management system that has five main objectives: (1) Increasing patient safety and quality of care through provision of personalized ubiquitous decision-support to the patients. (2) Semantic data integration into a personal health records. (3) Creation of a generic architecture that supports interoperation with a variety of portable sensors, and different hospital electronic health records. (4) Distribution of the decision support system (DSS), between a mobile DSS that runs on the patient's smart phone and a backend DSS that is accessible via the Internet by the patients' care providers. (5) Performance of intelligent data analysis, to discover clinical data patterns in individual patients, thus providing additional decision-support." In the GDM domain, blood glucose monitor and sphygmomanometer were connected to the patient's smart phone by Bluetooth.	"Continuous monitoring of the most important health parameters (glycaemia, ketonuria and BP for GDM patients) was performed at encouragingly high compliance rates by GDM patients. The compliance of the MobiGuide cohort was significantly higher than that of the historical cohort (1.01 vs. 0.87, with p-value of 0.0312). The fact that the measurement data were available to the physicians via the system without needing to rely on the patients bringing in their monitoring devices and paper diaries had a great benefit. Since the clinicians knew the real data values, they felt that the decisions were made faster and were better; as they could review the results before the visits, the time spent reviewing the data was shorter. They stated that they liked very much the system's ability to adapt to context. All AF and GDM clinicians agreed (i.e., provided ratings of 4 or 5) that MobiGuide helps them in identifying priorities and increases patient safety via its data quality awareness (which prompts patients to re-enter data, repeat measurements, thus improving the recommendations delivered by the system that depend on data quality). Overall, the sense of safety that the system has provided to the patients was its greatest asset."

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
9. Stroux *et al.*, (2016)	Mixed methods study of feasibility and acceptability. Paper describes findings of a mixed methods feasibility study to evaluate a smart phone based system designed to identify fetal compromise. The feasibility assessment was designed to evaluate whether frontline healthcare workers could operate the study equipment (1D foetal Doppler, pulse oximeter and recording application) and record signals successfully using a smart phone. The study also set out to gauge user need and to assess the acceptability by both healthcare provider and patient.	Guatemala n=22 pregnant women. Written feedback was provided by 6 members of staff.	Fetal com-promise	YES	YES	YES	YES	"A smartphone-based system including peripheral sensors, pulse oximeter and handheld Doppler for the identification of foetal compromise. Designed for use by illiterate birth attendants, the system uses pictograms, audio guidance, local and cloud processing, SMS alerts and voice calling."	"The six staff who provided written feedback found all system components easy to operate and independently agreed on the potential benefit of such system. Three key areas for successful foetal cardiac signal recording have emerged, the ability to operate the equipment provided, the clinical knowledge to identify and to target the best possible signal, and the degree of willingness to employ such technology. The technology-related difficulties experienced by the participants were largely related to the participants' educational level (including a very high illiteracy rate amongst traditional birth attendants) and experience in handling similar equipment. Several of the observed challenges could to some extent be attributed to a lack of appropriate training and guidance material. Several areas for improvement were identified during the feasibility testing. The familiarity with the technology and the clinical understanding of the physiological signals and their characteristics, the system's usability and ultimately signal quality, could all be improved by a combination of educational measures such as training and training manuals, an appropriate application interface and built-in guidance on the phone with real time quality feedback. The implementation of signal analysis capabilities, such as the discrimination of maternal from foetal cardiac signal by comparing the pulse oximeter to the ultrasound measure, would provide real-time quality improvement and reduce false readings. To be maximally inclusive the application interface was therefore adapted using a combination of audio and visual instructions only, replacing any written content. Likewise, the mechanism to record patient information manually was changed to voice and image capture, eliminating the need for written input. As a result, each screen presents an illustration serving as a visual clue to prompt a certain action. The findings of this study have informed for the next stage of development: 1. Mobile application ~ Continuum of care: Extension of the application from prenatal assessment only, to the inclusion of intrapartum and postnatal health checks: a) Comprehensive health checks: Inclusion of maternal blood pressure measurements and checks for pregnancy-related complications into the application work flow; b) User interface (UI): The design of a user-centred mobile application interface, to be inclusive of an illiterate user group; c) Signal analysis: Implementation of heart rate analysis including discrimination between the maternal and foetal rhythm; d) Emergency response: Implementation of logic to trigger calls to higher level care staff in case of detected emergencies. 2. Integration into medical records ~ Data consolidation: Automated upload of recorded signals, patient and health information to the medical record system, openMRS, a globally adopted open source electronic medical record (EMR) system. 3. User training and education ~ User manuals: The development of on-phone user manuals, inclusive of an illiterate user group. User training: The development of training sessions, which will teach participants in the application of all devices and the appropriate clinical knowledge to enable the recording of good quality physiological signals and the assessment of complications."

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
10. Tsai *et al.,* (2014)	Paper describes findings of a feasibility study aimed at determining the extent to which community health workers could be trained to conduct case finding using short and ultrashort screening instruments programmed into mobile phones. Pregnant women were recruited independently in two cross-sectional studies and assessed for antenatal depression.	Khayelitsha, South Africa, May 2009 to September 2010 (n=1,144) May 2010 to February 2011 (n=361)	Antenatal depression	YES	YES			"In both studies, the Xhosa version of the EPDS-10 was administered using survey software programmed into a mobile phone."	"The estimated operating characteristics based on data collected by community health workers using mobile phones during routine antenatal wellness care were comparable to those based on data collected by trained research assistants. Irrespective of whether the data were collected by research assistants or by community health workers, the socio-demographic profiles and estimates of reliability and validity were qualitatively similar across the two studies. The findings demonstrated the feasibility of using community health workers, who had no previous research training, to conduct case finding for antenatal depression using short and ultrashort screening instruments programmed into mobile phones. The findings have important programmatic implications for mHealth interventions and leveraging existing human resources to improve maternal mental health and child health in resource-limited settings."
11. Vélez *et al.,* (2014)	Mixed methods study evaluating a program using app. The Millennium Villages Project (MVP) was an integrated rural development program to achieve the Millennium Development Goals (MDGs) in low-income rural Africa by 2015. The Millennium Village Health System (MVHS) is a major component of the project, whose core strategy is to ensure universal access to services free of charge at the point of care, with a continuum of services from the household to the clinic and the referral hospital. This paper describes a descriptive usability study composed of 3 phases to evaluate an mClinic prototype: 1) hybrid lab-live software evaluation of mClinic to identify usability issues; 2) completion of a usability questionnaire; and 3) interviews that included low-fidelity prototyping of new functionality proposed by midwives.	Bonsaaso, Ghana, May 2011 All midwives working in the cluster of MVP (n=7)	Access to maternity care	YES	YES	YES		"A mobile health (mHealth) application, known as mClinic, captures data for managing patient care, program evaluation and monitoring, decision making, and management, and allows midwives to access the MVG-Net."	"Good ergonomics and minimalist design applied primarily to the QWERTY (keyboard) phone selected for testing. The keyboard was small and the midwives had difficulty pressing one button at a time, reading the keyboard, and using the function key to select numbers. There was greater success with the touch-screen phone. In respect of privacy, and social conventions, interviews revealed the necessity of application-level password protection because it is common for cellular phones to be shared among staff and family members, and therefore phone level locking would be inadequate. Midwives strongly agreed that mClinic was useful and were in agreement to neutral about ease of use and user control. In the interviews, some midwives indicated that they believed that mClinic will be helpful to them and reduce the time they spend creating monthly reports. After being shown the low-fidelity prototypes, several midwives expressed concern that the prototype maternal health form set would be too time intensive and cumbersome to use. All the midwives were dismissive of designs that included extensive free-text fields. More positive interest was generated for expanding the register-type forms and expanding them to capture monthly reporting data. Other potential benefits include lower start up and maintenance costs and improved accuracy and timeliness of data collection. As is consistent with the literature, the midwives preferred when the screen contained less data and did not require scrolling. A key factor to the success of eHealth implementation in developing countries is user acceptance. Methods for increasing user acceptance include providing adequate support and training for learning the new system, encouraging local ownership and data use, cultivating local leadership and project champions, and being sensitive to local culture. Additional studies have shown that alignment of the eHealth intervention with user needs and provider technical self-efficacy is also a significant factor in technology acceptance."

	Description of paper and study design	Setting, Time period & participants	Area of focus in pregnancy	App functions				App characteristics	Main Findings
				Decision support	Data Collection	Communi cation	Connect-ed Device		
12. von Dadelszen *et al.,* (2015)	Paper describing observations noted during development of app. This paper describes observations noted during development of the PIERS (Pre-eclampsia Integrated Estimate of RiSk) models that identify pregnant women with pre-eclampsia who are most likely to develop life-threatening complications, and suggests recommendations for development of mHealth in perinatal care. The authors had developed and validated two outcome prediction models, the PIERS (full and mini). Both models have accurate ability to identify women at low risk of developing imminent complications.	For use in low and middle income countries. 2011	Pre-eclampsia and other potentially life threatening conditions	YES	YES	YES	YES	"The PIERS on the Move (POM) smart phone app integrates miniPIERS and clinical decision algorithms to support community health care professionals (cHCPs) as they provide prenatal care, diagnose pre-eclampsia, and initiate lifesaving therapies in the woman's home prior to urgent transfer to an effective facility. The researchers have also developed a modified blood pressure device (Microlife 3AS1-2; Microlife, Widnau, Switzerland) specifically for use in low- and middle-income countries (LMICs), which fulfils WHO requirements for suitability for use in low-resource settings. A traffic light early warning system has been incorporated into the device, to alert users to abnormalities in blood pressure and pulse, using these developed shock index thresholds along with well-recognized thresholds to indicate hypertension in pregnancy."	"The full PIERS model, which includes demographics, symptoms, pulse oximetry, and maternal laboratory tests identifies clinical relevant risk categories (area under the curve of the receiver – operator characteristic [AUC ROC] 0 · 88 [95% CI, 0 · 84 – 0·92]. Currently, fullPIERS is undergoing external validation; a preliminary validation exercise is reassuring. The validated miniPIERS model is solely demographics-, symptom-and sign-based and can be administered by (1) cHCPs in the home and at primary health centres; and (2) facility-based practitioners as they initially triage women admitted with pregnancy hypertension prior to the availability of laboratory results (or in lieu of laboratory results in some less-developed settings) (AUC ROC 0.77 [95% CI, 0.74 – 0.80]). POM project results suggest that by adding pulse oximetry, using the same 25% risk threshold, the prediction rate is improved to 85% of women who will go on to suffer a severe complication. Engagement with decision makers and thought leaders from the initial design phase of an intervention will improve ownership and the likelihood of implementation at scale. In order to be attractive to those funding health care, strategies for mHealth-supported individualized care must be integrated into existing and evolving health systems, and health economic analyses should be carried out that clearly show to those who make often difficult decisions what the return will be on the resources invested."
13. Watson *et al.,* (2017b)	Study assessing the reliability of risk prediction scores incorporating in the app. Comparison of the QUIPP predicted risk within 7 days to the actual delivery rates using data on a cohort of women who presented in threatened preterm labour between 2010 and 2015. Also to investigate the impact of using the QUIPP app relative to a treat-all strategy at 24-29+6 weeks (as per NICE Preterm Labour guideline 2015).	UK Analyses carried out 2016 (n=355)	Preterm birth	YES				Risk of preterm delivery in symptomatic women calculated using risk factors and test results.	"Findings suggest the QUIPP app can safely and accurately inform clinician decision-making for women in threatened preterm labour, allowing outpatient management for the vast majority. The QUIPP app therefore confers considerable advantage over NICE's recommended treat-all strategy, which allows no women to be managed as outpatients."

2.5. Themes emergent from review of the included papers

A number of themes emerged from the review, which were: i) acceptability and satisfaction; ii) ease of use and portability; iii) multiple functionality and iv) the importance of user involvement in development and evaluation. These are discussed in detail below.

2.5.1. Acceptability and Satisfaction

All papers reporting on acceptability, feasibility, usability and/or satisfaction were generally positive, both with the mobile application being evaluated, and also with the care it was designed to support. This was demonstrated by direct questioning and evaluation tools, but also by increased patient engagement with, for example, compliance with self-monitoring (Jeon *et al.,* 2016; Mackillop *et al.,* 2014; Peleg *et al.,* 2017). Increased confidence of health providers, enhanced positive relationships and trust in the professionals and feelings of support and safety were also reported (Battle *et al.,* 2015; Jeon *et al.,* 2016; Mackillop *et al.,* 2014; Marko *et al.,* 2016). Validation of data and monitoring readings were often a feature of the application, and this was recognised by clinicians as a valuable improvement in care (Dunsmuir *et al.,* 2014; Stroux *et al.,* 2016). Additionally, the app could help clinicians identify priorities and they recognized the potential for the system to be time saving. The automatic transfer of data to electronic central databases or health records was also identified as a useful mechanism which could save clinicians' time as they could remotely review the data in advance of the patient's hospital appointment (Peleg *et al.,* 2017; Vélez *et al.,* 2014). Alerts systems were utilised in some applications to remind patients of, for example,

appointments, medication, and monitoring (Mackillop *et al.,* 2014; Marko *et al.,* 2016), or alert remote clinicians who could either respond with advice, either directly to the patient or their local care givers (Mackillop *et al.,* 2014; Stroux *et al.,* 2016).

2.5.2. Ease of use and portability

Most medical app users were familiar with smart phones, and the benefit of portability was regarded as a great asset (Battle *et al.,* 2015; Marko *et al.,* 2016). Some users reported problems which were often related to the phone's features, e.g. difficulties with entering data on a small mobile phone screen and the need for scrolling (Dunsmuir *et al.,* 2014; Lim *et al.,* 2015). Adaptation of features such as reducing the need for scrolling by having fewer data on each form, training and on-phone manuals were used to address these issues in later stages of app development (Jeon *et al.,* 2016; Stroux *et al.,* 2016).

With the relative low cost of smartphones and convenience in terms of weight and size, along with the increasing connectivity to mobile networks, mobile applications appear to be accepted as an excellent opportunity for improving healthcare, particularly for those in low resource settings. One reason, proposed by a number of authors of the papers included in this review, is that less educated health care staff can be trained in providing front-line care using devices that are easy to use, with internal validation and warning alerts, with the added benefit of support from remote experts (Stroux *et al.,* 2016; Tsai *et al.,* 2014; von Dadelszen *et al.,* 2015).

2.5.3. Multiple Functionality

The versatility and multi-functionality of smartphones appeared to be an important issue in the papers reviewed. As decision support tools, mobile apps can utilize statistical prediction models or decision trees and make recommendations for action based on input of individual risk factors and test results (Dunsmuir *et al.,* 2014; Peleg *et al.,* 2017; Watson *et al.,* 2017b). In addition to decision support, however, most apps (10/13) were also used for data collection, communication, or both. Other apps also incorporated Bluetooth internet connectivity with other devices: pulse-oximetry (Lim *et al.,* 2015; Stroux *et al.,* 2016); blood glucose monitors (Mackillop *et al.,* 2014; Peleg *et al.,* 2017); blood pressure monitors (Marko *et al.,* 2016; Peleg *et al.,* 2017); digital weighing scales (Marko *et al.,* 2016) and fetal Doppler devices (Stroux *et al.,* 2016). One mobile app utilized the smartphone's own camera for processing pictures used in the Congo Red Dot test, which assesses the presence of misfolded proteins in urine (Jonas *et al.,* 2016). This test has been proposed as a possible diagnostic test for pre-eclampsia that could be particularly useful in low resource settings where more sophisticated laboratory facilities are unavailable.

Communication between patients and healthcare workers, or between healthcare workers and colleagues or other experts, was valued as an important element in the success of the projects in which the apps played a central role (Battle *et al.,* 2015; Dunsmuir *et al.,* 2014; Mackillop *et al.,* 2014). This appeared to be so whether the communication was carried out directly through the app, or simply by the user being able to communicate using the same device, i.e. mobile phone.

Data collection, validation, transfer and integration with other health records and research databases, and the ability to set alerts, as noted above, along with other integrated features of mobile phone technology, such as time stamping and Global Positioning System (GPS) tracking of phone location, were also noted as important and useful attributes because, for example, the time and place of the clinical visit could be recorded (Dunsmuir *et al.,* 2014; Mackillop *et al.,* 2014; Peleg *et al.,* 2017; Stroux *et al.,* 2016; Vélez *et al.,* 2014).

Delivering healthcare interventions through mobile technology also provided the opportunity to adapt programmes relatively easily to account for specific needs of the end-users. Accessibility was enhanced, e.g. picture and video instructions for illiterate users (Stroux *et al.,* 2016). Language and cultural diversity issues were also relatively easily addressed and incorporated into different versions of the app (Dunsmuir *et al.,* 2014; Mackillop *et al.,* 2014; Stroux *et al.,* 2016).

2.5.4. The importance of user involvement in development and evaluation

The importance of user involvement in the development and evaluation of their app was emphasized in several papers (Dunsmuir *et al.,* 2014; Lim *et al.,* 2015; Vélez *et al.,* 2014; von Dadelszen *et al.,* 2015). The authors noted that this was not only a key step in enhancing the acceptability and usability of the device/programme, but also a mechanism by which they could foster engagement by local stakeholders, community leaders and healthcare funders. This interaction was seen as part of the pathway to ensure acceptability of the programme and maximize its chances of being sustained.

2.6. Summary and discussion

This literature review has identified and considered a number of relatively recent papers, mainly reporting early stage development and feasibility or acceptability studies designed to inform further development of the mobile application the paper was concerned with. The number of papers identified was relatively small compared to the number of medical apps readily available for download onto mobile devices. It is likely that many clinicians and other health care professionals are using them on an *ad hoc* basis. However, there are still only very few peer-reviewed publications in high quality professional journals that can confirm their utility, reliability and effect on outcomes. None of the papers reported application for regulatory approval by either the FDA or MHRA.

It is possible that the search strategy employed may have missed some important papers due to the lack of standardised search terms associated with the relatively new field of mobile healthcare. An extensive number of potentially eligible papers required a review of the full text because the nature of the decision support tool or mobile application was not clear from the title or abstract alone. In addition, the speed with which new papers are published makes efforts to undertake a truly comprehensive review of such a fast growing literature base challenging.

A number of themes emerged from the review and are reported above. The issue of data security, however, briefly mentioned in two papers (Dunsmuir *et al.,* 2014; Vélez *et al.,* 2014) did not appear to be particularly important. Where it had been raised as a

concern, password protection at app, rather than phone, level (Vélez *et al.,* 2014) and data encryption (Dunsmuir *et al.,* 2014) appeared to provide acceptable solutions. This may become a more important issue in the future, however, following recent scandals regarding the misuse of personal online data (Cadwalladr and Graham-Harrison, 2018).

This literature review has considered papers reporting on mobile phone applications for clinical decision support in pregnancy. It appears that the body of literature relating to this precise area remains sparse and relatively recent. No papers were found of studies reporting effects on clinical outcomes, although the two papers on programmes to improve healthcare utilization reported success. It is expected, however, that more publications will follow in due course, as the papers reviewed were largely reporting results of feasibility studies of projects that will have entered later phases of development. The findings of this review will be considered and incorporated into the later discussion around the development of the mobile application clinical decision support tool (the QUIPP app) which is the focus of this PhD thesis.

3. Literature review 2: Women's experience of threatened preterm labour

3.1. Introduction to literature review

A major element of this PhD project was to establish a deeper understanding of the experience from the woman's perspective in order to highlight areas for potential improvement in TPTL care. This second literature review aims to explore what is currently known about women's experience of threatened preterm labour and/or being at risk of preterm birth and how the care they received affected that experience.

3.2. Search Strategy

Inclusion and exclusion criteria for the review were devised in order to achieve the aim of the review and are listed in Table 4.

Table 4. Inclusion and exclusion criteria for the literature review "Women's experience of threatened preterm labour".

Inclusion	**Exclusion**
Focus on women's experience of threatened preterm labour, preterm labour and/or being at risk of preterm birth and related tests (i.e. fetal fibronectin and cervical length measurement) and interventions, (i.e. steroids and tocolysis)	Women's experience of other aspects of pregnancy or birth at term and related interventions
Primary research or literature reviews published in peer reviewed journals	Commentaries or editorials
Studies or reviews including studies using qualitative methodologies	Studies or reviews relating only to studies using quantitative methodologies
Full text papers published in English language	

The following electronic data bases were searched; Medline, CINAHL, HMIC, PsycINFO, Embase, Scopus, Maternity and Infant Care for papers published up to October 2017. Terms used included: “Obstetric Labor, premature OR preterm labour”, “preterm” AND “birth”; “MH Labor, premature”, “experience*” OR “views” OR “perceptions” OR “beliefs” OR “attitudes”; “fetal fibronectin” OR “cervical length” OR “cervical length measurement” OR “steroids” OR “tocolys*” AND “experience* OR “views”. Reference lists of papers considered suitable for inclusion were also reviewed. As the focus was on women’s experience the search was restricted to papers reporting studies using qualitative methods, or reviews including studies which had used qualitative methods. There was no geographical restriction on where studies had been carried out or year of publication. Papers where the full text was not available in the English language were excluded.

3.3. Results of search strategy

After removal of duplicates, searching the databases produced a total of 290 articles for screening. After review of the titles and abstracts 264 were deemed to be ineligible for inclusion in the review, Twenty six papers were assessed for eligibility by full text review, of which 11 were subsequently excluded for the reasons shown in the PRISMA flow diagram (Figure 9).

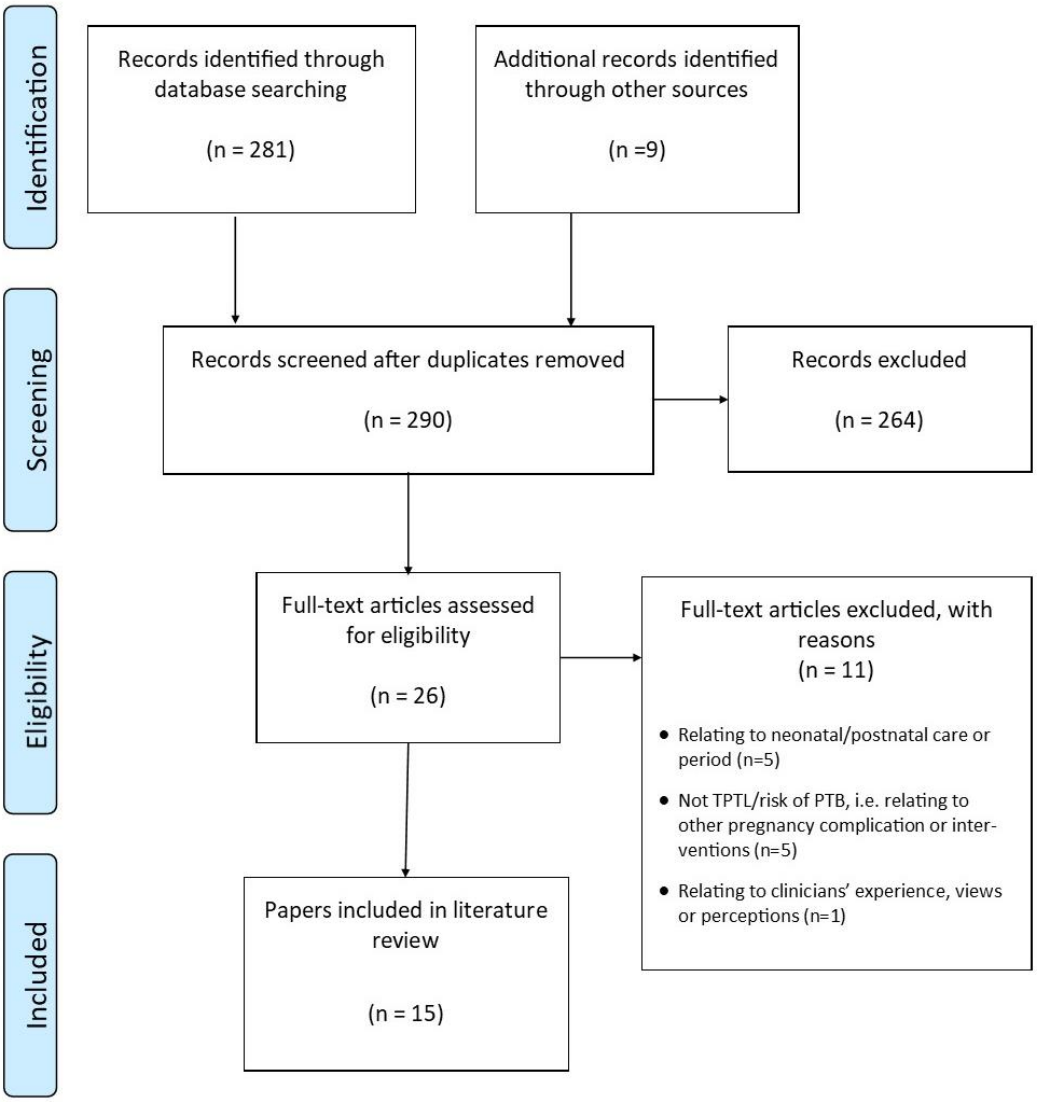


Figure 9. PRISMA 2009 Flow Diagram of search results for the literature review "Women's experience of threatened preterm labour".

3.4. Characteristics of the papers included in the review

Details of the 15 included papers are shown in Table 6. Thirteen primary research papers were included along with two literature reviews. One literature review focused on bed rest for women at risk of preterm birth (Maloni, 2010) while the other sought to identify research papers on TVS CL that reported additional, psychosocial effects (Vis *et al*., 2011). A quality assessment of the 13 papers reporting primary research was carried out using the Critical Appraisal Skills Programme (2018) CASP Qualitative checklist. As there is no consensus on the best method for assessing quality in reports of qualitative research (Dixon-Woods *et al*., 2004; Leung 2015) this method was chosen because it was designed to assist healthcare professionals assessing qualitative research and its application to practice. In order to reduce the danger of excluding important concepts, a decision was taken not to exclude studies on the basis on quality unless they were "fatally" flawed (Dixon-Woods *et al.*, 2006, p.4). However, all of the papers were of sufficient quality to be included. The results of this quality assessment are shown in Table 5.

Table 5. Quality assessment of studies included in the literature review "Women's experience of threatened preterm labour" using CASP Qualitative Checklist (Critical Appraisal Skills Programme, 2018).

Study reference	1. Was there a clear statement of the aims of the research?	2. Is a qualitative methodology appropriate?	3. Was the research design appropriate to address the aims of the research?	4. Was the recruitment strategy appropriate to the aims of the research?	5. Was the data collected in a way that addressed the research issue?	6. Has the relationship between researcher and participants been adequately considered?	7. Have ethical issues been taken into consideration?	8. Was the data analysis sufficiently rigorous?	9. Is there a clear statement of findings?	10. How valuable is the research?
Adler *et al.*, 2002	+	+	+	+	+	?	+	+	+	+
Barlow *et al.*, 2007	+	+	+	+	?	?	+	?	+	+
Coster-Schulz & Mackey, 1998	+	+	+	+	+	?	?	?	+	+
Hoglund and Dykes, 2013	+	+	+	+	+	+	+	+	+	+
Lowenkron, 1999	+	+	+	?	+	?	?	?	+	+
Mackey & Coster-Schulz, 1992	+	+	+	?	+	?	?	?	+	+
MacKinnon, 2006	+	+	+	+	+	?	+	+	+	+
O'Brien *et al.*, 2010	+	+	+	+	+	?	+	+	+	+
Palmer and Carty, 2006	+	+	+	+	+	?	+	+	+	+
Patterson *et al.*, 1992	+	+	+	+	+	?	?	+	+	+
Peterson *et al.*, 2014	+	+	+	+	+	?	+	+	+	+
Porcellato *et al.*, 2015	+	+	+	+	+	+	+	+	+	+
Weiss *et al.*, 2001	+	+	+	+	+	?	+	+	+	+

Key: Result of evaluation denoted by use of traffic light icons + = yes; - = no ? = can't tell.

3.5. Themes emergent from review of the included papers

A review of the included studies revealed a number of common themes that throw light on women's experience of threatened preterm labour. These themes are discussed below, and include: the onset of threatened preterm labour; living with threatened preterm labour and women's experience of TPTL tests and healthcare interventions.

3.5.1. Theme 1 - The onset of threatened preterm labour.

The experience of threatened preterm labour begins with the onset of symptoms that may not be immediately recognised by the woman as signs of early labour. A women may go through a process of attempting to understand what is causing the symptoms and whether they represent a threat to herself or her baby, before deciding to call for professional help.

3.5.1.1. Sub-theme 1: Seeking to understand the symptoms and being unbalanced

Pregnancy is a period of bodily transformation and it is difficult for women to recognise whether the symptoms of TPTL are simply part of normal pregnancy changes (Mackey and Coster-Schulz, 1992; Weiss *et al*., 2002). TPTL symptoms can be varied, from an increase in frequency or intensity of tightenings, abdominal or back pain, or watery or blood stained vaginal discharge. Symptoms are often difficult to distinguish from other symptoms that may have other causes. Tightenings may be Braxton Hicks contractions, abdominal or back pain could be a result of a gastric disturbance, urinary

tract infection or increased weight and posture changes, watery discharge could be caused by stress incontinence.

Patterson *et al*. (1992) describe this period as a state of "Diagnostic confusion". This confusion arises from the fact that PTL symptoms often lack clear distinguishing features or pattern and that it is difficult for women to differentiate between these and the "normal" discomforts of pregnancy. Another factor in this confusion is that most women have not considered that their symptoms might be early signs of labour. They will go through a process of becoming aware of the symptoms before comparing with past experiences, gathering extra data, such as timing their contractions, and seeking information from a variety of sources. They will then develop a "working diagnosis" which will direct their next actions. Strategies to deal with symptoms depend on the "working diagnosis" and the woman's assessment of whether the symptoms were "normal" or potentially threatening and could include ignoring the symptoms, trying not to think about it, positive thinking or waiting until perceived threat has become serious enough to warrant seeking professional help.

> *"Diagnostic confusion arises from the interplay of several factors. First, the nature of the symptoms of preterm labour contributes to confusion. The symptoms most likely to be attended to, i.e. pain, cramps, contractions, and pressure, often begin subtly and lack clear distinguishing features". (*Patterson *et al*. 1992, p.369).

Coster-Shultz and Mackey (1998) describe women's experience of PTL in five stages, the first two of these are the awareness that something is wrong which gives them a sense of unbalance, making sense of the experience and seeking to understand why

labour had started. Others report similar findings. Barlow and colleagues (2007) found that the onset of symptoms was often unexpected and that while some women had no idea what had caused it, others had some ideas of possible causes. Many women appear to attribute causes to something they had done, such as increased activity, the fact that they had been emotionally stressed, or other medical or physical problems (Mackey & Coster-Shultz, 1992; Weiss *et al*., 2001):

> *"One half of women (n=8) thought that physical activity could be a cause of their preterm labour. They primarily described excessive and continuous housework, sometimes on top of work outside the home, or coupled with caring for a small child." (*Mackey & Coster-Shultz, 1992, p.373).

> *"Several women identified stress associated with the pregnancy as a possible factor underlying the onset of preterm labor." (*Weiss *et al*., 2001, p.70).

3.5.1.2. Sub-theme 2: Deciding when to seek professional help

The decision of when to seek professional help appeared to depend on the women's judgement of the causes of the symptoms and whether they constituted a threat to their or their baby's well-being. Mackey & Coster-Shultz (1992) describe two types of women: the "waiters" and "non-waiters". The "non-waiters" were very anxious and called for help within minutes, while the "waiters" would first monitor the symptoms for some time, between 2 days and 2 weeks, before seeking help and in the meantime instigate strategies for dealing with the symptoms, such as resting, increasing fluid intake, taking warm baths and stroking their abdomens. Women struggle as they

become increasingly concerned by the symptoms, but do not want to been seen as "over-reacting" (Palmer *et al*. 1992). Both Patterson *et al*. (1992) and Weiss *et al*. (2001) found women often waited to seek help until the threat became immediate.

> *"When the above strategies for making sense of and dealing with symptoms of preterm labor fail to alleviate the diagnostic confusion and when symptoms continue, recourse to a professional for evaluation and/or treatment is deemed in order."* Patterson *et al.,* 1992, p.371

> *"In highly certain situations with no perceived threat, interaction with a health care provider was not sought. In situations of uncertainty, precautionary health care seeking was initiated to provide verification or clarification of symptom meanings. In situations characterized by certainty and perceived threat, the provider was contacted with very little delay."* Weiss *et al*., 2001, p. 72

Previous experiences with preterm labour or birth can affect a woman's decision making in a subsequent episode or pregnancy. Palmer and Carty (2006) explored the experience of women undergoing a second episode of TPTL and how they decided when to seek further help. They found that women compared symptoms to the first episode and judged whether they were different or more intense. They sensed that "something's not right", but still did not want to be seen as over-reacting. Weiss and colleagues (2001) found that, after having decided that the threat was real and seeking help, if they were told that the symptoms were nothing to worry about, this would result in delays to help-seeking in future episodes of TPTL symptoms:

> *"Women who had substantial concern about the threat to their pregnancies self-referred to hospitals or urgent care facilities. In these cases, if a physical examination did not validate the onset of preterm labor, the woman received validation of the normalcy and nonthreatening nature of her symptoms. This validation of the symptoms as non-problematic resulted in delays in care seeking for future symptom patterns."*p.72.

Women who had experienced preterm birth in an earlier pregnancy were less concerned about over-reacting. In their study of high risk women attending a specialist preterm clinic in a subsequent pregnancy, O'Brien *et al*. (2010) found that women often experienced guilt if they had dismissed symptoms they now considered may have been warning signs. These women were determined to trust their intuition and seek help more quickly this time.

3.5.2. Theme 2. Living with the threat of preterm birth

3.5.2.1. Sub-theme 1: Fear and uncertainty

The sense of imbalance and uncertainty that started in the early stages continues into the experience of TPTL. The implications of preterm birth are widely known, so the development of symptoms or problems that may indicate premature labour can cause considerable stress and anxiety. The women's primary concern is for the life and health of their unborn baby, but the uncertainty and loss of control over their lives is often reported as making the situation even harder to cope with (Lowenkron, 1999; Maloni, 2010).

> *"Stress resulted from feelings of nervousness related to their situation, lack of ability to control important aspects of one's life, and the happening of unexpected events." (*Lowenkron, 1999, p.557).

Coster-Schulz and Mackey (1998) described how the participants of their study prioritised keeping their unborn baby and themselves safe, fearing loss of the baby while feeling their life was "on hold". MacKinnon (2006) also talked about women "suspending their lives" whilst under threat of preterm labour and the women in Hoglund and Dykes' (2013) study described a great sense of insecurity, fear for the baby and lack of control over their bodies and symptoms.

> *"The most common symptoms were fatigue, back muscle soreness, sleep cycle changes, round ligament pain, dry lips, nasal congestion, reflux, indigestion, mood changes, tenseness, and boredom."p.470.*

Women with a previous history of preterm birth experience great anxiety throughout subsequent pregnancies, even before, or without, experiencing TPTL symptoms. Although they may find reassurance immediately following specialist preterm clinic appointments, the relief is only temporary and much of the pregnancy can feel like an emotional rollercoaster (O'Brien *et al*., 2010).

3.5.2.2. Sub-theme 2: Adjusting to life changes, loss of control and identity

Women whose symptoms do not quickly develop into established preterm labour appear to continue feeling this fear and sense of uncertainty. They may be admitted to hospital or advised to rest at home, and this means having to make and come to terms with albeit temporary life changes. This can have a profound effect on a

woman's sense of identity, as well as control over her life and even her body. As Adler and Zarchin (2002) explained:

> "*Unlike a normal pregnancy, in which a woman balances her own needs with those of her developing fetus, the woman on bed rest gives up virtually all of her own needs to maintain the pregnancy. This unbalanced living can cause a woman to feel as though she has given up her former identity and sense of self*." (Adler and Zarchin, 2002, p.424).

It can be very difficult for a woman to adjust to role changes from perhaps autonomous employee and/or caring for other children to focusing on herself and unborn baby while accepting support and practical help from others (Adler and Zarchin, 2002; Coster-Schulz and Mackey, 1998). Although restriction of activities and rest is intended to reduce stress, it may reduce physical stress, but often leads to increased emotional stress, and can lead to feelings of boredom, frustration, isolation and depression (Hoglund and Dykes, 2013; Mackey and Coster-Shultz, 1992). Coster-Schulz and Mackey (1998) described how this additional stress can threaten the woman's ability to maintain a sense of balance as she tries to follow medical advice, while adjusting to her changing role and possibly even dealing with financial hardship if she is unable to work outside the home. At the same time, women can feel a profound sense of personal responsibility for taking care of themselves and doing everything possible to reduce the risk of their baby being born too soon (MacKinnon, 2006).

> *"Overall, preterm labor was experienced as a profound sense of personal responsibility for preventing preterm birth and was practiced as being 'careful'."* (p.703).

3.5.2.3. Sub-theme 3: Effects on personal relationships

The experience of threatened preterm labour may also have an effect on the woman's relationships with other members of her family. Many women worry about neglecting the needs of other children, or placing an additional burden on their partners, who may be required to take on more household or childcare duties. Assistance may be sought from members of the wider family or friends and although some women do not find this is always forthcoming, others may develop deeper bonds with those who are able to help them at this time (Adler and Zarchin, 2002; Barlow *et al.*, 2007). The high risk women in O'Brien *et al*.'s (2010) study spoke about how the emotional burden of living with the threat of preterm birth had a profound effect on their partners which was often under acknowledged.

> *"Women acknowledged that whilst their own physical and emotional needs were considered and addressed, partners who were already struggling to cope emotionally were effectively ignored by health professionals and also expected to take on the added pressures in the home and family plus continue working as well."*p.83.

3.5.2.4. Sub-theme 4: Coping strategies

The available evidence throws some light on how women living with the threat of preterm birth cope. The women in Adler and Zarchin's (2002) study appear to have

developed a number of coping strategies, which included learning to accept the emotional and practical help of others and developing their relationship with their unborn baby which they saw as a positive effect of the bedrest they had been prescribed. Coster-Schulz and Mackey (1998) also described allowing others to take over responsibilities as a coping strategy employed by women in their study and, in an earlier paper, focusing on the baby and thinking positive thoughts (Mackey and Coster-Shultz, 1992). Thinking positively, not thinking at all or trying to think of something else, was a coping strategy identified by Höglund and Dykes (2013) in their study of women on sick leave for threatened preterm labour symptoms. These women also coped by taking each day or week as it came, rather than thinking too far ahead, which was a strategy also employed by the women in O'Brien *et al*.'s (2010) study:

> *"They were reluctant to look too far ahead to the future and would, instead, set themselves markers to reach, approaching the pregnancy journey through a series of 'baby steps'… [describing] how they lived 'week to week' and each successful clinic appointment was another target achieved",* (p.81).

3.5.3. Theme 3: Women's experience of PTL tests and healthcare interventions

In this project, we sought to explore both the women's experience of TPTL and the factors that influenced this experience, including women's views on the healthcare and interventions they received. The literature search revealed a notable paucity of evidence around women's experience and views on specific tests used as part of TPTL assessment or common interventions. There was only one study, identified in this literature review that explored the experiences of women who received fetal

fibronectin testing as part of their assessment for TPTL symptoms (Peterson *et al*., 2014). The authors concluded that the test was acceptable to women, but also described how participants felt increased anxiety as they waited for the results. Vis *et al*. (2011) undertook a systematic review of papers assessing the additional effects (such as reassurance) of cervical length measurement in threatened preterm labour, but did not find a single study that had measured the psychosocial effects.

In terms of interventions for reducing the risks associated with preterm birth, no qualitative studies were found on women's experience of antenatal corticosteroid use for fetal lung maturity, or the use of tocolysis to stop contractions, which are both common interventions offered to women with TPTL symptoms. One study described women's experiences of in utero transfer (IUT), where the woman is transferred to another hospital if no neonatal cots are available locally. Findings suggested that, despite little knowledge of IUT and feelings of unpreparedness, most women were resigned to accept the intervention (Porcellato *et al*., 2015):

> *"…there was resigned acceptance from those transferred for a higher level of care that IUT was necessary to optimise the welfare of their unborn child."*(p.5).

O'Brien *et al*. (2010) also found that women who had a cervical cerclage or received progesterone treatment to prevent preterm birth were prepared to accept them, without hesitation, despite being afraid of the procedure and unpleasant side effects.

Studies reporting women's experience of bedrest are included in the above as they demonstrate a more complete picture of the overall experience.

3.6. Summary and discussion

Literature on women's experience of preterm labour or being at risk of preterm birth is limited with most published studies being qualitative in nature with few participants. A picture emerges, however, of a challenging experience where women with symptoms of preterm labour try to cope with anxiety and uncertainty. They are called upon to make decisions on when to seek help, dealing with fears for the health of the baby, and often having to cope with a loss of control as they try to balance other responsibilities such as those to other children or work commitments. The experience of hospitalisation or home bedrest for preterm labour has been described by a number of authors where similar themes describe women's anxiety, loss of control and conflicting responsibilities. There is greater paucity of evidence around women's experience and views on specific tests used as part of TPTL assessment or common interventions, but that which exists tends to suggest that women are willing to accept them.

Many of the studies included in this review were carried out several years ago, with only one study relating to women's experience of TPTL in a UK setting (Barlow *et al*., 2007). Two other studies carried out in the UK related to women's experience of a specialist preterm clinic for women at high risk (O'Brien *et al.,* 2010) and women's experience of in utero transfer (Porcellato *et al*., 2015). There is clearly a need to further explore women's experience of TPTL and related interventions in current UK setting. The qualitative study undertaken as part of this PhD project was designed to contribute to this gap in knowledge.

Table 6. Characteristics, main findings, conclusions and implications for practice of papers included in the literature review "Women's experience of threatened preterm labour".

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
Adler and Zarchin, 2002 *"The "Virtual Focus Group": Using the Internet to Reach Pregnant Women on Home Bed Rest."*	Qualitative, exploratory, descriptive investigation, carried out through the use of a virtual focus group.	Data collection was conducted via the internet and consisted of a series of sequential questions presented by the researchers to the participants via e-mail over a 4-week period. USA.	August 1998.	A purposive sample of 7 women who were on home bed rest for the treatment of preterm labour.	"Three major categories and seven subcategories regarding the lived experience of home bed rest were identified: • the effect of bed rest on participants' lives (transitioning onto bed rest, loss of control and activities, changes in identity and role, coping and personal growth, transitioning off bed rest). • the effect of bed rest on relationships with others (relationships with the fetus and other children, relationships with husbands and extended family members), and • the virtual focus group as an online peer support group. Participants were unanimous in their appreciation of the virtual focus group. All participants stated that their participation was valuable and beneficial in helping them to cope with the hardships of bed rest."	"Confinement to bed rest at home dramatically alters women's daily activities, self-perceptions, and interpersonal relationships."	"The use of the virtual focus group allows nurses to embrace the technology of the Internet to study and connect women on home bed rest, as well as other isolated and understudied patient groups."

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
Barlow *et al.*, 2007 *"An exploratory, descriptive study of women's experiences of hospital admission during pre-term labor."*	The views of 8 women admitted to hospital with PTL were obtained through semi-structured interviews. Data were analysed using content analysis.	Women's Unit, University Hospital of Coventry and Warwickshire, Coventry, UK	Unclear.	n=8 Inclusion criteria were: admission to hospital at a gestational age of <37 weeks, singleton pregnancy, English-speaking, no physical or chronic condition, and no major cognitive or psychiatric disorder.	"A key aspect of women's experiences concerned their search for meaning to help them make sense of their sudden and unexpected hospital admission. Several women continued to feel anxious despite assurances from staff that everything was 'OK', whereas others had overcome initial anxiety and were excited about the imminent birth. There was consensus that the information received whilst in hospital was inconsistent, and some women believed that their concerns were being 'ignored'. Some women attributed PTL to daily stress, such as working long hours. Social support from women's mothers and other patients appeared important."	"Women admitted to hospital in PTL could be assisted in their search for meaning by provision of consistent information, having their views acknowledged, satisfactory social support, and dealing with any previous history of perceived traumatic birth experiences."	
Coster-Schulz and Mackey, 1998 *"The preterm labor experience: a balancing act."*	Naturalistic inquiry. Part of a larger study. Semi structured interviews.	USA	Unclear, but pre - 1995.	10 "mature" women (24+ years) with private insurance hospitalised for PTL. In order to compare with younger women on Medicaid.	"PTL experience occurred in 5 recursive stages: 1. Awareness of something wrong and sense of unbalance. 2. Making sense of experience, sought to understand why labour had occurred. 3. Attempting different strategies to re-balance lives. 4. Efforts to address other stressors that threatened ability to re-balance 5. Emergence from the PTL experience with added growth. Priority to keep unborn baby and themselves safe. Needed to learn to accept support and assistance from others."	"PTL experience can be conceptualized…as being caught in a storm." Great conflict between meeting their own needs and those of unborn child. Mature women had more available resources, but adolescents found it easier to accept help, especially from their own mothers."	"Nurses should provide opportunities for women to exert control over how they manage their PTL. That their concerns and decisions are respected and accepted."

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
Höglund and Dykes, 2013 *"Living with uncertainty: A Swedish qualitative interview study of women at home on sick leave due to premature labour."*	Qualitative, descriptive using open interviews.	10 antenatal clinics in the south of Sweden.	Unclear.	15 pregnant women who were on sick leave for premature labour.	"Four categories were identified: • How to interpret unpredictable contractions in the uterus. • Having concern regarding premature labour of their child, • Handling the new situation and finding a balance, and • From work to sick leave."	"To be on sick leave for premature contractions can be compared with enduring a situation of inactivity. The woman finds herself in a stressful situation which she must learn to handle this and find a balance."	"Supportive information offers the women in premature labour the opportunity of increased participation and responsibility which thereby positively affects her wellbeing."
Lowenkron, 1999 *"Coping with the Stress of Premature Labor."*	Theoretical framework: Lazarus's model of Stress, Coping, and Emotion. Descriptive correlational design	Pregnant women located in a large city in the Midwest USA.	Unclear, but pre-1999.	Women treated at home for premature labor. n=50. 20 questionnaire only; 10 interviewed only 20 completed the questionnaire and the interview.	"The women reported experiencing a moderate amount of stress. The women appraised their situation as both threatening and challenging. They described their emotional response most frequently as frustration because of fear concerning the pregnancy outcome, loss of control over their life, and inability to perform their usual roles of mother, wife, and worker."		"Women at risk for ineffective coping because of personal factors such as low self-esteem, overwhelming stressors in their environment, or inadequate social support should be identified and counselled appropriately."
Mackey and Coster-Schulz, 1992 *"Women's views of the*	Naturalistic approach. Semi-structured interviews, on process of becoming a PTL	South eastern USA. Regional perinatal centre.	Unclear.	20 women hospitalised for PTL.	"Women either waiting for a period of time before seeking care or sought care immediately. Women interpreted the experience by identifying causes of PTL and by worrying	"Women did report typical symptoms of PTL but did not respond in the same way. Waiting appeared to be related to previous experience with PTL, difficulty accessing care and	"The emotional and social needs of women should be addressed during routine

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
preterm labor experience."	patient and living with a diagnosis of PTL				about the outcome for the baby."	feeling changes were normal."	prenatal care and antenatal hospitalisation. Cannot separate medical from social and emotional needs."
MacKinnon, 2006 *"Living With the Threat of Preterm Labor: Women's Work of Keeping the Baby In."*	Institutional ethnography.	City in Western Canada.	Unclear.	Eight women who experienced preterm labour. 4 had PTB. 4 term delivery.	"Women spoke about their fear of going home and feeling alone with the responsibility for their work of " keeping the baby in. " Overall, preterm labour was experienced as a profound sense of personal responsibility for preventing preterm birth and was practiced as being " careful. " The work of keeping the baby in conflicts with family care work responsibilities and can cause significant hardships for some women and families."	"The assumption that the family is privately responsible for care work in the home results in the lack of assessment of resources for managing the medical plan on discharge and the lack of resources available or offered to assist families."	"Nurses need to listen carefully to what women have to say about their experiences, their needs, and the work they do in the family. Together we could help these women get the recognition and support they need for their work of keeping the baby in."

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
Maloni, 2010 *"Antepartum Bed Rest for Pregnancy Complications: Efficacy and Safety for Preventing Preterm Birth."*	Review.	Integrative review of literature provides a comprehensive analysis of the evidence for the practice of prescribing ABR and its physiologic, behavioural, and experiential side effects.	Unclear.	26 articles about physiological, behavioural, and experiential side effects of antenatal bedrest (ABR) , 17 articles comparing antepartum hospital and home care, 5 meta-analyses of RCTs of the effectiveness of ABR, and 4 articles about physician use of bed rest.	"There is a body of research that has identified numerous adverse physiological and behavioural effects of ABR upon pregnant and postpartum women. The experience of bed rest for mothers is harrowing and characterized by fear for self and fetus, the presence of a variety of negative emotions including depression and anxiety, and altered temporality that makes enduring the present a major task. Additionally, some research suggests that the fetus/infant may also be affected, particularly in the critical area of infant birth weight. However, as there are few and conflicting reports, further research is needed on the effects of ABR on fetal and infant health and well-being."		"Even with an understanding of some of the side effects of ABR, decisional conflict may contribute to continued use of bed rest. The continued use of bed rest indicates a neglect to consider the full range of evidence about both the efficacy and safety of bed-rest treatment for both the mother and the infant."
O'Brien *et al.,* 2010 *"Women's views of high risk pregnancy under threat of preterm birth."*	Qualitative interpretive approach, focus groups and one-to-one interviews.	A preterm antenatal clinic at a major tertiary referral centre in the North West of England.	Unclear.	14 pregnant women attending preterm surveillance clinic.	"Women struggled with 'balancing the risks' associated with the threat of preterm birth, they developed 'personal coping strategies to survive the pregnancy' and they watched as the strain made their 'whole family crumble'."	"Women's journey through pregnancy after a previous PTB experience is one of emotional and physical endurance."	"By setting mutually agreed short term goals, significant milestones can be reached so that women feel they are successfully progressing through a high risk pregnancy through a

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
							series of 'baby steps'."
Palmer and Carty, 2006 *"Deciding When It's Labor: The Experience of Women Who Have Received Antepartum Care at Home for Preterm Labor"*	Grounded theory method.	2 Canadian antepartum home care programs.	Unclear.	12 women who received antepartum care at home for preterm labour.	"Study participants reported knowing something's not right and followed decision guides to seek help. If, when they returned to the hospital to see what s going on , they felt dissonance between what their bodies were telling them (body knowledge) and what their health care providers were telling them (professional knowledge) an overriding tension developed between not wanting to take a risk for the baby versus not wanting to overreact. These women re-established their baselines of nonthreatening symptoms at a higher level by setting a new normal to avoid the humiliation associated with appearing to overreact. Attempting to ignore recurring symptoms of preterm labour delayed help seeking and caused anxiety."		"To avoid delayed help seeking, nursing interventions should be geared to reducing anxiety and validating the experiences of women with recurring preterm labour symptoms."

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
Patterson *et al*., 1992 *"Symptoms of preterm labor and self-diagnostic confusion."*	Grounded theory. Interviews	One private and one university hospital. Unclear which country but authors are based in USA.	Unclear.	28 women who had experienced PTL.	"Ambiguous symptoms, absence of a meaningful label to attach to symptoms and the context of pregnancy with its expected discomforts come together to create a situation of diagnostic confusion. Deliberate and protracted efforts to make sense of and deal with symptoms of PTL are attempted. Making sense consists of 3 sub-processes: 1. Comparing. 2. Gathering data. 3. Seeking information. Strategies used to deal with symptoms include: 1. Self-treating. 2. Ignoring. 3. Positive thinking. 4. Waiting. 5. Recourse to a professional is used as the strategy of last resort when symptoms can no longer be contained."	"Women who are not known to be at risk of PTL do not always seek help immediately (which was previously assumed)."	"Recommends research to quantify the duration of the care-seeking process and to determine if a relationship exists between duration of care seeking during PTL and cervical status on admission."
Peterson *et al*., 2014 *"Women's perspectives of the fetal fibronectin testing process: a qualitative descriptive study."*	Descriptive qualitative design was used, employing semi-structured telephone and face-to-face interviews.	Ontario, Canada. Five hospitals participated.	November 2010 and June 2011.	17 women.	"Fetal fibronectin testing as an emotional process that moves from expecting, to feeling, to hoping for reassurance; and then to re-defining what is required to feel reassured. Women described feeling anxious while waiting for fetal fibronectin results. When test results were negative, women described feeling a sense of relief that their symptoms would not likely lead to an imminent preterm birth. Women with positive results expressed feeling reassured by the care decisions and quick action taken by the health care team."	"Fetal fibronectin testing was acceptable and beneficial to these women with symptoms of preterm labour."	"These findings indicate the importance of providing comfort measures to minimize anxiety and increase reassurance during fFN testing, including clearly explaining test

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
							results to women and their partners."
Porcellato *et al*., 2015 *"'It's something you have to put up with'— service users' experiences of in utero transfer: a qualitative study."*	Qualitative descriptive study using semi-structured interviews.	Participant's home or hospital in the Midlands, UK.	August 2010 to December 2011.	Fifteen women transferred in utero to a tertiary level maternity hospital; five male partners and two grandmothers.	"Findings suggest that IUT is an emotional experience that financially disadvantages patients and their families. Male partners were perceived to be most negatively affected by the experience. The quality of the IUT experience was influenced by a range of factors, including the lack of proximity to home and the lack of information. Patients had little knowledge or awareness of IUT, and most felt unprepared for displacement. Despite this, there was resigned acceptance that IUT was a necessary rather than adverse experience."	"The experience of IUT for service users could be enhanced by ensuring that they are better informed about the process and the circumstances that necessitate displacement, that they are better informed about the hospital to which they are being transferred, and that they are transferred as close to home as possible."	"Efforts to minimise the emotional and socio-economic impact of IUT on women and their families also need to be considered."
Vis *et al*., 2011 *"Additional effects of the cervical length measurement in women with preterm contractions: a systematic review."*	Systematic review of the literature to identify articles reporting on cervical length measurements in women with symptoms of preterm labour.	Review of literature.	Unclear.	12 articles that reported additional effects of cervical length measurement in symptomatic women, such as the reassurance or the sensory consequences related to the transvaginal procedure. None of the articles quantified such additional effects	"There appears to be a gap between the presumed effects of cervical length measurement on patient outcomes, such as patients' reassurance, and the actual assessment of these effects during test evaluations. They did not find a single study that had measured the psychosocial effects of performing a cervical length measurement in women with symptoms of preterm labour. However, such additional effects were considered relevant by several authors, who often referred to them in the discussion section of their articles. Multiple authors have pointed to the potential of cervical length measurements to affect a range of patient outcomes, such	"This review illustrates that empirical evidence about an expected reassuring effect of cervical length measurement in women with threatened preterm labour is lacking."	"…suggest that future evaluations of prognostic preterm labour tests include a comprehensive assessment of patient outcomes. Future studies evaluating transvaginal cervical length measurement for preterm labour should

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
					as reassurance and anxiety, but these effects have not yet been measured."		include a more complete assessment of patient outcomes."
Weiss *et al*., 2001 *"Resolving the Uncertainty of Preterm Symptoms: Women's Experiences With the Onset of Preterm Labor."*	Qualitative, using grounded theory methods. Taped and transcribed interviews. Constant comparative method of analysis.	Described as "Southwestern" tertiary women's hospital, but unclear which country but authors based in USA. The interviews took place in each participant's room after PTL symptoms stabilized and were tape recorded with the woman's knowledge. Most of the interviews were completed within 72 hours after admission.	Unclear.	30 pregnant women who were less than 35 weeks gestation, had experienced PTL within the past 7 days, and had no previous experience with PTL.	"Themes that emerged from the interview data included the following: recognition and naming of sensations, a consistent pattern of attribution of symptoms, the threat or risk inferred by the attributed cause of the symptom pattern, the associated certainty or uncertainty about these attributions, the process of interpreting and verifying symptom meaning, and the decision to self-manage the symptoms or engage health care assistance. The core process of women experiencing the onset of PTL symptoms was identified as "resolving the uncertainty of PTL symptoms: recognizing and responding to the possibilities. PTL often is not within expectant women's consciousness. They may attribute the symptoms to nonthreatening causes, which results in delays in seeking care for PTL. Even previous term labour does not provide a good experiential background for recognizing PTL."	"The language used by expectant women in their descriptions of preterm labour symptoms should be incorporated in the educational materials available to all pregnant women to assist them in the early recognition of PTL. Every expectant woman needs education about the cues to use in recognition of preterm labour as differentiated from term labour. Expectant women should be given decision guides to assist them with self-management, timely contacts with the provider, and access points for seeking health care."	"Patient education should be directed not only toward providing materials to assist in recognizing and attributing symptom experiences PTL but also to increasing awareness among pregnant women of the possibility of PTL. Health educators must balance the need to de-medicalize the normal process of pregnancy and birth with the need to maintain sensitivity

Reference	Study Design	Setting/Country	Study time period	Participants	Main findings	Author Conclusions	Implications for practice
							among expectant women of the possibilities of health symptoms requiring their attention and action."

4. AIMS AND OBJECTIVES

4.1. Overall aim and overview of the PhD research

The overall aim of my PhD research was to improve the experience of women with symptoms of TPTL by addressing two issues: a) the need for better risk assessment in TPTL and b) the identification of areas where TPTL care could be enhanced. I hypothesised that this could be achieved through: i) the development of a clinical decision support tool that predicts individual risk of preterm delivery and ii) a qualitative study exploring women's experience of TPTL care. Figure 10 illustrates how the different parts of the research project, from literature review, prospective cohort study, current QUIPP app users study and women's experience study combine to achieve the intended outputs. The timeline of project activities is demonstrated in Figure 11.

The overarching study was called "PETRA", an acronym derived from some of the letters of the study title: "Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool & a qualitative exploration of women's experiences". PETRA comprised three components. The first was a prospective cohort study for the collection of data on risk factors, test results and outcome which were used in the validation of risk prediction algorithms in the development of the QUIPP app. PETRA Part 2 was the name of the qualitative study exploring women's experiences, and PETRA Part 3, was an additional qualitative study exploring the views of the clinicians who were using the first version of the QUIPP mobile phone application. This was known as Part 3 because it was the third part to be instigated, however, findings from

the QUIPP users study informed development of the app and therefore relate to the first study objective.

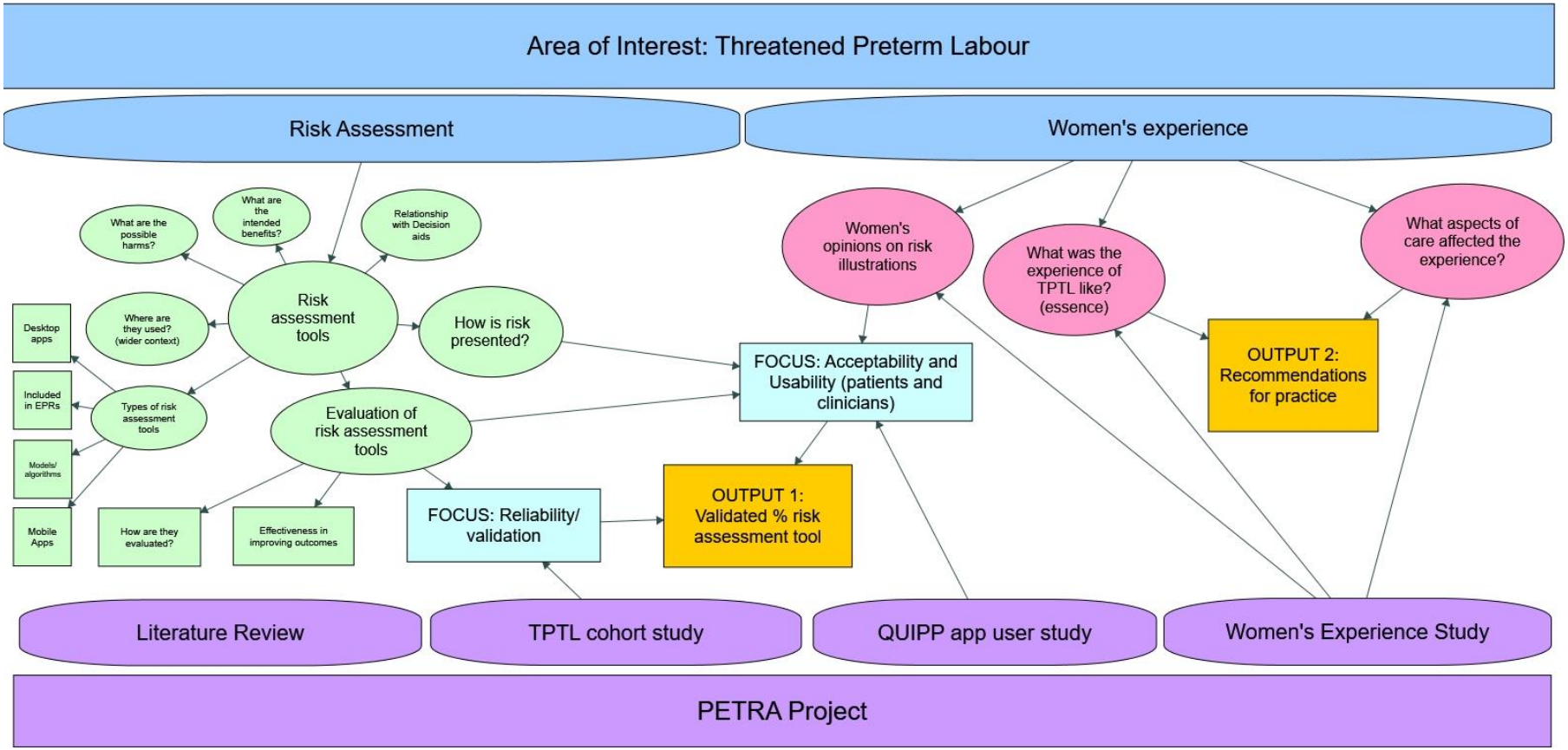


Figure 10. Schematic overview of the different elements of this PhD project.

Figure 11. GANTT chart demonstrating PETRA project timeline.

4.2. Rationale and research questions

Building upon our previous research, generated by the preterm birth group at KCL Department of Women and Children's Health, along with the knowledge that fFN and TVS CL are useful tools for prediction of preterm birth, the research questions addressed in this thesis were:

1. Can a combination of risk factors, fFN test results and CL measurements generate a reliable individual risk score for women with TPTL?
2. How can the QUIPP app be enhanced to increase its usefulness and acceptability to clinicians and women?
3. What is the experience of women with symptoms of TPTL, and how could assessment and management be improved?

4.3. Primary Objectives

The primary objectives of the PETRA study were:

1. To develop and validate a risk assessment tool (QUIPP) that generates individualised risk scores indicating likelihood (% risk) of birth within clinically significant time points.
2. To identify potential areas for improvement in care of women with symptoms of TPTL.

4.4. Secondary Objectives

Although evidence suggests that using both fFN and CL together may aid risk assessment (DeFranco *et al.,* 2013; van Baaren *et al.,* 2013), CL measurement of women with TPTL is less common than fFN testing in the UK. For this reason, the added value of using TVS CL in a UK setting was explored, along with appropriate use

of TPTL interventions (in relation to subsequent outcome). An overview of primary and secondary objectives, methods and intended outputs is shown in Table 7.

Table 7. PETRA study objectives, methods and intended outputs.

Objective	Methods	Intended outputs
1. To develop and validate a risk assessment tool (QUIPP) that generates individualised risk scores indicating likelihood (% risk) of birth within clinically significant time points (primary objective).	• Prospective cohort study combining risk factors and test results for quantification of risk of PTB (as per Kuhrt *et al.,* 2016) (PETRA Part 1). • Survey of women's and QUIPP app users' opinions on risk illustrations. (PETRA Parts 2 and 3).	• New QUIPP app with updated algorithms, including twins and CL in symptomatic women, and visual illustration of risk. • Inform next stage of development, the EQUIPTT study which will evaluate the app in clinical practice.
2. To identify potential areas for improvement in care of women with symptoms of TPTL (primary objective).	• Qualitative study using thematic analysis of women's experience of TPTL risk assessment and care management. (PETRA Part 2).	• Recommendations for practice and research.
3. To explore the added value of CL in a UK setting (predefined secondary objective).	• Comparison of risk prediction in women whose TPTL assessment included fFN alone, with those whose assessment included both fFN and CL.	• Demonstrate value, or otherwise, in use of TVS for CL in TPTL assessment.
4. To assess use of steroids and other management (i.e. admission, tocolysis, *in utero* transfer) in relation to test results (*post-hoc* objective).	• Analysis of administration of steroids, tocolysis, hospital admission and *in-utero* transfer. • Steroid use in relation to time from administration to delivery, and whether guided by fFN/CL results, before and after 30 weeks (as per NICE guidance).	• Demonstrate extent of intervention use in relation to preterm birth in our cohort.

5. Patient and Public Involvement and Research Governance

5.1. Patient and Public Involvement (PPI)

The KCL Department of Women and Children's Health Preterm Birth Studies PPI panel provides review and advises on study design and participant documents for all preterm studies. Panel meetings are held twice a year, and further advice is sought by email should the need arise. Advice was sought from this group prior to the PETRA protocol development and Research Ethics Committee approval application. The PPI group were kept informed on the progress of the study and utilised throughout, as shown in Table 8.

Table 8. Patient and public involvement (PPI) panel contribution to study development and implementation.

PPI meeting date	Feedback provided
27th March 2013	An outline of study proposal was presented. Views on the value of the study were sought. Specific advice sought, and given, on appropriate methods for obtaining qualitative data on women's experience and review of draft participant documents.
4th April 2014	Presentation of cohort and qualitative study design. Views were sought on design and planned outcome data points. The group reviewed the participant information sheets.
17th April 2015	The group was updated on the progress of the study, which started recruitment in early March 2015. The current recruitment strategy was discussed, which included attempting to meet up with women at future hospital appointments when they have been assessed for TPTL but have been discharged overnight and at the weekend. For those women who do not have further hospital appointments the group were asked whether they would consider it acceptable for researchers to telephone these women "out of the blue". The group felt that it would not be acceptable, unless a midwife or doctor mentioned the study at the time of TPTL assessment and obtained oral consent to call.
4th Sept 2015	Presentation of study recruitment progress.
6th May 2016	Progress of cohort and qualitative study discussed, as well as plan for interviews with current QUIPP app users. The group was updated on recruitment which was going well at St Thomas' and that although there had been delays with local governance approvals at other sites, this had now

	improved. A discussion followed, and concerns were raised, about the variance in tests offered to women around the country. We also spoke about the way fetal fibronectin results were given (i.e. qualitative vs quantitative), particularly the language "positive/negative". Having a negative test was perceived as more reassuring perhaps than being given a numeric value, but being given a "positive test" causes anxiety even if the value is relatively low. A suggestion was made that a "traffic light" system may help, however an "amber" group may be too big a group to be useful. Generally, the group felt that being given a % risk was easier for women to understand.
23rd Sept 2016	The group were updated on study recruitment and on initial themes that were beginning to emerge from analysis of the qualitative data. Themes at this stage included "Coping", "Conflicts and Responsibilities", "Maternity Care", and "Emotions". There was a general consensus that the themes resonated with the members, who were also given copies of the models incorporating the codes, and asked to consider these and provide feedback when they had had more time.
19th May 2017	Presentation of study recruitment progress.
1st Dec 2017	The group were informed that the cohort study had completed on time and target on 31st October. The final qualitative findings were presented and members commented that they felt they were a credible representation of women's experience of TPTL.

5.2. Ethical considerations

5.2.1. Informed Consent

It was anticipated that women presenting with symptoms of threatened preterm labour may be anxious and unwilling, or unable, to consider research participation and give informed consent. Potential participants were only approached if the midwife or doctor providing their clinical care considered it appropriate. If deemed appropriate, they were given verbal information about the study, and informed there was no obligation to participate in this, or any other research. If willing to consider participation, they were given a copy of the participant information sheet (Appendix 17.2) to read. If happy to proceed, they were asked to sign a written consent form. They were also asked if they would be willing to be contacted about the qualitative study, and if so, were asked to provide a contact number. A further information sheet

was provided that explained the qualitative part of the study and written consent was taken prior to the interview taking place.

Participants were reminded that they are free to withdraw at any time, without giving a reason, and that their decision would not affect their care. It was also made clear that they could withdraw permission for the data to be used, at any time in the prospective cohort study, and within two weeks of the interview, after which time material may have been integrated in the analysis.

5.2.2. Confidentiality

Participants were given a study identification number and data collected for the prospective cohort study was entered on to a secure study database. Contact details were kept separately and securely to ensure confidentiality. In the qualitative study transcripts, names and any information that makes it possible to identify participants were removed to maintain anonymity.

5.2.3. Potential burdens to participants

Women presenting with symptoms of threatened preterm labour were clinically assessed in exactly the same way whether or not they participated in this study. The only difference was that they agreed to information about them and their care being collected and used to determine whether a risk assessment tool can accurately predict preterm birth. The midwives and doctors undertaking the assessments knew all tests results and care was provided in the usual way.

Participating in the prospective cohort study required the participant giving up some of her time, in the process of consent, and in answering some questions about her medical and obstetric history. Those also agreeing to the qualitative study were required to give around another hour of their time.

If they had been unhappy about their experience or the care they received it was possible that women participating in the qualitative study might find talking about it upsetting. If this happened they were reminded that they were free to stop the interview at any time, and, if necessary, the interviewer could arrange for the provision of any further support, e.g. debriefing or counselling.

5.3. Research Ethics Committee (REC) approval

The study was conducted in compliance with the Research Governance Framework for Health and Social Care and Good Clinical Practice (GCP). The London – South East NRES Committee approved the study in December 2014 (REC reference 14/LO/1988) and local R&D approval was obtained in March 2015 (RJ115/N074). Approval documents are shown in Appendix 17.1. Annual progress reports were submitted to the REC as required.

5.4. REC Substantial Amendments

Following commencement of recruitment in March 2015, four substantial REC amendments were approved. Details and summary of changes are listed in Table 9.

Other approved minor amendments related to addition of new sites and changes of Principal Investigators.

Table 9. List of Research Ethics Committee (REC) substantial amendments and summary of changes.

Substantial Amendment No. and Dates	Summary of changes
No. 1. ***28th May 2015*** **Approved:** ***17th June 2015***	1. Addition of multiple pregnancy to eligibility criteria. In the original protocol, multiple pregnancies were excluded because "evidence supporting the predictive value of quantitative fetal fibronectin in multiple pregnancies is currently insufficient". Since then, a meta-analysis (Conde-Agudelo and Romero, 2014) was identified that suggested that a negative (<50ng/ml) fetal fibronectin result could identify women with twin pregnancies who are unlikely to deliver within 7 days, and that further prospective studies in this area are needed. 2. Women who are assessed for TPTL are sometimes discharged before being given the opportunity to participate (e.g. overnight and at weekends when staff are not available to consent). These women can be identified from ward registers and fetal fibronectin machines. Permission was requested to identify and approach these women when they attend for follow up appointments. This was important because the majority of women with TPTL do not go on to deliver early and excluding those who are discharged quickly may result in an imbalanced sample. 3. Occasionally, participants experienced further episodes of TPTL, and the assessment and test results was recorded in the maternity notes. Permission was requested to capture data from these episodes and to amend the participant information sheet in order to highlight this possibility to the participants. 4. Revised study start and end dates (to 3rd March 2015 to 31st October 2017) due to delays in R&D approval.
No. 2 ***9th Oct 2015*** **Approved:** ***25th Nov 2015***	1. Name of Sponsor's (Lead and Co-sponsor) Representatives changed. 2. Permission requested to change eligibility criteria to allow recruitment of participants who are assessed with either, or both, tests. Current eligibility criteria stipulated that the TPTL assessment must include fFN testing, with or without TVS CL.
No. 3 ***11th July 2016*** **Approved:** ***2nd Nov 2016***	1. New sites added where site specific information (SSI) form was started prior to HRA changes in April 2016 but not completely through approval process. 2. New sites expressing an interest since April 2016. 3. Amendment to Part 2 (qualitative study) interview schedule asking women to consider cards showing different ways of illustrating risk and explain their views on them. This was in order to enable us to develop the risk assessment tool in ways that are most useful from the women's perspective.

	4. Addition of Part 3: QUIPP app users' experience and views - a qualitative study exploring clinicians' use of the QUIPP app and views on illustrations of risk. The first version of the app was by this stage being used in practice in the care of high risk women. Understanding the users' experience and views of the app to date would inform further development.
No. 4 ***7th July 2017*** **Approved:** ***18th Oct 2017***	1. Change to eligibility and extension to end date beyond 31st October 2017. The number of participants with TVS CL measurements over the initial study period was lower than anticipated. This amendment requested permission to continue recruitment of women having both tests for a further three years. The data collected will be used to further strengthen the prediction algorithms used in respect of cervical length measurements in later QUIPP app development. 2. Revision of the PIS and consent form to remove information about the qualitative part of the study which had finished recruitment.

5.5. Study management meetings

As the Chief Investigator, my first supervisor, Rachel Tribe, other academic supervisors and myself, as the study co-ordinator, met at least monthly, to ensure satisfactory progress of the study and timely management of any arising issues, e.g. unanticipated problems with recruitment and data management. Following an initial site initiation visit or teleconference, additional site Principal Investigators and research midwives were invited to contact me if they had any queries or problems.

5.6. Study database and data quality assurance

The KCL Department of Women and Children's Health Preterm Birth Studies database, built by the Swedish company, MedSciNet, was adapted in order to accommodate data collection for the prospective cohort part of this study (Preterm Birth Studies Database, 2018). MedSciNet develops and supports web-based databases for many research organisations, groups and universities throughout the world. Their databases

and web-based applications which allow access to the data are built using the MedSciNet Clinical Trial Framework, a self-contained environment that enables development, hosting, support and management of individual web-based solutions for clinical trials and studies, quality registries, medical biobanks and other required solutions within the field of academic medicine. The databases conform to relevant FDA, NIH and UK and EU data protection regulations.

Authorised users were provided access through individual login names and passwords. Data quality was assured by use of the MedSciNet database data monitoring facility. Data monitors, including myself, and other trained research midwives at GSTfT, regularly reviewed the forms throughout the recruitment period and raised queries if data were missing or appeared erroneous. The site users then checked the data and responded to the query, after which the monitor either accepted the answer and locked the form, or raised another query.

6. Methods 1: Prospective cohort study

6.1. Study Design

A multi-centre prospective cohort study design was chosen as the most appropriate for the collection of data necessary for creating and testing the prediction algorithms for use in the QUIPP app (PETRA Part 1). This design was chosen as it reduced the risk of bias in subject selection as well as outcome interpretation, as the participant is recruited before the outcome is known, i.e. spontaneous onset of labour resulting in preterm birth.

6.2. Setting

During the set up period an outline of the study was emailed to previous research collaborators and members of the UK Preterm Clinical Network (clinicians with an interest in preterm birth). Sites expressing an interest were assessed for suitability, i.e. able to assess pregnant women in threatened preterm labour, including quantitative fFN (qfFN) testing and TVS CL, and with a reasonable expectation of recruiting approximately two participants per week, and/or approximately 200 participants in total. Recruitment commenced on 4th March 2015 at the main site when final governance approvals were in place, with phased introduction of additional sites as local governance approvals were obtained.

6.3. Participants

Pregnant women presenting with symptoms of TPTL, i.e. abdominal pain and/or uterine contractions were approached by myself, and/or other research midwives, when they presented at participating sites with symptoms of threatened preterm labour, either at Antenatal Day Assessment Units (ADU), labour wards or other areas, such as specialist preterm clinics.

When recruitment initially commenced in March 2015, the inclusion criteria stipulated that only women with singleton pregnancies with TPTL assessment that included fFN with or without TVS CL were eligible. Later protocol amendments allowed for inclusion of multiple pregnancies and qfFN or TVS for CL (Section 5.4). Final inclusion and exclusion criteria are detailed below:

6.3.1. Inclusion criteria

- Gestation between 23^{+0} and 34^{+6} weeks.
- Symptoms suggestive of TPTL.
- TPTL assessment includes qfFN and/or TVS for CL.
- Willing and able to give informed consent.

6.3.2. Exclusion criteria

- Definitive diagnosis of labour (i.e. regular painful contractions with cervical change diagnosed on speculum or digital examination).
- Confirmed ruptured membranes (on speculum examination).
- Antepartum haemorrhage.

The above exclusions were justified because: i) the study aimed to improve care where preterm labour is uncertain, rather than confirmed and ii) fFN testing is contraindicated when membranes have ruptured and in the presence of vaginal bleeding, as both liquor and blood can lead to false positive results (Hologic Inc., 2018).

6.4. Clinical assessment and test procedures

TPTL assessment was carried out according to individual sites' local guidelines, but all included an assessment by midwife and/or doctor taking a medical and obstetric history, cardiotocographic (CTG) monitoring, speculum or digital vaginal examination, fFN swab and/or TVS CL. Fetal fibronectin tests were analysed in the clinical area using Hologic Inc.'s Rapid fFN® 10Q System (Hologic Inc., 2018). TVS CL was carried out by qualified clinical staff.

6.5. Screening for eligible participants

Participating sites employed site-specific methods for screening for eligible participants as procedures for registering women with TPTL symptoms varied. At GSTfT, the main site, the procedure was as follows:

The ADU patient register was regularly reviewed, by myself and/or other research midwives, at least daily, for women with potential TPTL symptoms who had arrived and were still waiting to be seen. A message slip (Figure 12) was attached to the front of the women's notes for the clinician to see prior to TPTL assessment to contact

researchers, if they felt it appropriate, so the woman could be approached, informed of the PETRA study and offered TVS for CL measurement.

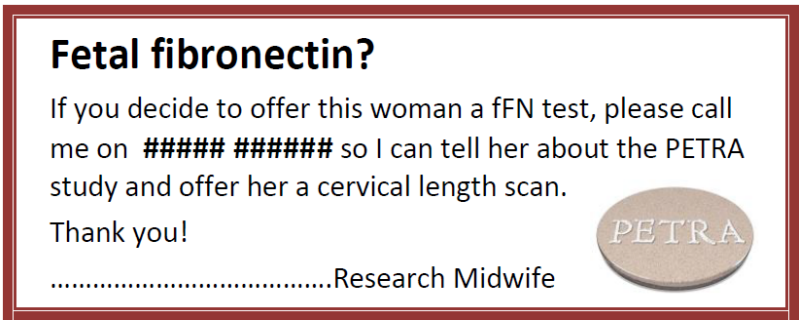


Figure 12. Message slip to highlight potential recruit to clinical staff.

The below sign (Figure 13) was placed next to the Rapid fFN® 10Q analysers in the ADU and Hospital Birth Centre, to encourage clinicians who were about to undertake an fFN test to contact researchers.

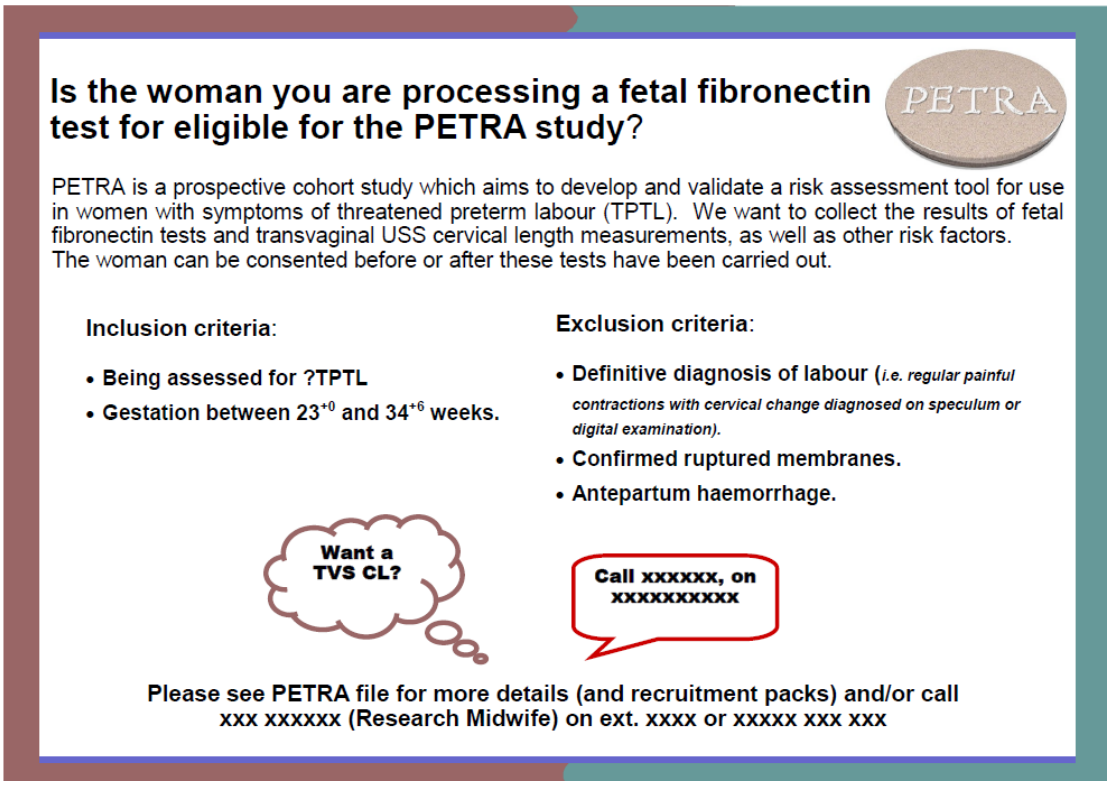


Figure 13. Rapid fFN® 10Q analyser sign to highlight potential recruits to clinical staff.

The number of fFN tests being carried out in the hospital was monitored and it soon became apparent that many women were not being recruited if they presented with symptoms of TPTL outside office hours when researchers were unavailable. A substantial amendment to the protocol (Section 5.4) was, therefore, submitted requesting REC approval to approach eligible women at any time up to delivery of the baby. In order for data to be considered prospectively, rather than retrospectively collected, participant recruitment had to occur prior to the outcome of interest (in this case, gestation at birth). This change to recruitment strategy improved integrity of the study because the majority of women with TPTL do not go on to deliver early and excluding those who are discharged quickly may result in an imbalanced sample. Strategies were therefore developed in order to identify and approach eligible women before their babies were born as well as at the time of TPTL assessment.

A screening log was devised, based on details retrieved from the Rapid fFN® 10Q analysers. This included the date and time of test, hospital number and result. Gestation at time of test was checked by review of the hospital's electronic maternity record (using hospital number). If the gestation was within the eligible range for the study a note of the woman's next hospital appointment and plans were made to meet her in order to confirm eligibility (e.g. appropriate symptoms) and consent, if willing.

If the woman had no appointments arranged, the hospital appointments system was checked weekly until either she had delivered, or three weeks after her expected date of delivery. After this time, it was assumed birth of the baby had occurred, and she

would no longer be eligible, as the outcome data would then be retrospective in nature.

6.6. Sample size

The sample size was determined using data from the symptomatic cohort of the EQUIPP study (Abbott *et al.,* 2013) which investigated the predictive value of fFN in 300 women with symptoms of TPTL. This study was also carried out at GSTfT so the population was comparable to the principal recruitment site for PETRA. The true preterm labour (PTL) rate at 34 weeks' in this cohort was approximately 10%. Combination of symptoms and fFN in the EQUIPP study identified a small higher-risk group with a 50% chance of delivery at less than 34 weeks' and a larger standard risk group with a lower risk of approximately 7%. In undertaking the power calculation for the PETRA study, we anticipated that clinicians would be willing to view women in the lower risk group as closer to the normal (i.e. standard risk) if the true rate of PTL in this group could be demonstrated (with 95% confidence) to be lower than the background rate (i.e. lower than 10% with a best estimate of 6.7%), and concluded that full data on 550 standard risk women and 61 high risk women (total 611 women) in the proposed validation would be sufficient to achieve 80% power in the PETRA study. Allowing for 95% compliance & completion, a recruitment target of 643 women was considered adequate to validate the predictive value of each test (qfFN and CL) with data from an additional 300 to be used as a training set.

FFN testing in TPTL was, and remains, more common than CL measurement in the UK (only 155 of the 300 women in the EQUIPP study had CL measurement). So while qfFN testing was a mandatory requirement for inclusion in this study, all recruiting sites were encouraged to undertake CL measurement if possible, but it was not mandatory. Training initiatives were planned and it was anticipated that, as more clinicians were trained in transvaginal ultrasonography, CL measurement would become increasingly common. It was estimated that of the first 300 participants (weeks 1 to 41), approximately 50% would also have had CL measurement. After this, with raised awareness and increased number of trained clinicians, it was estimated that 90% would have also have CL measurement. To ensure an adequate sample to validate the predictive value of both qfFN and CL a total sample of 1181 participants was set (Table 10).

Table 10. Recruitment target based on estimated cervical length (CL) measurements.

Recruitment week	Total Participants n=	Participants with CL	Comments
1-41	300	150 (50% of total)	TVS training initiatives initiated
42-140	881	793 (90% of total)	Training initiatives ongoing
Total	1181	943	300 training set plus 643 validation set

6.6.1. Feasibility of sample recruitment target.

The overall recruitment target of 1181 represented the total for all sites recruiting over period of 32 months. For the main site the target was 540 participants. This was based on a feasibility calculation using ADU records which indicated that approximately 30-40

women every month between 23^{+0} and 34^{+6} weeks' pregnant presented with symptoms of TPTL. This estimate provided an adequate number of potential participants from which to approach the approximately 25 women per month needed, if 80% agreed to participate. The study was not considered to be particularly onerous for participants as it required only consent to use of clinical data. Experience of previous similar research recruitment, carried out at this hospital, suggested that it would be reasonable to assume that 80% of women approached would consent. It was estimated that if approximately 20 women consent each month (four per week), the local target recruitment (n=540) would be achieved in 32 months (140 weeks). It was planned that the remaining 641 participants would be recruited from additional sites over 29 months (allowing three months from start at main site for local approvals). If three additional sites were ready to commence recruitment by week 14, it was considered reasonable to expect that each site would be able to recruit 214 participants overall (1.7 per week, per site).

6.6.2. Recruitment of participants with cervical length measurement

In order to achieve sufficient recruitment to develop and validate the risk assessment tool with CL, it was estimated that at least 50% of participants would need this measurement in addition to the mandatory qfFN test. Prevalence of CL measurement was monitored, and within 3 months it was clear that the target was not being achieved at the main site (Table 11).

Table 11. Participants with cervical length (CL) measurement in first 3 months of recruitment at main site.

	Participants (n)	with CL
Mar-15	8	3 (38% of total)
Apr-15	27	4 (15% of total)
May-15	44	6 (14% of total)

The study management team concluded that this was likely to be due to a number of factors:

- Clinical staff engagement and referral of potential participants to research teams is slow when a study is new and unfamiliar.
- Cervical length measurements were not routinely performed on women with symptoms of TPTL, even at the main site.
- Ultrasound scanners were not always available even when trained staff are on hand to use them.

In order to address these factors, the following actions were undertaken:

- Efforts were made to increase the profile of the study, through face to face communications and on clinical study days, encouraging ADU staff to call me or the research team if a woman presented with symptoms.
- Clinical staff were encouraged to train in TVS CL (an in-house focused course was developed with support from the ultrasound training department).
- Availability of USS machines was addressed by the purchasing of vaginal probes for the hospital birth centre USS machine and the Medical Ultrasound MSc course machine. These probes were purchased using funds from the Preterm Surveillance Clinic NHS Innovations Challenge Prize fund, which was won by Professor Shennan and his team in 2013.

6.7. Data collection

After participants had provided written consent, data was collected via either paper forms, or entered directly onto the study database (www.medscinet.net/ptbstudies) via electronic case report forms which included:

i. Demographic data: age, ethnicity, postcode (for conversion to indicator of socio-economic index code), height and weight.
ii. Risk factors: previous preterm birth or late miscarriage, history of cervical surgery, history of recurrent urinary tract infections, group B streptococcal infection, bacterial vaginosis recreational drug use, smoking, uterine abnormality, domestic violence.
iii. Obstetric history: year of pregnancy, gestation at delivery, onset of labour, mode of delivery.
iv. Current pregnancy: expected date of delivery, obstetric or medical problems this pregnancy.
v. Current episode: gestation; symptoms, qfFN result, cervical length.
vi. Outcomes: antenatal inpatient nights, steroid administration for fetal lung maturation, tocolytic drug administration for TPTL symptoms, intra-uterine transfer to unit with appropriate level of neonatal care, date of delivery, onset of labour, mode of delivery, neonatal unit admission, neonatal complications.

6.8. Data Monitoring and Cleaning

Data monitoring, as outlined in section 5.6, occurred throughout the study recruitment period. After the recruitment period was complete, on 31st October 2017, and before data were analysed, a number of additional data monitoring checks were performed and sites contacted and asked to make every effort to address shortcomings. These

included: outstanding queries; missing data (e.g. ethnicity, lower super output area (LSOA)); visit outcome (e.g. discharge or admission); antenatal and postnatal nights; eligibility of visits (e.g. within gestational range, appropriate symptoms, test results); correct recording of interventions (e.g. two doses of steroids recorded as one full course); that onset of labour and gestation at delivery matched primary outcome indicator; that if congenital abnormality was recorded whether it was appropriate for exclusion.

6.9. Data analysis

Using SPSS version 23.0 (IBM SPSS Statistics), data were first analysed descriptively in order to explore the characteristics, use of interventions and outcomes of the cohort and also to investigate the predictive value of qfFN and CL by category. The development and validation of the new risk prediction algorithms for use in the QUIPP app was then carried out using enlarged datasets, consisting of new and previously analysed data from earlier studies, as described in section 1.8.3.

6.9.1. Participant characteristics

Participant characteristics, including demographics and risk factors, were explored using descriptive statistics (i.e. frequencies and percentages) and stratified by delivery outcome, sPTB <34 and <37 weeks' gestation. Means and standard deviations (e.g. age and BMI) were compared using independent samples Student's t-tests, while other

categorical variables were compared using Pearson's Chi-squared tests. Differences were considered statistically significant if the p value was ≤0.05.

6.9.2. Prediction of preterm birth by fFN and CL test category

Prior to development of quantitative fFN bedside analyser machines, which now provide exact fFN concentrations ranging from 0 ng/ml to >500 ng/ml, fFN test results were presented as negative or positive, depending on a threshold of 50 ng/ml. Although awareness of the actual fFN concentration is likely to be much more useful than a qualitative result, NICE Preterm Labour guidance still uses the threshold of 50 ng/ml as a basis for recommending or withholding intervention (NICE, 2015). Our group, however, have suggested that using categories of ranges of concentrations, such as <10, 10-49, 50-199, 200-499 and 500 ng/ml or more may be more useful (Abbott *et al.,* 2013). Using data from the whole PETRA cohort, the prediction utility of qfFN by these categories was examined using Kaplan Meier survival analysis. This is a commonly used non-parametric statistical method for predicting the "survival" i.e. whether an event of interest has occurred, in this case spontaneous preterm birth, within certain time points (Goel *et al.,* 2010). A survival curve can be created which allows the reader to visually compare different categories of the test result (as these cannot be measured in the same way as continuous variables). Relative risks for spontaneous PTB at less than 34 and 37 weeks, and within 7 and 14 days of testing were also calculated, using the lowest category, 0-9 ng/ml as the reference category using binomial logistic regression. This method was chosen because the dependent variable (sPTB – yes or no) is dichotomous, whereas in linear regression the

relationship between the independent and dependent variables is assumed to be linear, and it cannot be used with categorical data (qfFN and CL groups).

Cervical length was similarly investigated by categories: <15, 15-24 and 25+ mm. These categories were chosen because literature suggests risk of preterm birth increases with CL measurement of less than 25 mm (Iams *et al*., 1996). Additionally, 25 mm is generally accepted by preterm birth specialists as a threshold under which interventions are indicated (Carter *et al*., 2016) and current NICE guidance recommends withholding treatment for symptomatic women with a CL >15 mm after 30 weeks' gestation (NICE, 2015).

6.9.3. Intervention use in the PETRA cohort

Further objectives of the PETRA study included exploring use of steroids and other management, i.e. admission, tocolysis, IUT, neonatal unit (NNU) admission, in a cohort of women with TPTL symptoms and these were explored by independent sample Student t-tests for comparing means of continuous variables with normal distribution, or Mann Whitney U tests for comparing medians where data are not normally distributed. Non-parametric chi-squared tests were used for comparing categorical data (e.g. whether steroids had been given or not).

The use of steroids was examined in more detail than the other interventions because it was the most prevalent intervention in this cohort, and because of the increasing

concern about its overuse in women with symptoms of threatened preterm labour (Levin *et al*., 2016).

The prevalence of preventative interventions (e.g. cerclage, progesterone) in this cohort was also compared between high and low risk women, and whether they went on to experience spontaneous preterm birth.

6.9.4. Predictive model generation

As explained in section 1.8.3, it was necessary to update the prediction algorithms prior to completion of the PETRA study before the start of the EQUIPTT study. The generation of the prediction models was, therefore, based on data already gathered in PETRA (as at the end of May 2017) along with relevant participant data from earlier studies (EQUIPP REC Ref. 10/H0806/68 and POPPY REC Ref. 09/H0802/97). This pragmatic decision meant the data was not split randomly between "training" and "validation" sets, as is customary, and that there was a time delay of approximately 10 months between model generation (which was tested by calibration before being used in the new version of the QUIPP app) and formal validation using the latest PETRA data.

In total, six prediction algorithms were needed for the new version of the QUIPP app. The algorithm is selected according to whether the woman is asymptomatic high risk or symptomatic (any risk status) and whether her TPTL assessment includes qfFN testing alone, CL measurement alone, or both tests. Data were therefore split and

tested in six groups: i) asymptomatic high risk with fFN test result; ii) asymptomatic high risk with CL measurement; iii) asymptomatic high risk with both test results; iv) symptomatic (any risk status) with fFN test result; v) symptomatic (any risk status) with CL measurement; vi) symptomatic (any risk status) with both test results. Data from women with symptoms were used in three of the six data sets. For the purposes of this thesis, the methodology below relates to development of the three algorithms appropriate for the symptomatic cohorts.

The advanced statistical analysis required for the development and validation of the prediction algorithms was carried out using Stata SE software (version 14.2; StataCorp, College Station, Texas, USA) by the KCL Department of Women and Children's Health statistician, Mr Paul Seed, with support from this PhD candidate who worked closely with him throughout the analyses. As explained above, the "training set" was comprised of PETRA, EQUIPP and POPPY data. Exclusions were made for: incomplete data; invalid visits (out of gestation range, inappropriate symptoms, invalid or missing test results, sexual intercourse within 24 hours) and major fetal abnormality. Women with twin pregnancies were included, using the first twin gestation at delivery, but triplets and higher order multiples were excluded due to inadequate numbers. Women whose labour was induced or had caesarean section following PPROM were regarded as having had spontaneous preterm birth.

Cox's proportional hazards regression was used to determine which predictive risk factors to use in the model. This is a simple, widely used, statistical method that is used to indicate which factors have an effect on outcome (Lin and Wei, 1988). Factors

tested included demographic characteristics (i.e. age, BMI, ethnicity, deprivation score and smoking), risk factors (i.e. previous history of preterm birth or PPROM, late miscarriage, cervical surgery, twin pregnancy) and test results (qfFN and TVS CL).

Simple regression methods were not sophisticated enough for creation of the QUIPP app prediction models because time to delivery after testing has to be very precise, with very smooth survival curves, and therefore parametric survival analysis was used. This process involved testing the data using several different parametric survival analysis functions, namely exponential, gamma, Gompertz, log-logistic, log-normal and Weibull. The different models function differently depending on the statistical distribution of the data and describe the probability of an outcome, in this case sPTB, at any given time point (gestation) between testing and delivery.

When an individual woman had more than one visit for TPTL assessment, later results were introduced as time-updated covariates, i.e. if delivery has not occurred before the next visit, prediction was recalculated with the next visit gestation.

In survival analysis, data are "censored" if the outcome of interest has not occurred during the follow up period (Kleinbaum and Klein, 2010). In this study, the data were censored, if spontaneous preterm birth had not occurred by 37 weeks' gestation. A number of ways were considered for dealing with data from women who experienced iatrogenic preterm birth. The options were: i) to exclude them from the analysis altogether; ii) to censor them at the time of the iatrogenic, i.e. medically indicated, preterm birth and iii) to treat them as non-events and censor them at term. Although

none of the options are perfectly satisfactory, due to the limitations of current statistical methods, option iii) was chosen. This was for a number of reasons: (a) when the data were collected, the outcome was unknown, and this reflects the situation when the app is used for prediction of outcome in future cases; (b) censoring at time of iatrogenic preterm birth would lead to an over-estimation of the number of events and (c) excluding all iatrogenic cases from the analysis would be a *post-hoc* decision which may introduce bias.

Checks were undertaken to determine whether the data needed to be transformed before analysis using fractional polynomials. Fractional polynomial regression compares possible power transformations (here powers -3, -2, -1 -0.5 0 (log transformed), 0.5, 1 (unchanged or identity transformation), 2, 3) of a continuous predictor, to see which fits best with, and in particular whether any of them is better than power 1. The entire procedure was repeated for each of the three datasets of symptomatic women, and different models produced in each case.

The best model to use with this data was then determined by reference to Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). This is a method developed for comparing non-nested regression models where significance tests are not available (Royston and Sauerbrei, 2008). When comparing models, the lowest values are considered to have the best fit to the data.

Before formal validation could be undertaken after completion of the PETRA study, the prediction models were tested by simple calibration. This meant comparing individual

tests of clinically significant groups to confirm the actual event rates were consistent with the predicted probability of the event. A 5% prediction rate for spontaneous preterm birth within 7 days of testing was used as the threshold because this was the lowest value of a range of 5-15% that our TPTL Delphi consensus survey suggested should be recommended for intervention (Carter *et al.,* 2016). The calibration tests provided reassurance that the models were acceptable to proceed with development of the QUIPP app before formal validation was undertaken.

6.9.5. Predictive model validation

As explained in section 1.8.3, the "validation set" comprised the remainder of PETRA participants whose data had not be used for the model development and where outcome data had been gathered after the end of May 2017.

Predictive statistics, including sensitivity, specificity, balanced accuracy [(sens.+spec.)/2], likelihood ratios, positive (PPV) and negative predictive values (NPV) and separation probabilities (PPV+NPV-100%) were calculated using a % risk of ≥5% as an indication of a positive test. This cut off was chosen because, as stated above, it is the lower end of a 5-15% range above which clinicians would recommend intervention (Carter *et al.,* 2016). Results are presented in tables with statistics for both the training and validation sets, by test group (fFN, CL and fFN+CL) for prediction of spontaneous preterm birth at less than 30, 34 and 37 weeks' gestation, and within 7 and 14 days post-test. These time points were chosen because: i) the gestations at delivery are clinically important indicators for likely neonatal morbidity and ii) they are useful in guiding appropriate management, such as the timing of steroids. Receiver operating

characteristic (ROC) curves were drawn and areas under the curve (AUC) were calculated. The ROC curve is a graphical plot which demonstrates the diagnostic ability of a test by showing the true positive rate (sensitivity) over the false positive rate (100-specificity). The AUC indicates how accurate the diagnostic test is, with 1.0 representing a perfect test, with no false positives or false negatives, and 0.5 being a worthless test. Receiver Operating Characteristic (ROC) curves are particularly appropriate for evaluating the predictive ability of the QUIPP app because they demonstrate the predictive ability of a test at different thresholds (in this case % risk of sPTB) rather than using a threshold under which a result is negative, and over which a result is positive.

In addition to development of the risk assessment tool, which was a primary aim of the PETRA study, further objectives included exploring the added value of CL in a UK setting. This was investigated by the production of ROC curves and comparing AUCs of the prediction models using fFN alone, CL alone and both tests in the cohort of women who had had both tests.

7. Methods 2: QUIPP app users and Women's experience and views qualitative studies

The two qualitative studies explored i) current QUIPP app users' experience and views and ii) women's experiences of risk assessment and management of threatened preterm labour, perception of risk and the factors that influence decision making. The same methods were employed for both qualitative studies and are thus addressed together in this chapter.

7.1. Introduction to chapter

The overall aim of this research project was to improve the management and experience of women with symptoms of TPTL, which included addressing the emotional burden associated with being at risk of PTB. In the cohort study (Part 1) data were collected for the development of an algorithm that would be used in a risk assessment tool for assessing the individual likelihood of preterm birth. As described in section 1.8.2, the first version of the QUIPP app had been released just prior to the recruitment phase of the PETRA project (January 2015) and clinicians assessing preterm birth risk in asymptomatic high risk women started to use it in practice. After its use had become established, the opportunity was taken to explore the experiences and views of current users, how it was used in practice, and identify potential enhancements to its utility, for example, alternative and visual methods of illustrating individual risk. An addition to the PETRA protocol was approved by the REC as detailed in section 5.4. In the women's experience study, I aimed to explore

the experience of women with TPTL symptoms, their views on the care they received and the aspects they believed could be improved. A proportion of women were also asked to consider, comment and express preferences on a series of visual risk illustrations in order to inform development of the risk assessment tool. This chapter gives a detailed account of the methods and qualitative methodology utilized in undertaking both qualitative parts of the study.

> *"Qualitative research is a generic term that refers to group of methods and ways of collecting and analysing data that are distinctly different from quantitative methods because of the absence of quantification and statistical analysis." (Smith et al., 2011, p.3).*

Qualitative methods are based on an ontology, that is, an understanding of being, that holds that human experiences are subjective and both the subject and the researcher will be influenced by their background, culture and experience. Quantitative methods, that seek to measure a phenomenon using objective measures, are therefore not appropriate in these parts of the study.

7.2. Selecting a theoretical perspective

From the vast choice of theoretical perspectives available, the qualitative researcher must select the most appropriate for their particular study and be confident that the chosen methodology gives the best chance to both answer the research question and that the robustness of its findings can be soundly evaluated. Within qualitative

research, many different philosophies and theoretical frameworks have been developed over recent decades. Examples of these are Phenomenology (Husserl, 1982), Grounded Theory (Strauss and Corbin, 1994) and Narrative Analysis (Riessmann, 1993). Each have their place in the "paradigm" of qualitative research, and come with their own rules and structures which guide the researcher. As Reeves *et al.,* (2008) explain:

> *"Theories give researchers different 'lenses' through which to look at complicated problems and social issues, focusing their attention on different aspects of the data and providing a framework within which to conduct their analysis." (p.631).*

Some have argued, however, that being restricted to a particular theoretical perspective can constrict the researcher and possibly even lead to the findings being made to "fit" rather than truly speak for themselves. Sandelowski (2000) suggests that researchers using strict theoretical frameworks may be "obliged to put much more of their own interpretive spin on what they see and hear…" and that "…This spin derives, in part, from these methodologies themselves." (p.336).

Some commentators argue that, particularly in healthcare research, simpler approaches can be used legitimately and to good affect (Milne and Oberle, 2005; Neergaard *et al.,* 2009; Sandelowski 2000; Smith *et al.,* 2011). Neergaard *et al.,* (2009) describes one such approach, Qualitative Description, as allowing for "a rich, straight description of an experience or an event…" and proposes that it is "…founded in

existing knowledge, thoughtful linkages to the work of others in the field and clinical experience of the research group." (p.2).

The aims of the qualitative parts of this study were to not to investigate phenomena where very little is known, nor the development of explanatory theories. A Qualitative Description methodology was selected for both, utilizing thematic analysis and Ritchie and Spencer's Framework Approach (Richie and Spencer, 1994). The QUIPP app users study was a simple exploration of clinicians' experience of using the tool. In the women's experience study, the consequences of preterm birth are well known and therefore women experiencing symptoms of TPTL are likely to be anxious. Therefore, the aim was to gain a deeper understanding of women's experience and also to identify specific aspects of their care that had an effect on that experience, particularly those with negative effects that could be modified.

7.3. Qualitative Description and thematic analysis

Milne and Oberle (2005) describe "Qualitative Description" as "…a stand-alone method that affords a comprehensive summary of human experience without an in-depth level of interpretation. The goal is to stay close to the surface of data while capturing all the elements of that experience" (p.413).

Neergaard *et al.,* (2009) suggests that Qualitative Description is particularly useful in mixed methods healthcare research where gaining "first-hand knowledge of patients', relatives' or professionals' experience with a particular topic" is the goal (p.5). They

also explain that Qualitative Description can be influenced by and have "overtones" of other theoretical perspectives. They consider this both acceptable and preferable to trying to fit the whole study into a theoretical framework which is not entirely suitable (Neergaard *et al.,* 2009). In the women's experience study, I suggest two overtones that influenced my perspective: i) phenomenological, because the "lived experience" of the participants, a concept in phenomenology, was being explored, and ii) feminist, because I intended to listen for hints that women may be feeling pressured into accepting treatments they were not entirely happy with and if there remained any remnants of a medical model of childbirth that was so prevalent in the 1970s and 80s.

Miles and Huberman (1994) describe six analytical strategies in Qualitative Description:

a. Coding of data from notes, observations or interviews.

b. Recording insights and reflections on the data.

c. Sorting through the data to identify similar phrases, patterns, themes, sequences and important features.

d. Looking for commonalities and differences among the data and extracting them for further consideration and analysis.

e. Gradually deciding on a small group or generalizations that hold true for the data.

f. Examining these generalizations in the light of existing knowledge.

This is very similar to straightforward thematic analysis which, according to Braun and Clark (2006), should be considered an analytical tool in its own right and which, "through its theoretical freedom…provides a flexible and useful research tool, which can potentially provide a rich and detailed, yet complex, account of data" (p.78). They go on to define it as "… a method for identifying, analysing and reporting patterns

(themes) within data." (Braun and Clarke, 2006, p.79). The phases of thematic analysis, and their descriptions are listed in Table 12:

Table 12. Phases of thematic analysis (from Braun and Clarke, 2006, p.87).

Phase	Description of the process
1. Familiarizing yourself with your data.	Transcribing data (if necessary), reading and re-reading the data, noting down initial ideas.
2. Generating initial codes.	Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code.
3. Searching for themes.	Collating codes into potential themes, gathering all data relevant to each potential theme.
4. Reviewing themes.	Checking if the themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic 'map' of the analysis.
5. Defining and naming themes.	Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.
6. Producing the report.	The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.

In order to provide further structure and elements that are considered to add to the research rigour, a decision was made to also utilise the Framework Approach for data analysis (Ritchie and Spencer, 1994). This method will be discussed in more detail in the Data Analysis section, below.

7.1. Study procedures – QUIPP app users study

Current users of the QUIPP app were invited to participate and were identified through the UK Preterm Clinical Network, which is a network of clinicians with an interest in preterm birth clinical care and research. Data were collected through semi-structured, one-to-one interviews, in person and by telephone during March and April 2017.

Following informed consent, participants were asked by the researcher, using a pre-determined interview schedule (Appendix 17.4), to talk about their experience and views of the QUIPP app. Participants were asked specific questions about what they considered to be positive attributes of the QUIPP app, as well as what they saw as its limitations, and how they thought the app could be improved. At the end of the interview they were asked to consider a number of visual illustrations of risk (Figure 14) and encouraged to discuss how they felt about each one and which they would find most useful if it was included in the next revision of the app. Interviews were audio recorded, data were transcribed verbatim and managed using NVivo software.

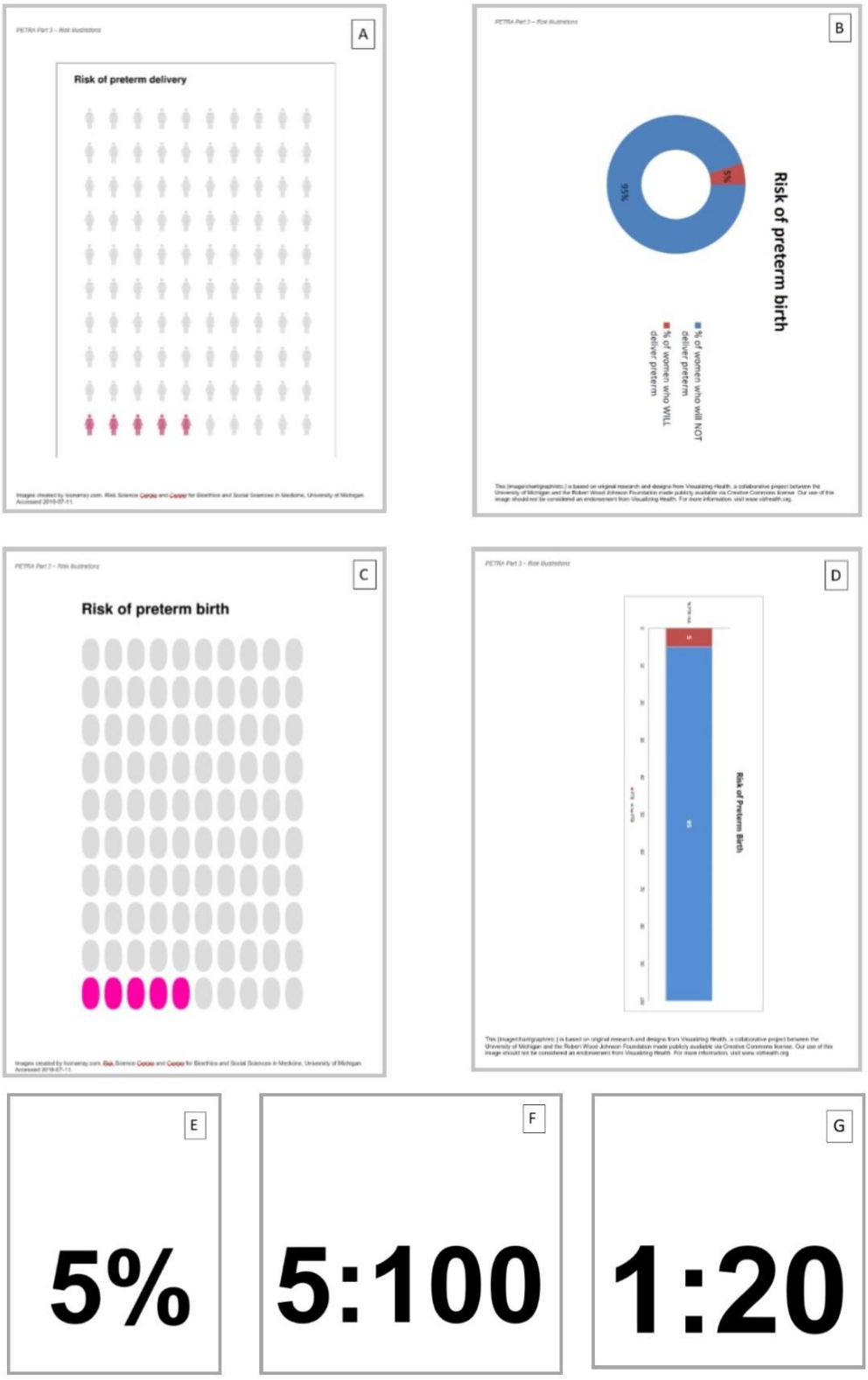


Figure 14. Visual illustrations of risk used in QUIPP app users and Women's experience qualitative studies.

7.2. Study procedures – Women's experience study

7.2.1. Participant selection and recruitment

A number of cohort study participants, who had indicated on the PETRA Part 1 consent form they were willing to be contacted, were invited to participate in the women's experience study. Willing participants were given written information to consider before an interview was arranged. In an effort to capture the experience of a wide variety of women, a purposive sampling strategy was used. Sample size was determined using maximum variation sampling (Patton, 2005) in order to explore the experiences of women with different backgrounds (e.g. ethnicity, parity), risk factors (e.g. no known risk factors, previous preterm birth) and interventions (e.g. discharge, hospitalisation). Required sample size was estimated to be 20-30 (Bourgeault *et al*., 2010), however, no new themes appeared to be emerging after 19 interviews, so data saturation was considered to have been achieved and no further interviews were carried out.

7.2.2. Setting

Participants received care at a large inner city teaching hospital which provides a specialist service for women at risk of preterm birth. The team, led by an internationally renowned expert in the field, offers clinical care through their preterm surveillance clinic and provides information and advice for both women and clinicians, locally and nationally.

7.2.3. Data collection

Data were collected through semi-structured, one-to-one interviews which were carried out by myself between March 2015 and January 2017. Following the taking of written informed consent, participants were asked to talk about their experience and views on their care and any interventions they may have received. Interviews took place in a private room in the hospital or at home, at a time convenient to the participant as soon as possible after the initial assessment for TPTL, in order to reduce the chance of recall bias. The interviews lasted approximately one hour and were recorded, with participants' consent, on digital audio equipment. The interviews were then transcribed, by myself and a professional transcriber, and prepared for analysis.

As discussed in Section 1.7, the ways people perceive risk can be substantially different. The ongoing PETRA study provided the opportunity to discuss different visual illustrations of risk with women who had experienced threatened preterm labour and to explore their views. The findings were then used to inform development of the second version of the QUIPP app. An amendment to the interview schedule of the ongoing qualitative study was submitted in order to capture the women's views on proposed illustrations. All women interviewed following REC approval of the amendment, as outlined in Section 5.4, (n=10) were asked to consider a selection of cards showing different ways of visually illustrating risk (Figure 14) and to elaborate on their views and preferences.

7.2.4. Interview schedule

The interview schedule (Appendix 17.4) was designed following literature review, consultation with clinical colleagues and in collaboration with the local preterm birth studies PPI panel. A second version of the interview schedule which included extra questions about visual illustrations of risk was used following Research Ethics Committee amendment approval (Section 5.4).

7.3. Data analysis

Alongside the Qualitative Description method, the Framework Approach (Ritchie and Spencer, 1994) was used for data analysis. This approach was developed by researchers at the National Centre for Social Research as a method to manage and analyse qualitative data in policy research where aims are highly focused and topic guides structured to allow for exploration of specific *a priori* issues. (Smith and Firth, 2011). Although similar to thematic analysis, Framework allows the researcher to easily explore the data by theme or by case and guides the researcher through a transparent, systematic process which enhances rigour and therefore the credibility of the findings (Smith and Firth, 2011). The key features of the Framework Approach are that it is:

i) *Grounded or generative*: it should be heavily based in, and driven by, the original accounts and observations of the participants.
ii) *Dynamic*: it is open to addition and amendment throughout.
iii) *Systematic*: allowing methodical treatment of all similar units of analysis.
iv) *Comprehensive*: allowing full review of the material.

v) *Enables easy retrieval* and access to the original material.

vi) *Allows between and within case analysis*: enabling comparisons and associations to be made.

vii) *Accessible to others*: so that the analytic process, and the resulting interpretations, can be viewed and evaluated by others.

Framework shares a similar approach to thematic data analysis, with five key stages, which are:

1) *Familiarisation of the data*: where the researcher listens to the interview recordings and reads and re-reads the transcripts.
2) *Identification of a thematic framework*: which can be drawn from *a priori* issues drawn from the research aims, new issues raised by the participants' testimonies or analytic themes arising from patterns of issues identified as the analysis progresses.
3) *Indexing*: (or coding) of the data.
4) *Charting*: where codes are organised into categories and themes.
5) *Mapping and interpretation*: where cases, categories and themes are considered in relation to each other and the researcher attempts to bring the key characteristics of the data together and interpret the data set as a whole.

Analysis of the data collected for the qualitative parts of this study followed these stages. As soon as possible after the interviews had been carried out and transcribed, I listened and re-listened to the recordings whilst reading through the transcripts. I used NVivo qualitative data management software (version Pro.v11) and before reviewing each interview I created a memo for each participant, where I documented participant characteristics, my thoughts and reflections on the interview itself, where it

had occurred, how long it had taken, how I perceived the participant had felt during the interview and any initial ideas and thoughts I had about emerging themes.

I began coding the data and although I had an initial structure based on the elements of the interview schedule, the number of codes continued to expand at a considerable pace. I created a "code book" where I listed and defined the meaning, as I interpreted it, and regularly reviewed the coding structure as it developed. This code book was revised on several occasions as I started to organise the codes into categories and then the categories into themes.

Throughout the process I also kept a research journal, where I documented my thoughts on emerging themes, relationships between cases, how issues I saw in the data related to the literature I had read on relevant topics, and where I felt issues were missing or not being discussed by the participants as much as I had expected. I also reflected on how my experience as a midwife, and one that had worked with women at risk of preterm birth for several years, may be influencing my interpretation of the data.

7.4. Demonstrating study rigour

To demonstrate study rigour, a framework proposed by Whittemore *et al*. (2001) for ensuring rigour in generic qualitative studies was chosen. This framework consists of four elements, and are described by Milne and Oberle (2005, p.414) as:

(1) Authenticity, or attention to the voices of participants.
(2) Credibility, a reflection of how believable results are.

(3) Criticality, the critical appraisal of every decision made throughout the research process.
(4) Integrity, demonstrated by on-going reflection and self-criticality of the researcher.

The rigour of this study is demonstrated in the following sections that pair: Authenticity and Credibility, and Criticality and Integrity, as suggested by Milne and Oberle (2005):

> *"The credibility of a qualitative study is a factor of strategies to promote authenticity, the ability to remain true to the phenomenon under study, while the integrity is a reflection of its criticality, or the attention paid to each and every research-related decision." (p.414).*

7.4.1. Authenticity and Credibility

A starting point for evaluating the authenticity and credibility of a qualitative study's findings is whether, and to what extent, the research question has been answered. In the qualitative parts of this study, the aim was to explore clinicians' experience of the first version of QUIPP and women's experience of TPTL and the factors that affected that experience. In order to answer the research questions, then, it was important to explore the experience of a variety of enough clinicians and women with different experiences and backgrounds, to allow them to speak freely and comprehensively about their experience, and to ensure that the process of analysing the data represented these experiences accurately.

It was important to first recruit an appropriate and varied selection of participants who had had the experience in question. The purposive, maximum variation sampling strategy allowed for a constant review of participant characteristics, including parity, ethnicity and preterm birth risk, which ensured that the final participant group consisted of women with a variety of backgrounds and experience. The semi-structured interview method and interview schedule allowed participants to talk freely, and the women to reflect and talk, in their own words, while keeping focused on the TPTL experience. The use of probing, for clarity and depth, ensured that the recounting of the experience was as complete as possible. In terms of whether enough participants were recruited, it is customary in qualitative research that data collection continues until no new themes appear to be emerging from the data, a phenomenon commonly known as "data saturation". Whether this can ever truly occur, however, is open to debate. As Milne and Oberle (2005) point out:

> *"Theoretical saturation means that a qualitative sample may be considered adequate when data inform existing findings but do not add anything new to them. True saturation, however, may be a myth in that a second interview with the same participants could yield new information." (p.415)*

So, whilst accepting that true "saturation" may be impossible, in this study it became obvious, after ten QUIPP app users and nineteen women had been interviewed, that the main issues important to participants had been identified.

Ensuring that participants' perspectives are accurately represented in the analysis is more difficult, but use of a systematic method of data management and analysis, and

reporting of the steps taken, can make evaluation easier and adds credibility to the findings.

The analysis process begins with the transcribing of the interviews *verbatim*. In this study, while for most cases, this was carried out by a professional transcriber, I listened to the recordings and read through the transcripts as soon as they were available, checking them for accuracy, dealing with errors and omissions, if my memory was certain, in any areas of text where the recording had been unclear to the transcriber. Because I had taken field notes and recorded memos about the interviews, I was able to maintain a sense of context and relate the actual words spoken by the participants to feelings and unspoken language not always apparent in the written transcripts or even the sound recordings.

Another factor that contributes to the credibility of the study is the credibility of the researcher, and how capable they are of carrying out a study and producing a report of quality. Although a novice qualitative researcher, this being my first qualitative study, I have been fortunate to have had the opportunity to undertake high quality training in qualitative methods, organised not just by KCL (Advanced Qualitative Methods, Spring 2015; Qualitative Data Analysis, Summer 2016; Introduction to NVivo workshop); but also the National Centre for Social Research (NatCen) (Depth Interview Skills, May 2015; Introduction of Framework in NVivo, Nov 2015); the University of Surrey (2 day NVivo workshop, Jan 2016) and Social Research Association (SRA) (Reporting Qualitative Data, Dec 2017).

7.4.2. Criticality and Integrity

The authenticity and credibility of a qualitative study are also dependent on integrity, which can only be evaluated, let alone established, if there is evidence of constant critical appraisal of every aspect of the study. It is particularly important that consideration is given to how the researcher themselves may influence both what the participant says, as well as how it is interpreted. This is often described, in qualitative research, as reflexivity, which can be defined as:

> *"…thoughtful, conscious self-awareness. Reflexive analysis in research encompasses continual evaluation of subjective responses, intersubjective dynamics, and the research process itself. It involves a shift in our understanding of data collection from something objective that is accomplished through detached scrutiny of "what I know and how I know it" to recognizing how we actively construct our knowledge." (Finlay, 2002, p.532).*

Being a midwife, with experience of working with women at risk of preterm birth, may have been an advantage and contributed to accuracy of the interpretation. However, in other ways, preconceived ideas and understanding may have influenced my understanding of the women's experience and led to bias in the analysis. I was aware of this possibility from the beginning and endeavoured to minimize this by constantly questioning myself as to whether I was truly representing the voices of women or merely reporting what I expected to hear.

Another method of ensuring integrity, as well as accuracy, in qualitative data collection is to feedback to the research participant and ask them to confirm, or refute, whether what they see in the report is a true representation of their experience. This is difficult, however once the data has been synthesised as the participant may not recognise their own individual experience. Additionally, later understanding of their experience may be affected by recall bias and may differ after further reflection, time and, indeed, the outcome of their pregnancy. In this study, attempts to confirm that data collection reflected the true experience were made at the end of every interview, when the researcher summarised the issues raised and asked the participant to confirm whether the summary was correct and whether there was anything else they wanted to add.

Peer review is also an important part of establishing integrity in qualitative research. A proportion of transcripts, and identification and development of categories and themes, were regularly reviewed by, and discussed with, an academic supervisor. Interim findings were periodically presented at meetings of the preterm birth studies PPI panel, which comprised of women with experience of TPTL and preterm birth. Panel members were asked to reflect on the findings and their feedback was taken into consideration in further development of the thematic structure and final analysis.

8. Results 1: Prospective cohort study

8.1. Recruitment over time

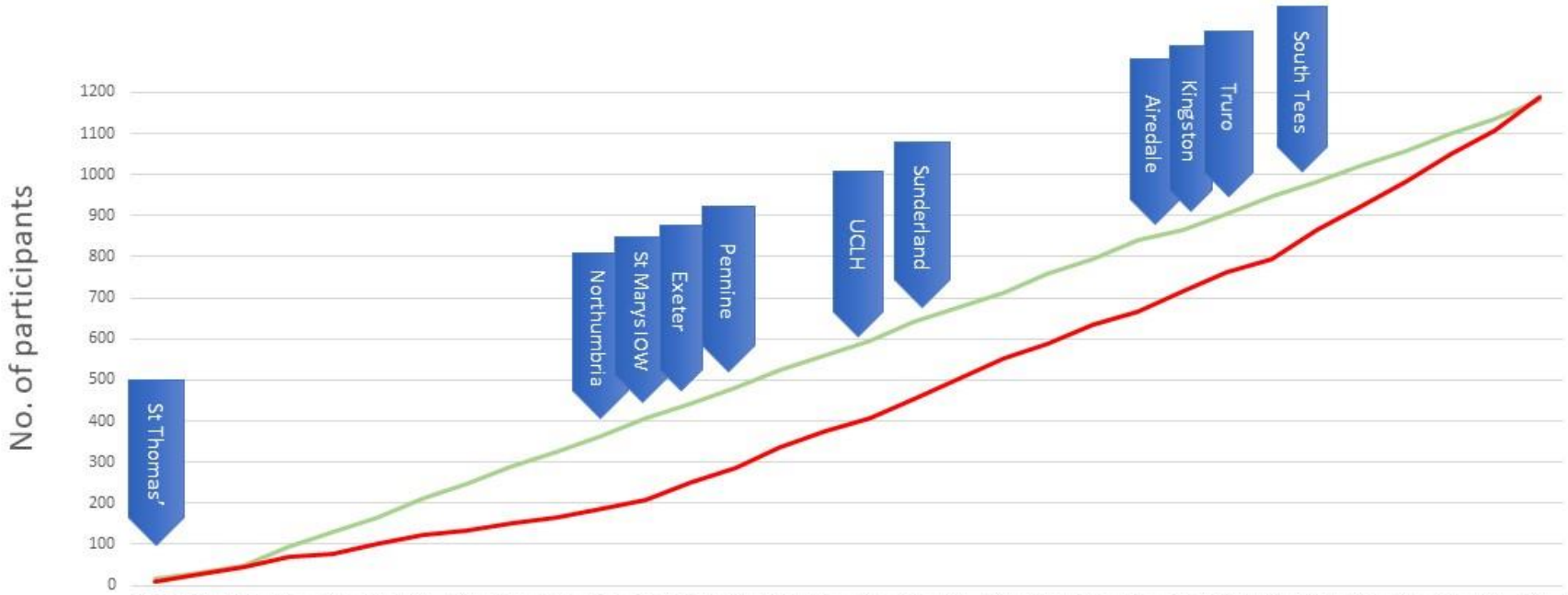
Recruitment commenced at the main site, GSTfT, in March 2015. Delays with local governance approvals meant additional sites were unable to start until 10 months later, which resulted in monthly recruitment targets being missed. Despite these delays, however, recruitment rates improved and final target was met, on time, at end of October 2017. Figure 15 shows recruitment compared to monthly target along with indicators when new sites commenced recruitment.

8.2. Recruitment by site

By the end of cohort study recruitment, 11 sites were participating. Table 13 shows start dates and total recruitment for each site.

Table 13. PETRA cohort study recruitment numbers and percentages by site with start dates.

NHS Trust	Site name	Start date	n=	%
Guy's & St Thomas'	**St Thomas'**	04/03/2015	560	47
Northumbria Healthcare	**Northumbria**	11/01/2016	17	1
Isle of Wight	**St Mary's, IOW**	08/02/2016	55	5
Royal Devon & Exeter	**Exeter**	09/02/2016	16	1
Pennine Acute Hospitals	**Pennine**	19/02/2016	215	18
University College London Hospital	**UCLH**	01/07/2016	174	15
City Hospitals Sunderland	**Sunderland**	31/08/2016	63	5
Airedale NHS Foundation Trust	**Airedale**	10/02/2017	37	3
Kingston Hospital	**Kingston**	15/02/2017	21	2
Royal Cornwall Hospital	**Truro**	17/02/2017	9	1
South Tees Hospitals	**South Tees**	05/05/2017	19	2
			1186	100



	Mar-15	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17
Recruitment target	16	32	48	93	129	165	210	246	291	327	363	408	444	480	525	561	597	642	678	714	759	795	840	867	903	948	984	1020	1056	1101	1137	1182
Recruitment to date	8	27	44	69	78	102	122	135	152	167	188	208	251	286	337	376	406	454	503	553	590	633	667	717	761	795	867	923	984	1050	1107	1187

Figure 15. PETRA study recruitment numbers (red line) plotted against target recruitment (green line) and month additional sites started. Monthly recruitment and target numbers shown in table below graph.

8.3. Final recruitment process and numbers

. As explained in Section 6.5, each site devised its own screening strategy. Figure 16 shows flow of potential participants at St Thomas' only.

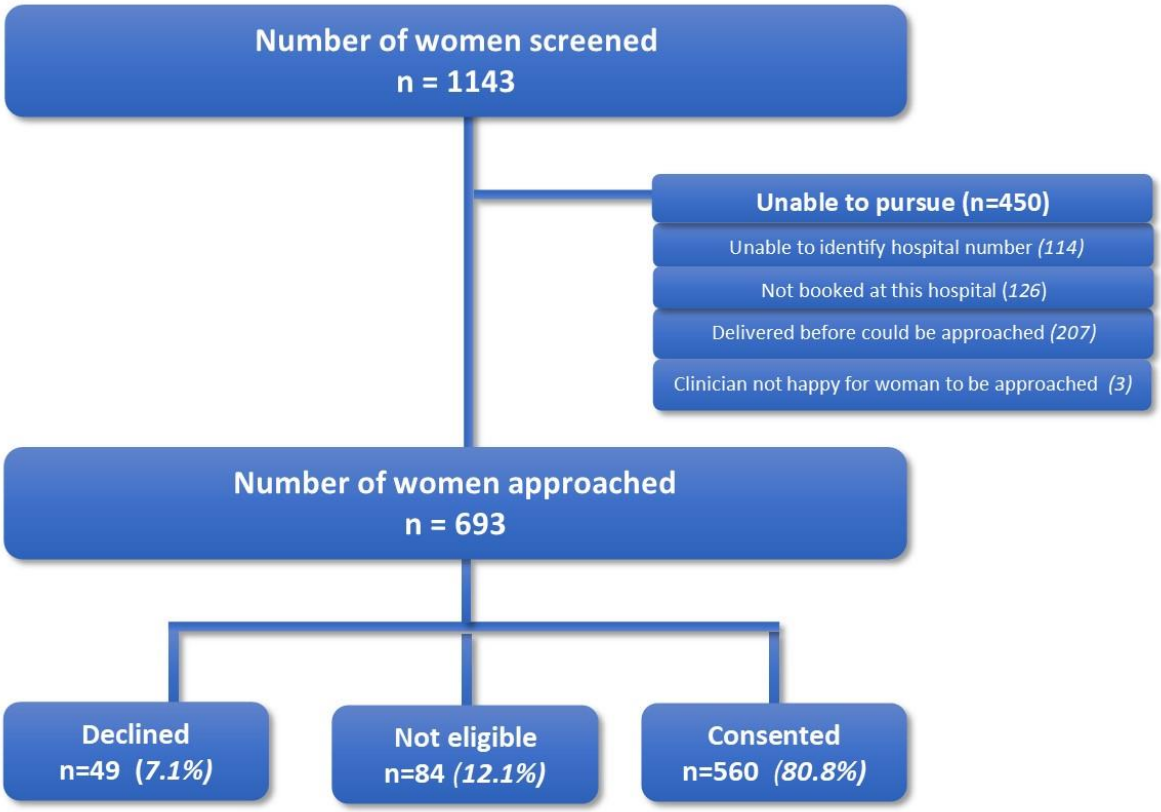


Figure 16. Flow chart showing number of women screened and approached at main site, St Thomas', with outcome of approach.

Of the 1143 women who were screened for eligibility, it was not possible to pursue 450 for consent. When women were discharged before they could be recruited, hospital records were checked for further opportunities to approach them (i.e. further antenatal hospital appointments) an average of 7.9 times (range 1-17). The number of times depended on gestation at testing and delivery. For example, if a woman was 34^{+6} weeks pregnant at testing, and delivered at 38 weeks, records were checked 3 times.

Despite these efforts, 207 women delivered before they could be approached. Other reasons why potential participants were not approached are shown in Table 14.

Table 14. Number of women screened at main site with reasons for non-recruitment.

Number of women screened at St Thomas'		
	n	**%**
Unable to identify hospital number	114	10.0%
Not booked at this hospital	126	11.1%
Delivered before could be approached	207	18.2%
Clinician was not happy for the woman to be approached	3	0.3%
Total number of women approached	693	60.8%
TOTAL	1143	100%

Of the 693 women who were approached, 560 (80.8%) consented, 49 (7.1%) declined and 84 (12.1%) were subsequently deemed ineligible. Of the 84 ineligible women: 13 had had inappropriate symptoms; 16 were unable to understand English sufficiently; five were outside the gestation range (where it had not been previously confirmed) and two were subsequently diagnosed with spontaneous ruptured membranes. In addition, one woman was ineligible because she had been diagnosed with established, rather than threatened, preterm labour, one was under 18 years old, one was planning to move outside the UK for delivery and one had learning disabilities and her ability to give informed consent was unclear.

Of those who declined (n=49), 34 women did not provide a reason, eight had concerns about confidentiality, three were too busy or too stressed, three "just didn't want to do research" and one declined because her husband did not want her to take part.

8.4. Participants

The full dataset including participants from all sites, was finalised after exclusions, as shown in Figure 17. Participants were excluded if: i) they did not have at least one valid visit (i.e. no qfFN or CL test or inappropriate symptoms); ii) they had reported sexual intercourse within 24 hours of qfFN test (as this is known to interfere with fFN test results); iii) their pregnancy outcome was unknown; iv) their baby was found to have a major congenital abnormality that may have affected their risk of preterm birth (as listed in Table 15) or v) they had an iatrogenic preterm birth (e.g. for preeclampsia or other clinical indication for terminating the pregnancy preterm).

Table 15. Participants excluded for major fetal congenital abnormality with details of abnormality.

Participant	Major congenital abnormality details
A	Absent cavum septum pellucidum, possible mild facial dismorphism and mild dolichocephaly
B	Congenital diaphragmatic hernia
C	Congenital heart disease (double outlet right ventricle, VSD and coarctation of the aorta).
D	Congenital malformation of lung, respiratory system, patent ductus arteriosis, patent formen ovale, renal dysplasia congenital scoliosis, talipes equinovarus
E	Congenital malformations of trachea
F	Costello syndrome (Dysmorphology) - SVT; Ventriculomegaly -Macroglossia
G	Downs Syndrome
H	Exomphalos minor, absent corpus callosum, bilateral diaphragmatic hernia with small lung. Suspect Donnai Barrow Syndrome
I	Gastroschisis
J	Gastroschisis
K	Imperforate anus, congenital absence atresia/stenosis anus with fistula
L	Mitochondrial cytopathy with associated muscular hypotonia
M	Trachea oesophageal fistula
N	Trisomy 21
O	Ventriculomegaly - congenital, Patent Forman Ovale (PFO), Toxoplasmosis - congenital,

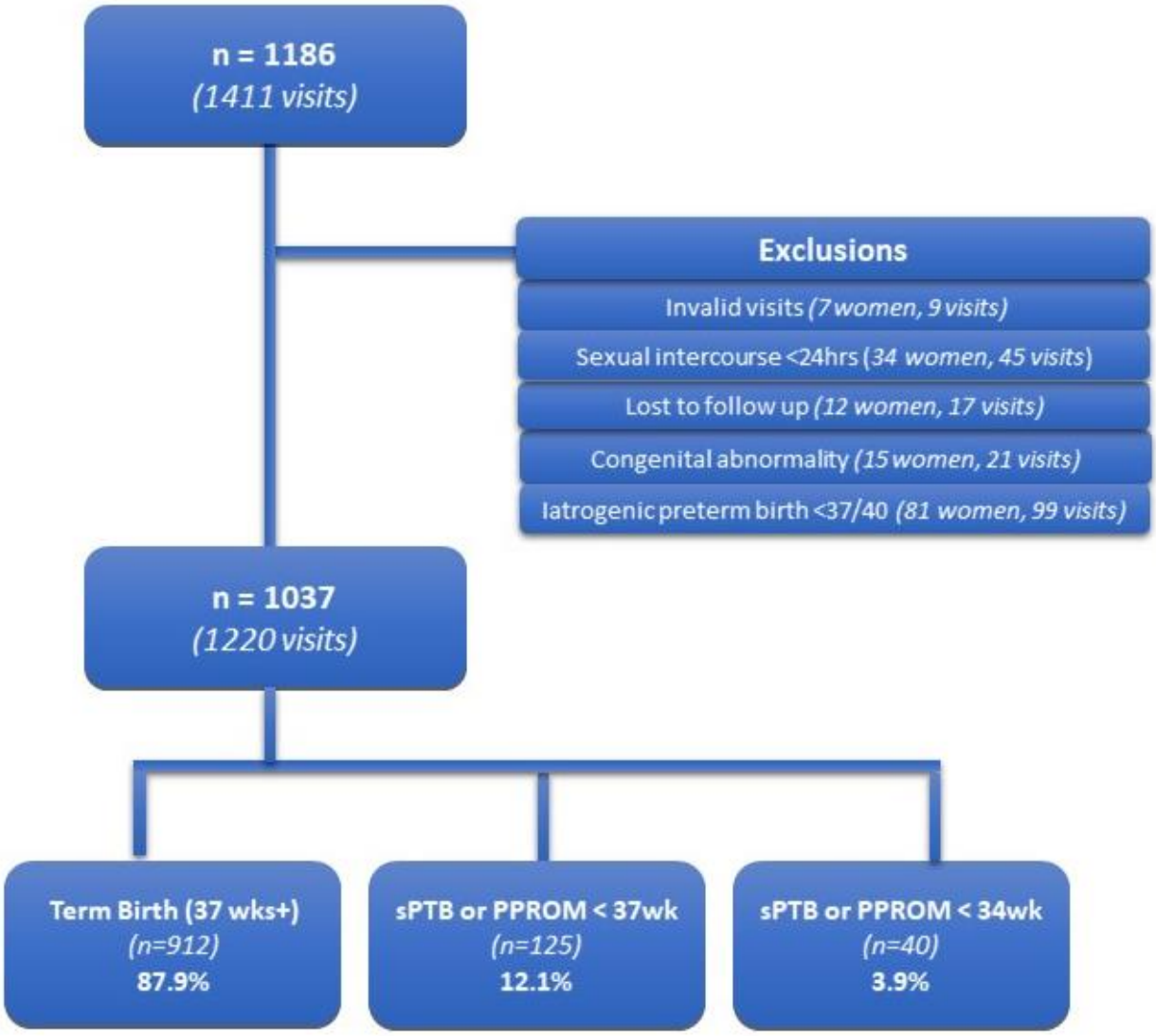


Figure 17. PETRA cohort study flow chart showing recruitment, exclusions and gestation outcomes.

8.4.1. Participant characteristics – demographics

Participant demographic characteristics are reported in Tables 16 and 17, below, stratified by the primary outcome, spontaneous onset of labour or premature rupture of membranes leading to preterm birth (sPTB), at less than 37 and 34 weeks respectively. There were no neonatal deaths in any group.

Table 16. Comparison of participant demographic characteristics by birth at term and spontaneous preterm birth (sPTB) < 37 weeks' gestation.

	Term birth	sPTB < 37 weeks	p value	All
n (%)	**912** ***(87.9)***	**125** ***(12.1)***		**1037** ***(100)***
Age – mean (SD)	30.7 *(5.7)*	30.3 *(5.6)*	0.683[a]	30.1 *(5.7)*
BMI (kg/m2) – mean (SD)	26.2 *(6.0)*	25.7 *(4.8)*	0.336[a]	26.2 *(5.9)*
n (%)	**849** ***(88.0%)***	**116** ***(12.0%)***		**965** ***(100%)***
IMD deprivation score – mean (SD)†	31.2 *(14.7)*	30.7 *(15.8)*	0.706[a]	31.1 *(14.8)*
Ethnicity	n ***(% within group)***	n ***(% within group)***	0.243[b]	**n** ***(% within cohort)***
European	544 *(87.3)*	79 *(12.7)*		623 *(60.1)*
African or Caribbean	200 *(88.9)*	25 *(11.1)*		225 *(21.7)*
Asian (India/Pakistan/Bangladesh)	59 *(83.1)*	12 *(16.9)*		71 *(6.8)*
Other (incl. Chinese)	109 *(92.4)*	9 *(12.1)*		118 *(11.4)*

SD=standard deviation; BMI=Body Mass Index; IMD=Index of Multiple Deprivation.

†some values missing

[a] Independent samples t-test.

[b] Pearson Chi-Square Asymptotic Significance (2-sided).

Table 17. Comparison of participant demographic characteristics by birth after 34 weeks and spontaneous preterm birth (sPTB) <34 weeks' gestation.

	Birth >34 weeks	sPTB < 34 weeks	p value	All
n (%)	**997 *(96.1)***	**40 *(3.9)***		**1037 *(100)***
Age – mean (SD)	30.0 *(5.7)*	30.4 *(5.7)*	0.756 [a]	30.1 *(5.7)*
BMI (kg/m2) – mean (SD)	26.2 *(5.9)*	25.9 *(5.3)*	0.738 [a]	26.2 *(5.9)*
n (%)	**928 *(96.2%)***	**37 *(3.8%)***		**965 *(100%)***
IMD deprivation score – mean (SD)†	31.1 *(14.8)*	32.1 *(15.4)*	0.679 [a]	31.1 *(14.8)*
Ethnicity	**n *(% within group)***	**n *(% within group)***	0.134 [b]	**n *(% within cohort)***
European	599 *(96.1)*	24 *(3.9)*		623 *(60.1)*
African or Caribbean	217 *(96.4)*	8 *(3.6)*		225 *(21.7)*
Asian (India/Pakistan/Bangladesh)	65 *(91.5)*	6 *(1.7)*		71 *(6.8)*
Other (incl. Chinese)	116 *(98.3)*	2 *(1.7)*		118 *(11.4)*

SD=standard deviation; BMI=Body Mass Index; IMD=Index of Multiple Deprivation.

†some values missing

[a] Independent samples t-test.

[b] Pearson Chi-Square Asymptotic Significance (2-sided).

There was no difference between the groups, either at 37 or 34 weeks, in respect of age, BMI, IMD deprivation score or ethnicity.

8.4.2. Participant characteristics – risk factors

Participant risk factors are shown Tables 18 and 19, below, by spontaneous onset of labour or premature rupture of membranes leading to preterm birth at less than 37 and 34 weeks' respectively.

Table 18. Comparison of participant risk factors by gestation at term and spontaneous preterm birth (sPTB) < 37 weeks' gestation.

	Term birth	sPTB < 37 weeks		All
n (%)	**912 *(87.9)***	**125 *(12.1)***		**1037 *(100)***
	n ***(% within group)***	n ***(% within group)***	**p value**[a]	**n *(% within cohort)***
Major risk factors				
At least one major risk factor	209 *(72.8)*	78 *(27.2)*	<0.001	287 *(27.7)*
Previous PTB < 37 weeks	116 *(79.5)*	30 *(20.5)*	0.001	146 *(14.1)*
Previous PPROM < 37 weeks	57 *(71.3)*	23 *(28.8)*	<0.001	80 *(7.7)*
Previous late miscarriage	44 *(77.2)*	13 *(22.8)*	0.014	57 *(5.5)*
Cervical surgery	40 *(72.7)*	15 *(27.3)*	0.001	55 *(5.3)*
Uterine abnormality	10 *(76.9)*	3 *(23.1)*	0.199	13 *(1.3)*
Twin pregnancy	16 *(41.0)*	23 *(59.0)*	<0.001	39 *(3.8)*
Other risk factors	*(Past or present history of):*			
Recurrent UTI in pregnancy	91 *(87.5)*	13 *(12.5)*	0.492	104 *(10.0)*
Group B Strep	123 *(89.1)*	15 *(10.9)*	0.384	138 *(13.3)*
Bacterial Vaginosis	60 *(83.3)*	12 *(16.7)*	0.145	72 *(6.9)*
APS/Lupus antibodies	18 *(90.0)*	2 *(10.0)*	0.559	20 *(1.9)*
Fibroids	39 *(92.9)*	3 *(7.1)*	0.233	42 *(4.1)*
Domestic Violence	55 *(88.7)*	7 *(11.3)*	0.940	62 *(6.0)*
Recreational drug use	36 *(87.8)*	5 *(12.2)*	0.563	41 *(4.0)*
Current smoking	110 *(87.9)*	20 *(12.1)*	0.136	130 *(12.5)*

PTB=preterm birth; PPROM=prelabour preterm ruptured membranes; UTI=urinary tract infection. APS=antiphospholipid syndrome.

[a] Chi squared tests of significance

Table 19. Comparison of participant risk factors by birth after 34 weeks' and spontaneous preterm birth (sPTB) < 34 weeks' gestation.

	Birth >34 weeks	sPTB < 34 weeks		All
n (%)	**997 *(96.1)***	**40 *(3.9)***		**1037 *(100)***
	n ***(% within group)***	n ***(% within group)***	**p value**[a]	**n *(% within cohort)***
Major risk factors				
At least one major risk factor	261 *(90.9)*	26 *(9.1)*	<0.001	287 *(27.7)*
Previous PTB < 37 weeks	135 *(92.5)*	11 *(7.5)*	0.017	146 *(14.1)*
Previous PPROM < 37 weeks	71 *(88.8)*	9 *(11.3)*	0.002	80 *(7.7)*
Previous late miscarriage	51 *(89.5)*	6 *(10.5)*	0.019	57 *(5.5)*
Cervical surgery	48 *(87.3)*	7 *(12.7)*	0.004	55 *(5.3)*
Uterine abnormality	13 *(100)*	0 *(0.00)*	0.598	13 *(1.3)*
Twin pregnancy	32 *(82.1)*	7 *(17.9)*	<0.001	39 *(3.8)*
Other risk factors	*(Past or present history of):*			
Recurrent UTI in pregnancy	102 *(98.1)*	2 *(1.9)*	0.215	104 *(10.0)*
Group B Strep	132 *(95.7)*	6 *(4.3)*	0.445	138 *(13.3)*
Bacterial Vaginosis	71 *(98.6)*	1 *(1.4)*	0.218	72 *(6.9)*
APS/Lupus antibodies	19 *(95.0)*	1 *(5.0)*	0.548	20 *(1.9)*
Fibroids	42 *(100)*	0 *(0.0)*	0.185	42 *(4.1)*
Domestic Violence	62 *(100)*	0 *(0.0)*	0.223	62 *(6.0)*
Recreational drug use	41 *(100)*	0 *(0.0)*	0.193	41 *(4.0)*
Current smoking	126 *(96.9)*	4 *(3.1)*	0.423	130 *(12.5)*

PTB=preterm birth; PPROM=prelabour preterm ruptured membranes; UTI=urinary tract infection. APS=antiphospholipid syndrome.

[a] Chi squared tests of significance

There were statistically significant differences between women with and without major risk factors in both outcome groups. Women with any one of the major risk factors, apart from uterine abnormality, were more likely to have spontaneous preterm birth at both less than 37 and less than 34 weeks. None of the other factors recorded for this study, identified in literature as potential risk factors for preterm birth, were found to be statistically significantly different in this cohort.

8.4.3. Prevalence of preventive preterm birth interventions

As demonstrated above, 27.7% of participants had at least one major risk factor, and may have been under the care of specialist preterm clinics. This specialist care may have included regular surveillance (qfFN and TVS CL) with and without interventions intended to prevent preterm birth, such as progesterone therapy, cervical cerclage or Arabin pessary (a silicon ring placed around the cervix). Although data on specialist clinic attendance and surveillance were not captured in this study, data on preventative interventions were recorded and are shown in Table 20.

Table 20. Prevalence of preterm birth prevention interventions within cohort.

	All participants* (n=1016)		
Intervention**	No	Yes	*(%)*
Progesterone	955	61	*(6.0)*
Transvaginal cerclage	972	44	*(4.3)*
Transabdominal cerclage	1008	8	*(0.7)*
Arabin pessary	1010	6	*(0.6)*
No intervention	101	915	*(90.1)*

*where status known
**some women may have had more than one intervention, therefore % totals do not equal 100%

Unsurprisingly, women with at least one major risk factor for preterm birth were more likely to have had a preventative intervention (Table 21).

Table 21. Comparison of preterm birth prevention interventions in women with and without at least one major risk factor.

	Risk group		
	High (n=279)	**Low (n=737)**	**p value** [a]
Intervention	n *(% of women with intervention)*	n *(% of women with intervention)*	
Progesterone (n=61)	44 *(72.1)*	17 *(27.9)*	<0.001
Transvaginal cerclage (n=44)	39 *(88.6)*	5 *(11.4)*	<0.001
Transabdominal cerclage (n=8)	8 *(100)*	0 *(0.0)*	<0.001
Arabin pessary (n=6)	5 *(83.3)*	1 *(16.6)*	0.007
No intervention	199 *(21.7)*	716 *(78.3)*	<0.001

[a] Pearson Chi squared test

Interventions to prevent preterm birth were also more likely in women who experienced spontaneous preterm birth in this cohort (Table 22). It is difficult to draw conclusions from these comparisons, however, as these interventions were much more likely in high risk women who were, of course, more likely to have preterm birth, and the aim of this study was not to evaluate the efficacy of these interventions.

Table 22. Comparison of preterm birth prevention interventions in women with and without spontaneous preterm birth (sPTB) <37 weeks' gestation.

	sPTB < 37 weeks		
	Yes (n=125)	**No (n=912)**	**p value** [a]
Intervention	n *(% of women with intervention)*	n *(% of women with intervention)*	
Progesterone (n=61)	24 *(39.3)*	37 *(60.7)*	<0.001
Transvaginal cerclage (n=44)	15 *(34.1)*	29 *(65.9)*	<0.001
Transabdominal cerclage (n=8)	1 *(12.5)*	7 *(87.5)*	0.652
Arabin pessary (n=6)	3 *(50.0)*	3 *(50.0)*	0.027
No intervention	89 *(9.7%)*	826 *(90.3%)*	<0.001

[a] Pearson Chi squared test

As these preventative interventions are intended to reduce risk of sPTB, although the number of women receiving them in this cohort was small, their use may have influenced the prediction algorithms.

8.4.4. Participant characteristics by centre

Although the proportions of participants by Index of Multiple Deprivation (IMD) quintile varied across the sites, as demonstrated by Figure 18, a comparison of mean IMD scores by centre did not show statistical difference (Figure 19).

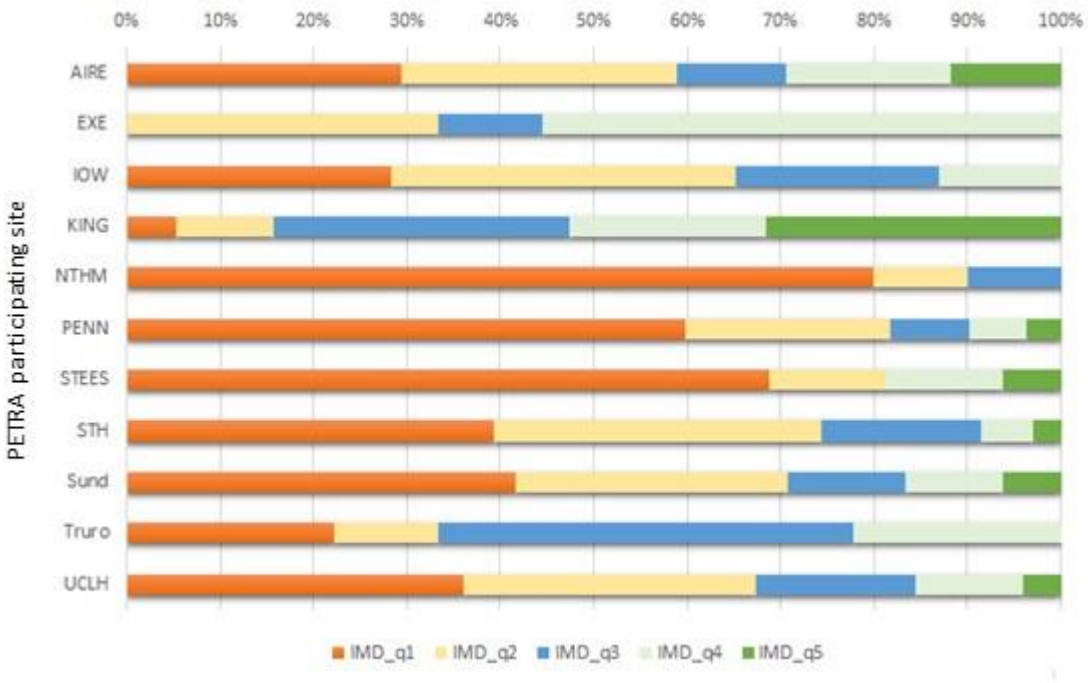


Figure 18. Percentage distribution of Index of Multiple Deprivation (IMD) quintiles* by recruitment centre.

**IMD_q1=IMD score falls within 1-20% in UK population, most deprived (orange); IMD_q2=IMD score within 21-40% (yellow); IMD_q3=IMD score within 41-60% (blue); IMD_q4=IMD score within 61-80% (light green); IMD_q5=IMD score within 81-100%, least deprived (dark green).*

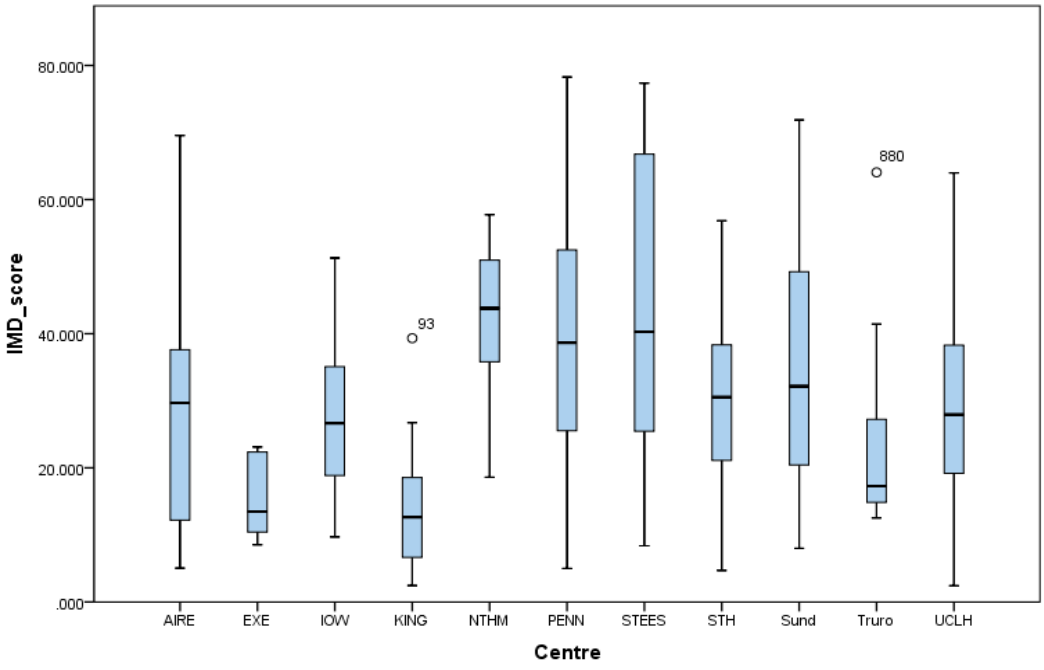
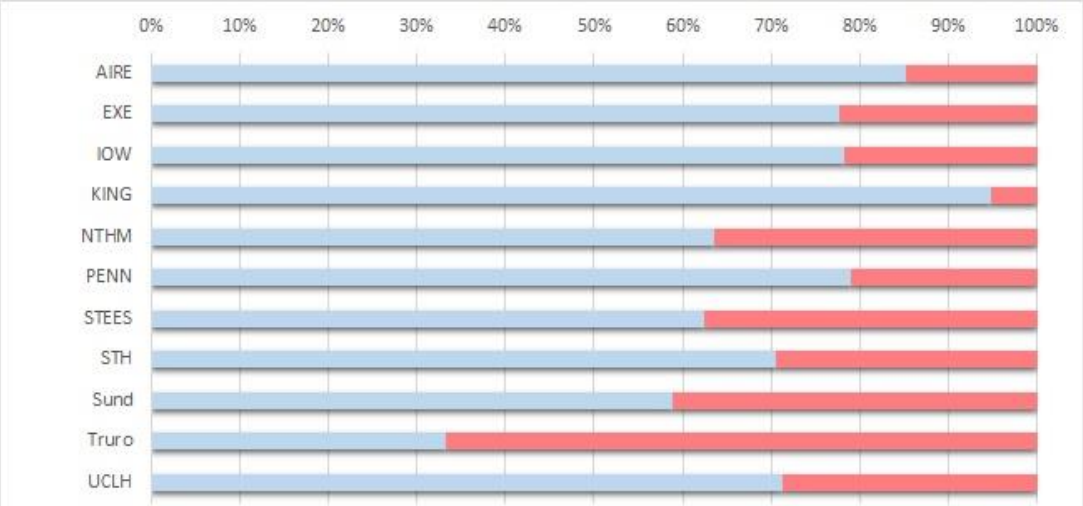


Figure 19. Box plots of mean Index of Multiple Deprivation (IMD) scores with confidence intervals, by recruitment centre.

Overall, approximately 30% of women in this cohort were high risk (i.e. had at least one major risk factor) (Figure 20). It appears that a larger proportion of participants from Truro were high risk (defined as having at least one major risk factor, however, the overall numbers for this site were small (total n=9).



	UCLH	Truro	Sund	STH	STEES	PENN	NTHM	KING	IOW	EXE	AIRE
Low Risk n=	112	3	30	358	10	140	7	18	36	7	29
High Risk n=	45	6	21	150	6	37	4	1	10	2	5

Figure 20. Participant risk status by recruitment site. *Low risk=no major risk factors for preterm birth; High risk=at least one major risk factor for preterm birth*.

8.5. Prediction of preterm birth by fFN and CL categories

In this cohort, the utility of fFN test and CL by category was examined using Kaplan-Meier Survival Analysis (Figures 21 and 22) and relative risks for sPTB at less than 34 and 37 weeks' gestation, and within 7 and 14 days of testing (Tables 23 and 24). For the purposes of this analysis, the last TPTL assessment visit and test results were used.

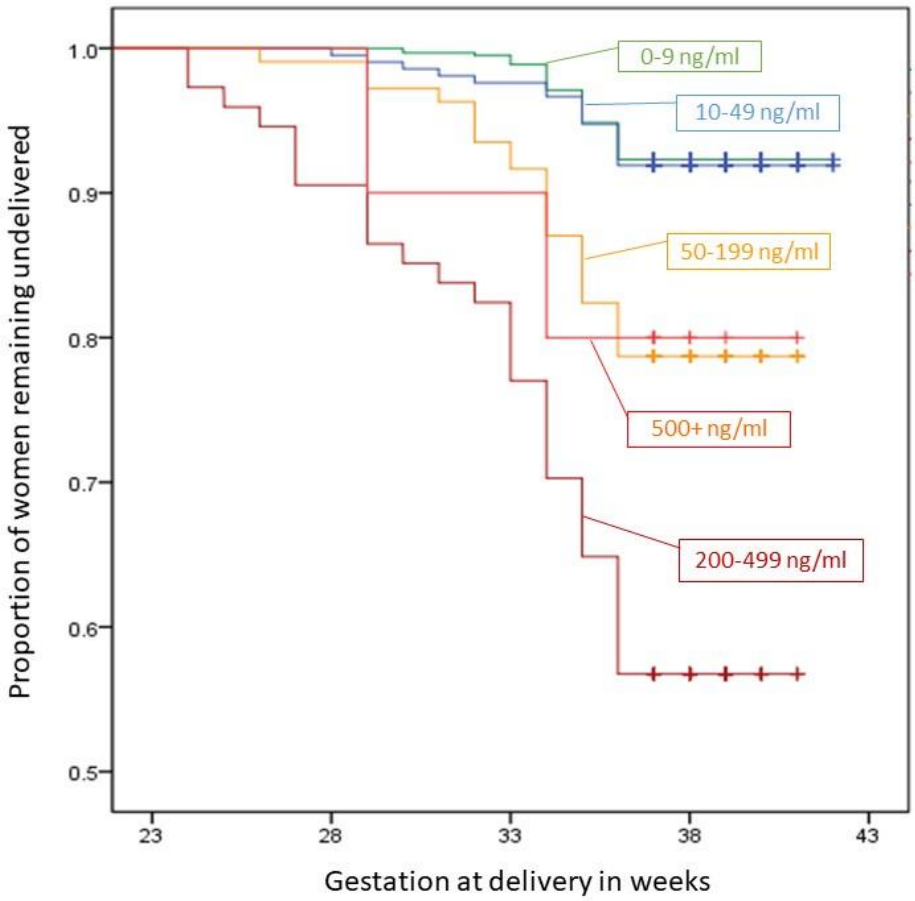


Figure 21. Kaplan-Meier survival curve showing probability of sPTB by fFN categories 0-9, 10-49, 50-199, 200-499 and 500+ ng/ml. Where participant had more than one TPTL episode, the latest quantitative fFN test result is used. † indicates censoring of deliveries.

These data demonstrate increasing risk of sPTB with fFN categories higher than 50 ng/ml and CL measurement of less than 15 mm, which correlates with findings from the current body of literature on the subject, except in the 500+ ng/ml category.

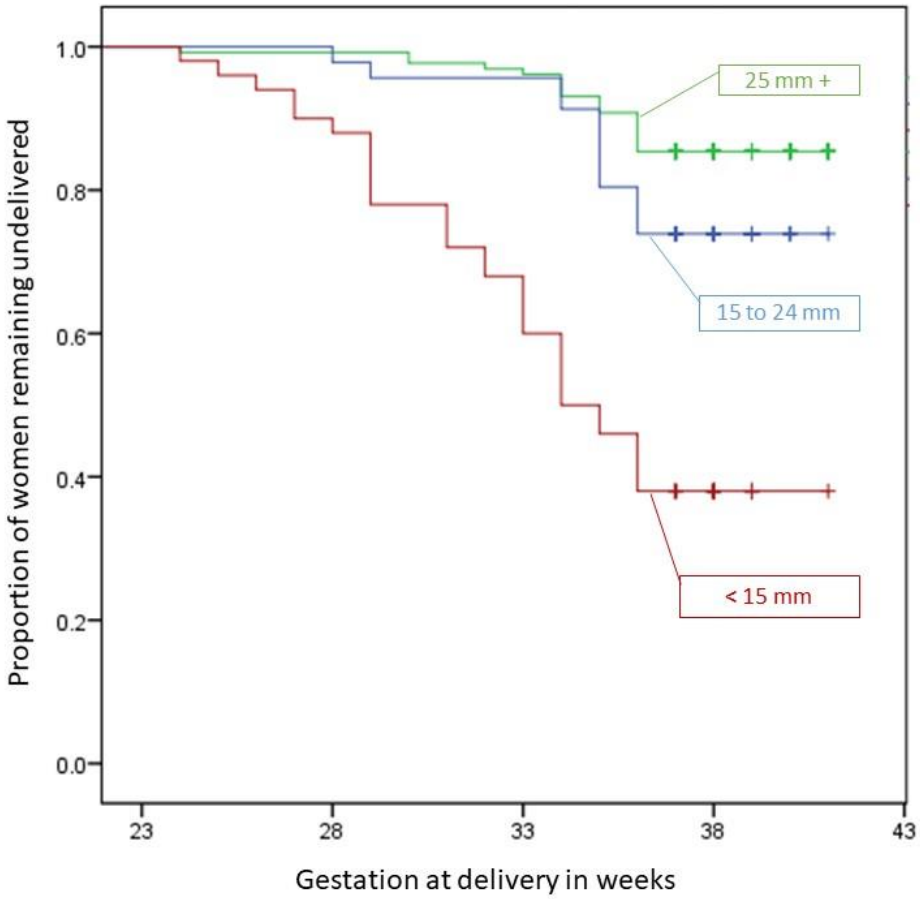


Figure 22. Kaplan-Meier survival curve showing probability of sPTB by CL categories 25+, 15-24 and <15 mm. Where participant had more than one TPTL episode, the latest CL measurement is used. † indicates censoring of deliveries at term (37 weeks' gestation).

Rates of sPTB outcomes by fFN and CL category are shown in Table 23, while relative risk between categories, using as reference categories fFN 0-9 ng/ml and CL 25 mm plus are show in Table 24. These findings again confirm the higher the fFN and the shorter the CL, the greater the risk of sPTB.

Table 23. Number and rates (%) of spontaneous preterm birth (sPTB) at <34 and 37 weeks' gestation, and within 1 and 2 weeks of testing by fFN and CL categories.

		Spontaneous preterm birth			
		< 34 weeks	< 37 weeks	< 1 week of testing	< 2 weeks of testing
Predictive test	N	n *(%)*	n *(%)*	n *(%)*	n *(%)*
fFN category (1026 tests)					
<10 ng/ml	624	7 *(1.1)*	48 *(7.7)*	4 *(0.6)*	8 *(1.3)*
10-49 ng/ml	210	5 *(2.4)*	17 *(8.1)*	0 *(0.0)*	0 *(0.0)*
50-199 ng/ml	108	9 *(8.3)*	23 *(21.3)*	1 *(0.9)*	5 *(4.6)*
200-499 ng/ml	74	17 *(23.0)*	32 *(43.2)*	14 *(18.9)*	19 *(25.7)*
500 ng/ml plus	10	1 *(10.0)*	2 *(20.0)*	1 *(10.0)*	2 *(20.0)*
CL category (226 tests)					
25 mm plus	130	5 *(3.8)*	19 *(14.6)*	2 *(1.5)*	5 *(3.8)*
15-24 mm	46	2 *(4.3)*	12 *(26.1)*	0 *(0.0)*	3 *(6.5)*
Less the 15 mm	50	20 *(40.0)*	31 *(62.0)*	9 *(18.0)*	13 *(26.0)*

N=total in category; n=total sPTB in category; fFN=fetal fibronectin; CL=cervical length.

Table 24. Relative risk of spontaneous preterm birth (sPTB) at <34 and 37 weeks' gestation, and within 1 and 2 weeks of testing by fFN and CL categories.

	Spontaneous preterm birth							
	< 34 weeks		< 37 weeks		< 1 week of testing		< 2 weeks of testing	
Predictive test	RR[a]	*95% CI*[b]	RR[a]	*95% CI*[b]	RR[a]	*95% CI*[b]	RR[a]	*95% CI*[b]
fFN category								
10-49 ng/ml	2.1	*0.7-6.6*	1.1	*0.6-1.8*	3.016E-8†	*.000*	1.508E-8†	*.000*
50-199 ng/ml	7.4	*2.8-19.5*	2.8	*1.8-4.4*	1.4	*0.2-12.8*	3.6	*1.2-10.8*
200-499 ng/ml	20.5	*8.8-47.8*	5.6	*3.9-8.2*	29.5	*10.0-87.3*	20.0	*9.1-44.1*
500 ng/ml plus	8.9	*1.2-65.9*	2.6	*0.7-9.3*	15.6	*1.9-127.4*	15.5	*3.8-64.4*
CL category								
15-24 mm	1.1	*0.2-5.6*	1.8	*0.9-3.4*	1.257E-8	.000	1.7	*0.4-6.8*
Less the 15 mm	10.4	*4.1-26.2*	4.2	*2.7-6.8*	11.7	*2.6-52.3*	6.8	*2.5-18.0*

RR=relative risk, fFN=fetal fibronectin; CL=cervical length.

[a]fFN relative risk relative to fFN cat 0-9 ng/ml; CL relative risk relative to CL cat 25mm+

[b]95% Wald Confidence Intervals for Exp(B)

† "set to system missing due to overflow"

Although relative risk (RR) of sPTB generally rises as the fFN concentration increases, the RR of sPTB was lower in the fFN 500+ ng/ml than the 200-499 ng/ml category (8.9 vs 20.5). The 95% confidence interval is also particularly wide for the 500+ ng/ml

category, most likely due to the small number of events in the group. It is also possible that some test results were carried out within 24 hours of sexual intercourse, but they were not excluded because either the women did not disclose this information, or the attending clinician did not record it in the woman's maternity notes.

8.6. Interventions following TPTL assessment and healthcare utilisation

Another aim of the PETRA study was to assess use of steroids and other management (e.g. admission, tocolysis, IUT). Table 25 shows prevalence of these interventions within the whole cohort.

Table 25. Prevalence of interventions, and number of antenatal day unit visits and antenatal ward nights in whole cohort.

	All participants		
Intervention	n*	No *(%)*	Yes (%)
Steroids	1024	715 *(69.8)*	309 *(30.2)*
Tocolysis	1022	936 *(91.6)*	86 *(8.4)*
In utero transfer	1023	1002 *(97.9)*	21 *(2.1)*
Admission to Neonatal unit	1015	896 *(88.3)*	119 *(11.7)*
In Neonatal unit at 28 days	1015	999 *(98.4)*	16 *(1.6)*
***Antenatal day unit visits** – median (range)*	1022	3 *(0-33)*	
***Antenatal ward nights** – median (range)*	1022	1 *(0-87)*	

*where intervention status is known.
** Mann U Whitney non-parametric test was used for comparison as data not normally distributed.

When these interventions, ADU visits and antenatal ward (ANW) nights were assessed by pregnancy risk factors, women with at least one major risk factor were more likely to have received all interventions, except for the number of antenatal day unit visits (Table 26).

Table 26. Prevalence of interventions and numbers of antenatal day unit visits and antenatal ward nights by risk group.

	Risk group		
	High (n=287)	Low (n=750)	p value*
Intervention	n *(%)*	n *(%)*	
Steroids	129 *(44.9)*	180 *(24.0)*	<0.001
Tocolysis	36 *(12.5)*	50 *(6.7)*	0.007
In utero transfer	13 *(4.5)*	8 *(1.1)*	0.001
Neonatal unit admission	57 *(19.9)*	62 *(8.3)*	<0.001
In Neonatal unit at 28 days	10 *(3.5)*	6 *(0.8)*	0.003
Antenatal day unit visits* – median (range)	3 *(0-22)*	3 *(0-33)*	0.057
Antenatal ward nights* – median (range)	2 *(0-87)*	1 *(0-37)*	<0.001

* Mann U Whitney non-parametric test was used for comparison as data not normally distributed.

8.6.1. Steroid use by outcomes

The use of steroids was examined in more detail than the other interventions as it was the most prevalent intervention in this cohort, and because of the increasing concern about its overuse in women with symptoms of threatened preterm labour. Table 27 shows steroid use by the outcomes of term delivery and sPTB or PPROM at <34 weeks', <37 weeks' gestation and within 1 week of testing.

Table 27. Administration of steroids by spontaneous preterm birth (sPTB) <37, <34 weeks' gestation and within 1 week of testing.

	Term	sPTB <37 weeks	sPTB <34 weeks	sPTB < 1week	ALL
	n *(%)*	n *(%)*	n *(%)*	n *(%)*	n *(%)*
Steroids - YES	216 *(24.0)*	93 *(74.4)*	36 *(90.0)*	18 *(90.0)*	309 *(30.2)*
Steroids - NO	683 *(76.0)*	32 *(25.6)*	4 *(10.0)*	2 *(10.0)*	715 *(69.8)*
TOTALS	899 *(100)*	125 *(100)*	40 *(100)*	20 *(100)*	1024 *(100)*

Three quarters (74.4%) of women recruited to the study with TPTL resulting in PTB received steroids. However, this was not necessarily within the crucial 7 day window where the benefits are optimal. Reassuringly, 76% of women with TPTL but a term

delivery did not receive steroids. Of the 32 women who delivered preterm, but did not receive steroids, all were over 32 weeks, and 28 of them were over 34 weeks.

Regarding administration of steroids within the optimum 7 days before delivery window, 90% of women (18/20) in TPTL who delivered within 7 days did receive steroids. Of the two women who were not given steroids but did deliver within 7 days, one was 32^{+3}, and the other was 34^{+6} weeks. Of the women who did not deliver within 7 days, 71.0% (713/1004) did not receive steroids (Table 28), which was appropriate management.

Table 28. Number of women given steroids by delivery within 7 days of administration.

	del >7 days	del ≤ 7 days	ALL
	n *(%)*	n *(%)*	n *(%)*
Steroids - YES	291 *(29.0)*	18 *(90.0)*	309 *(30.2)*
Steroids - No	713 *(71.0)*	2 *(10.0)*	715 *(69.8)*
TOTALS	1004 *(100)*	20 *(100)*	1024 *(100)*

TPTL test results appear to have influenced steroid administration. The NICE preterm labour guideline (NICE, 2015) recommends steroids are given to symptomatic women if they have a cervical length of less than 15 mm or a fetal fibronectin of 50 ng/ml or more. Approximately 85% of women were treated according to the guideline (Table 29) with 87.4% (181/207) receiving steroids, while 84.3% (689/817) with longer cervix or lower fetal fibronectin did not receive steroids.

Table 29. Number of women given steroids according to NICE (2015) guidance (cervical length (CL) ≥15mm or fetal fibronectin (fFN) <50 ng/ml).

	CL≥15mm or fFN<50 ng/ml	CL<15mm or fFN≥50 ng/ml	ALL
	n *(%)*	n *(%)*	n *(%)*
Steroids - YES	128 *(15.7)*	181 *(87.4)*	309 *(30.2)*
Steroids - NO	689 *(84.3)*	26 *(12.6)*	715 *(69.8)*
TOTALS	817 *(100)*	207 *(100)*	1024 *(100)*

8.6.2. Repeated courses of antenatal corticosteroids

There is growing concern about the unnecessary administration of antenatal corticosteroids, particularly when repeated doses are given. This is because there is an increasing body of evidence of possible long term harm to the children (Asztalos *et al.,* 2014; Murphy *et al.,* 2008; Norberg *et al.,* 2013). In the PETRA cohort, of the 1024 women where steroid administration status was known, 309 (30.2%) received steroids on at least one occasion. In 289 cases, they had received the full course (2 doses 12-24 hours apart). Reassuringly, only 14 women in this cohort required steroids for a second episode of TPTL, and of these 11 were "rescue" doses, i.e. only one dose was given, rather than the full course, as per American College of Obstetricians and Gynecologists (ACOG) guidelines (ACOG, 2017). Three women had steroids three times, two of which had "rescue" doses. This was probably because they had not delivered within seven days of previous administration and the attending clinician felt a further dose, or course, was advised.

8.7. Development and validation the QUIPP app risk prediction algorithms

As explained in Section 1.8.3, the "training set" comprised all women included in the QUIPP app development carried out in June 2017, while the validation set comprised PETRA participants whose outcomes were gathered after this time point and were not included in the training set. The master "training" dataset included symptomatic women between 23^{+0} and 34^{+6} weeks' gestation, with and without risk factors. After exclusions, 1173 observations from 1032 women with fFN test results and 229 observations from 204 women (with both fFN and CL) were available for analysis. Twenty four sets of twins were included, where the first baby outcomes were used in the analysis.

8.7.1. Participant characteristics of the training and validation sets

None of the predetermined demographic factors affected prediction of sPTB. In testing the model with the cohort of women who had both fFN and CL test results, multivariate regression showed that only previous cervical surgery provided additional predictive power to fFN and CL test results in women with symptoms of TPTL. However, the composite of risk factors used in the asymptomatic prediction algorithm for the QUIPP app (i.e. multiple pregnancy, history of sPTB or PPROM, late miscarriage or cervical surgery) was tested to establish whether it affected the prediction in the symptomatic model. There was little difference, so a decision was made to use the composite of risk factors for the symptomatic algorithms for consistency.

Participant characteristics for each set are shown in Tables 30 and 31. The sets were further split and analysed by groups of women who had had fFN, CL and both tests. Whether differences are significant or not between the groups in training and validation sets is not important. If they are too similar the test is not necessarily useful in other cohorts. The best test would work in all situations with all cohorts (Altman and Royston, 2000).

Table 30. Demographic characteristics of women in the predictive model training and validation sets.

		Training set†		Validation set†		Both groups combined†	
AGE	**n=**	1032		506		1538	
	mean *(SD)*	29.9	*(5.7)*	29.8	*(6.0)*	29.9	*(5.8)*
BMI (kg/m2)	**n=**	1025		506		1531	
	mean *(SD)*	26.1	*(5.9)*	26.0	*(6.1)*	26.1	*(5.9)*
IMD deprivation score		947		504		1451	
	mean *(SD)*	31.3	*(13.5)*	30.2	*(15.2)*	30.1	*(14.1)*
ETHNICITY	**n=**	1024 *(%)*		506 *(%)*		1530 *(%)*	
	European	562 *(54.9)*		326 *(64.4)*		888 *(58.0)*	
	African or Caribbean	70 *(6.8)*		33 *(6.5)*		103 *(6.7)*	
	Asian (India/Pakistan/Bangladesh)	277 *(27.1)*		92 *(18.2)*		369 *(24.1)*	
	Other (incl. Chinese)	115 *(11.2)*		55 *(10.9)*		170 *(11.1)*	

SD=standard deviation; BMI=Body Mass Index; IMD=Index of Multiple Deprivation.
†Numbers in groups differ when data is missing.

Table 31. Major risk factors of women in predictive model training and validation sets.

	Training set n=1032	Validation set n=506	Both groups combined n=1538
	n *(%)*	n *(%)*	n *(%)*
Previous PTB < 37 weeks	158 *(15.3)*	83 *(16.4)*	241 *(15.7)*
Previous PPROM < 37 weeks	74 *(7.2)*	34 *(6.7)*	108 *(7.0)*
Previous late miscarriage	79 *(7.7)*	13 *(2.6)*	92 *(6.0)*
Cervical surgery	65 *(6.3)*	26 *(5.1)*	91 *(5.9)*
Twin pregnancy	41 *(4.0)*	33 *(6.5)*	74 *(4.8)*

PTB=preterm birth; PPROM=prelabour preterm ruptured membranes.

As explained in Methods section 6.9.4, three algorithms were developed so that the QUIPP app could be used in different scenarios, i.e. when a women has: i) fFN testing alone, ii) CL measurement alone, or iii) both tests. Data were, therefore sub-divided and are presented in these three groups. Tables 32, 33 and 34 (one table for each group) show the similarity or differences in fFN concentration and CL measurement between the training and validation sets. In the fFN group, data was included from 1,534 women having had 1749 fFN tests: 1,173 (from 1,032 women) in the training set and 576 (from 502 women) in the validation set.

Table 32. Number of women by fetal fibronectin (fFN) concentration category for training and validation sets in the group of women who have had fFN test.

fFN test group	Training set n=1173 *(1032 women)*		Validation set n=576 *(502 women)*		Comparison (95% CI)		p=
	median*	*(quartiles)*	median*	*(quartiles)*			
	5.0	*(2.0, 26.0)*	8.0	*(4.0, 44.5)*	2.0	*(3.0, 1.0)*	<0.001
fFN category	n *(%)*		n *(%)*		RR	*(95% CI)*	0.264
< 10 ng/ml	704 *(60.0)*		317 *(55.0)*				
10 – 19 ng/ml	128 *(10.9)*		64 *(11.1)*		1.09	*(0.83-1.44)*	
20 – 49 ng/ml	118 *(10.1)*		61 *(10.6)*		1.12	*(0.85-1.49)*	
50 – 99 ng/ml	72 *(6.1)*		36 *(6.3)*		1.10	*(0.75-1.61)*	
100 – 199 ng/ml	59 *(5.0)*		40 *(6.9)*		1.45	*(0.99-2.12)*	
200 ng/ml +	92 *(7.8)*		58 *(10.1)*		1.34	*(0.99-1.82)*	

**median is used as more appropriate than mean, as distribution of fFN is skewed.*
RR = risk ratio as compared to reference group < 10 ng/ml.

Overall the median of the fFN concentration differed between the training and validation groups. However, the proportion of women in each fFN category did not differ significantly.

In the CL measurement group, data was included from 336 women having had 344 CL measurements. 229 (from 204 women) in the training set and 155 (from 132 women) in the validation set.

Table 33. Number of women by cervical length (CL) measurement category for training and validation sets in the group of women who have had CL measurement.

CL test group	Training set n=229 *(204 women)*		Validation set n=155 *(132 women)*		Comparison (95% CI)		p value
	mean	*(SD)*	mean	*(SD)*			
	25.2	*(12.7)*	25.7	*(12.7)*	0.54	*(-2.1-3.13)*	0.685
CL length category	**n**	***(%)***	**n**	***(%)***	**RR***	***(95% CI)***	**0.377**
< 15 mm	56	*(24.5)*	36	*(23.2)*			
15 – 24 mm	48	*(21.0)*	42	*(27.1)*	1.17	*(0.87-1.56)*	
25 mm +	125	*(54.6)*	77	*(49.7)*	0.99	*(0.84-1.16)*	

**RR = risk ratio as compared to reference group < 15 mm*

The proportion of women in each CL category did not differ significantly between training and validation sets. Where women had had both fFN and CL test, data was included from 332 women having had 372 CL measurements. 229 (from 204 women) in the training set and 143 (from 128 women) in the validation set.

Table 34. Number of women in fetal fibronectin (fFN) and cervical length (CL) categories for training and validation sets in the group of women who have had both tests.

fFN + CL group	Training set n=229 *(204 women)*		Validation set n=143 *(128 women)*		Comparison (95% CI)		P value
fFN concentration	median*	*(quartiles)*	median*	*(quartiles)*			
	14.0	*(4.0, 101.0)*	32.0	*(5.0, 162.0)*	3.0	*(7.0, 0.0)*	0.027
fFN category	n *(%)*		n *(%)*		RR*	*(95% CI)*	0.433
< 10 ng/ml	99 *(43.2)*		57	*(39.9)*			
10 – 19 ng/ml	24 *(10.5)*		9	*(6.3)*	0.70	*(0.35-1.41)*	
20 – 49 ng/ml	24 *(10.5)*		12	*(8.4)*	0.89	*(0.48-1.67)*	
50 – 99 ng/ml	23 *(10.0)*		15	*(10.5)*	1.11	*(0.62-1.98)*	
100 – 199 ng/ml	21 *(9.2)*		18	*(12.6)*	1.37	*(0.78-2.40)*	
200 ng/ml +	38 *(16.6)*		32	*(22.4)*	1.30	*(0.88-1.91)*	
CL measurement	mean *(SD)*		mean *(SD)*				
	25.2 *(12.7)*		25.7 *(12.8)*		0.49	*(-2.18-3.17)*	*0.717*
CL length category	n *(%)*		n *(%)*		RR*	*(95% CI)*	0.446
< 15 mm	56 *(24.5)*		34 *(23.8)*				
15 – 24 mm	48 *(21.0)*		38 *(26.6)*		1.14	*(0.85-1.55)*	
25 mm +	125 *(54.6)*		71 *(49.7)*		0.98	*(0.83-1.15)*	

**RR = risk ratio as compared to reference group <10 ng/ml for fFN and reference group < 15 mm for CL*

Again, overall the median of the fFN concentration differed between the training & validation groups. However, the proportion of women in each fFN category did not differ significantly between training and validation sets, and neither did the proportion of women in each CL category.

8.7.2. Comparison of outcomes in the training and validation sets

The prevalence of outcomes of spontaneous preterm birth at 30, 34 and 37 weeks' gestation, and at or less than 7 and 14 days of test for each of the test groups, and between training and validation sets are shown in Tables 35, 36 and 37.

Table 35. Number of tests in the fetal fibronectin test group with outcomes by training and validation set and spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing.

Women with fFN test						
	Training set			Validation set		
sPTB	Total	n=sPTB *(%)*	*95% CI*	Total	n=sPTB *(%)*	*95% CI*
<30wk*	574	22 *(3.8)*	*2.4-5.7*	272	10 *(3.7)*	*1.8-6.7*
<34wk**	1066	60 *(5.6)*	*4.3-7.2*	520	26 *(5.0)*	*3.3-7.2*
<37wk	1173	144 *(12.3)*	*10.5-14.3*	576	68 *(11.8)*	*9.3-14.7*
<1wk	1173	15 *(1.3)*	*0.7-2.1*	576	13 *(2.3)*	*1.2-3.8*
<2wk	1173	38 *(3.2)*	*2.3-4.4*	576	18 *(3.1)*	*1.9-4.9*

Table 36. Number of tests in the cervical length group with outcomes by training and validation set and spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing.

Women with CL test						
	Training set			Validation set		
sPTB	Total	n=sPTB *(%)*	*95% CI*	Total	n=sPTB *(%)*	*95% CI*
<30wk*	147	17 *(11.6)*	*6.9-17.9*	92	9 *(9.8)*	*4.6-17.8*
<34wk**	214	41 *(19.2)*	*14.1-25.1*	150	17 *(11.3)*	*6.7-17.5*
<37wk	229	69 *(30.1)*	*24.3-36.5*	155	32 *(20.6)*	*14.6-27.9*
<1wk	229	8 *(3.5)*	*1.5-6.8*	155	7 *(4.5)*	*1.8-9.1*
<2wk	229	21 *(9.2)*	*5.8-13.7*	155	8 *(5.2)*	*2.3-9.9*

Table 37. Number of tests in the fetal fibronectin test and cervical length group with outcomes by training and validation set and spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing.

Women with fFN and CL test						
	Training set			Validation set		
sPTB	Total	n=sPTB *(%)*	*95% CI*	Total	n=sPTB *(%)*	*95% CI*
<30wk*	147	17 *(11.6)*	*6.9-17.9*	83	8 *(9.6)*	*4.3-18.1*
<34wk**	214	41 *(19.2)*	*14.1-25.1*	138	16 *(11.6)*	*6.8-18.1*
<37wk	229	69 *(30.1)*	*24.3-36.5*	143	31 *(21.7)*	*15.2-29.3*
<1wk	229	8 *(3.5)*	*1.5-6.8*	143	7 *(4.9)*	*2.0-9.8*
<2wk	229	21 *(9.2)*	*5.8-13.7*	143	8 *(5.6)*	*2.4-10.7*

*some women were recruited after 30 weeks therefore not included here.
**some women were recruited after 34 weeks therefore not included here.

As demonstrated by the 95% confidence intervals shown on these tables, the prevalence of the outcomes in the training and validation sets is similar in all test groups. This is confirmed by the overlap of confidences intervals in all outcomes.

8.7.3. Predictive statistics

The prediction models created generated formulae that provide individual risk scores dependent on risk factors and test results (Appendix 17.5). Predictive statistics were calculated using a % risk of ≥5% as an indication of a positive test. Tables 38, 39 and 40 show predictive statistics when the algorithms are tested on both the training and validation set, by test group (fFN, CL and fFN+CL) for prediction of sPTB at less than 30, 34 and 37 weeks' gestation, and within 7 and 14 days post-test.

Table 38. Predictive statistics for spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with fetal fibronectin (fFN) tests by training and validation set.

fFN test group	sPTB at less than						sPTB within			
Outcome	30 wk	*95% CI*	34 wk	*95% CI*	37 wk	*95% CI*	1 wk	*95% CI*	2 wk	*95% CI*
Sensitivity %										
Training	81.8%	*(59.7-94.8%)*	80.0%	*(67.7-89.2%)*	82.6%	*(75.4-88.4%)*	73.3%	*(44.9-92.2%)*	81.6%	*(65.7-92.3%)*
Validation	90.0%	*(55.5-99.7%)*	84.6%	*(65.1-95.6%)*	80.9%	*(69.5-89.4%)*	53.8%	*(25.1-80.8%)*	83.3%	*(58.6-96.4%)*
Specificity %										
Training	92.9%	*(90.5-94.9%)*	74.2%	*(71.3-76.8%)*	62.7%	*(59.6-65.6%)*	94.0%	*(92.4-95.3%)*	86.6%	*(84.5-88.5%)*
Validation	90.8%	*(86.7-94.0%)*	70.9%	*(66.6-74.8%)*	56.9%	*(52.5-61.2%)*	92.0%	*(89.5-94.1%)*	84.2%	*(80.9-87.2%)*
Balanced accuracy *((Sens.+Spec)/2)*										
Training	87.38%	*(76.66-93.58%)*	77.08%	*(71.41-81.91%)*	72.66%	*(68.98-76.05)*	83.64%	*(68.78-92.23%)*	84.09%	*(76.81-89.41%)*
Validation	90.42%	*(75.96-96.57%)*	77.73%	*(69.54-84.22%)*	68.89%	*(63.28-73.99%)*	72.93%	*(56.27-84.94%)*	83.78%	*(73.07-90.77%)*
Likelihood ratio - positive										
Training	11.58	*(8.07-16.62)*	3.10	*(2.63-3.65)*	2.21	*(1.99-2.47)*	12.13	*(8.29-17.75)*	6.09	*(4.93-7.53)*
Validation	9.83	*(6.37-15.16)*	2.90	*(2.34-3.60)*	1.88	*(1.61-2.19)*	6.74	*(3.79-11.98)*	5.28	*(3.99-7.00)*
Likelihood ratio - negative										
Training	0.20	*(0.08-0.47)*	0.27	*(0.16-0.45)*	0.28	*(0.19-0.40)*	0.28	*(0.12-0.66)*	0.21	*(0.11-0.42)*
Validation	0.11	*(0.02-0.71)*	0.22	*(0.09-0.54)*	0.34	*(0.20-0.55)*	0.50	*(0.28-0.90)*	0.20	*(0.07-0.56)*
Positive Predictive Value (%)										
Training	31.6%	*(19.9-45.2%)*	15.6%	*(11.7-20.1%)*	23.7%	*(20.0-27.6%)*	13.6%	*(7.0-23.0%)*	16.9%	*(11.8-23.2%)*
Validation	27.3%	*(13.3-45.5)*	13.3%	*(8.5-19.4%)*	20.1%	*(15.5-25.3%)*	13.5%	*(5.6-25.8%)*	14.6%	*(8.4-22.9%)*
Negative Predictive Value (%)										
Training	99.2%	*(98.0-99.8%)*	98.4%	*(97.3-99.2%)*	96.3%	*(94.5-97.6%)*	99.6%	*(99.1-99.9%)*	99.3%	*(98.5-99.7%)*
Validation	99.6%	*(97.7-100%)*	98.9%	*(97.1-99.7%)*	95.7%	*(92.8-97.7%)*	98.9%	*(97.5-99.6%)*	99.4%	*(98.2-99.9%)*

Table 39. Predictive statistics for spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with cervical length (CL) by training and validation set.

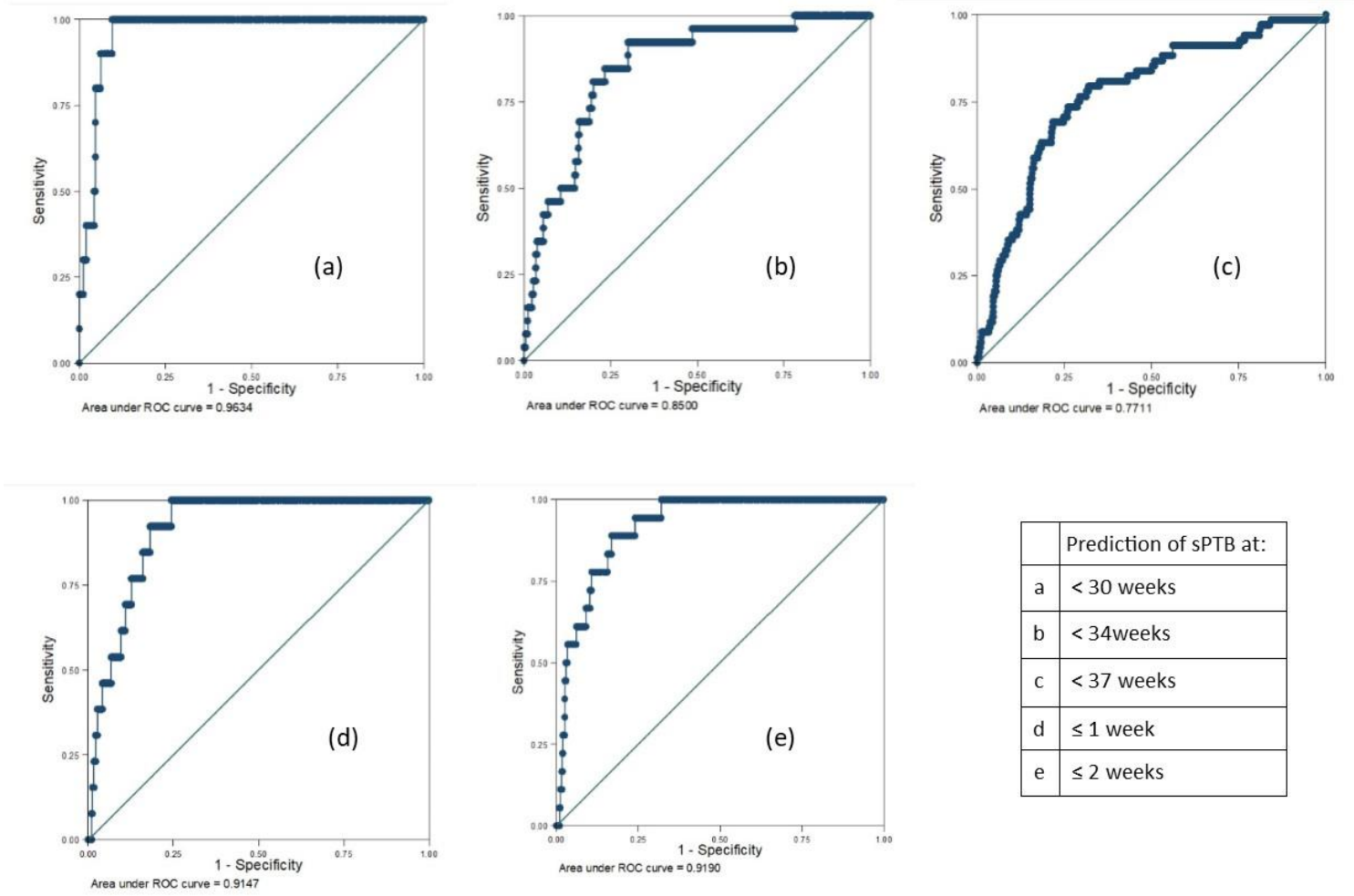
CL group	sPTB at less than						sPTB within			
Outcome	30 wk	*95% CI*	34 wk	*95% CI*	37 wk	*95% CI*	1 wk	*95% CI*	2 wk	*95% CI*
Sensitivity %										
Training	94.1%	*(71.3-99.9)*	92.7%	*(80.1-98.5%)*	100%	*(94.8-100%)*	87.5%	*(47.3-99.7%)*	81.0%	*(58.1-94.6%)*
Validation	88.9%	*(51.8-99.7%)*	100%	*(80.5-100%)*	100%	*(89.1-100%)*	57.1%	*(18.4-90.1%)*	75.0%	*(34.9-96.8%)*
Specificity %										
Training	63.8%	*(55.0-72.1)*	35.8%	*(28.7-43.5%)*	8.1%	*(4.4-13.5%)*	81.0%	*(75.2-85.9%)*	66.8%	*(60.0-73.2%)*
Validation	61.4%	*(50.1-71.9%)*	34.6%	*(26.6-43.3%)*	5.7%	*(2.3-11.4%)*	78.4%	*(70.9-84.7%)*	63.3%	*(54.9-71.1%)*
Balanced accuracy *((Sens.+Spec)/2)*										
Training	78.98%	*(69.94-85.86%)*	64.26%	*(56.75-71.13%)*	54.06%	*(47.19-60.78%)*	84.25%	*(68.68-92.88%)*	73.89%	*(63.78-81.97%)*
Validation	75.17%	*(60.75-85.55%)*	67.29%	*(57.50-75.78%)*	52.85%	*(43.43-62.06%)*	67.76%	*(46.69-83.45%)*	69.13%	*(51.77-82.37%)*
Likelihood ratio - positive										
Training	2.60	*(2.01-3.37)*	1.44	*(1.25-1.66)*	1.09	*(1.04-1.14)*	4.60	*(3.16-6.72)*	2.44	*(1.84-3.24)*
Validation	2.31	*(1.61-3.29)*	1.53	*(1.35-1.73)*	1.06	*(1.02-1.11)*	2.64	*(1.30-5.38)*	2.04	*(1.30-3.21)*
Likelihood ratio - negative										
Training	0.09	*(0.01-0.62)*	0.20	*(0.07-0.62)*	0.00	-	0.15	*(0.02-0.97)*	0.29	*(0.12-0.69)*
Validation	0.18	*(0.03-1.16)*	0.00	-	0.00	-	0.55	*(0.23-1.29)*	0.40	*(0.12-1.32)*
Positive Predictive Value (%)										
Training	25.4%	*(15.3-37.9%)*	25.5%	*(18.7-33.3%)*	31.9%	*(25.8-38.6%)*	14.3%	*(5.9-27.2%)*	19.8%	*(12.0-29.8%)*
Validation	20.0%	*(9.1-35.6%)*	16.3%	*(9.8-24.9%)*	21.6%	*(15.3-29.1%)*	11.1%	*(3.1-26.1%)*	10.0%	*(3.8-20.5%)*
Negative Predictive Value (%)										
Training	98.8%	*(93.5-100%)*	95.4%	*(87.1-99.0%)*	100%	*(75.3-100%)*	99.4%	*(96.9-100%)*	97.2%	*(93.0-99.2%)*
Validation	98.1%	*(89.7-100%)*	100%	*(92.3-100%)*	100%	*(59.0-100%)*	97.5%	*(92.8-99.5%)*	97.9%	*(92.6-99.7%)*

Table 40. Predictive statistics for spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with both fetal fibronectin (fFN) and cervical length (CL) by training and validation set.

fFN test + CL group	**sPTB at less than**						**sPTB within**			
Outcome	**30 wk**	***95% CI***	**34 wk**	***95% CI***	**37 wk**	***95% CI***	**1 wk**	***95% CI***	**2 wk**	***95% CI***
Sensitivity %										
Training	100%	*(80.5-100%)*	92.7%	*(80.1-98.5%)*	94.2%	*(85.8-98.4%)*	100%	*(63.1-100%)*	90.5%	*(69.6-98.8%)*
Validation	100%	*(63.1-100%)*	93.8%	*(69.8-99.8%)*	100%	*(88.8-100%)*	85.7%	*(42.1-99.6%)*	100%	*(63.1-100%)*
Specificity %										
Training	68.5%	*(59.7-76.3%)*	44.5%	*(37.0-52.2%)*	16.3%	*(10.9-22.9%)*	78.7%	*(72.7-83.9%)*	69.2%	*(62.5-75.4%)*
Validation	60.0%	*(48.0-71.1%)*	39.3%	*(30.6-48.6%)*	16.1%	*(9.8-24.2%)*	75.7%	*(67.6-82.7%)*	60.0%	*(51.2-68.3%)*
Balanced Accuracy *((Sens.+Spec)/2)*										
Training	84.23%	*(77.72-89.11%)*	68.60%	*(61.40-74.99%)*	55.23%	*(48.37-61.89%)*	89.37%	*(83.77-91.19%)*	79.85%	*(71.41-86.28%)*
Validation	80.00%	*(69.22-87.68%)*	66.55%	*(55.66-75.91%)*	58.04%	*(48.82-66.72%)*	80.72%	*(63.55-90.96%)*	80.00%	*(70.46-87.03%)*
Likelihood ratio - positive										
Training	3.17	*(2.46-4.08)*	1.67	*(1.43-1.96)*	1.12	*(1.03-1.23)*	4.70	*(3.65-6.06)*	2.94	*(2.30-3.76)*
Validation	2.50	*(1.89-3.30)*	1.55	*(1.28-1.87)*	1.19	*(1.10-1.29)*	3.53	*(2.31-5.40)*	2.50	*(2.03-3.07)*
Likelihood ratio - negative										
Training	0.00	-	0.16	*(0.05-0.49)*	0.36	*(0.13-0.98)*	0.00	-	0.14	*(0.04-0.52)*
Validation	0.00	-	0.16	*(0.02-1.07)*	0.00	-	0.19	*(0.03-1.16)*	0.00	-
Positive Predictive Value (%)										
Training	29.3%	*(18.1-42.7%)*	28.4%	*(20.9-36.8%)*	32.7%	*(26.2-39.7%)*	14.5%	*(6.5-26.7%)*	22.9%	*(14.4-33.4%)*
Validation	21.1%	*(9.6-37.3%)*	16.9%	*(9.8-26.3%)*	24.8%	*(17.5-33.3%)*	15.4%	*(5.9-30.5%)*	12.9%	*(5.7-23.9%)*
Negative Predictive Value (%)										
Training	100%	*(95.9-100%)*	96.3%	*(89.4-99.2%)*	86.7%	*(69.3-96.2%)*	100%	*(97.9-100%)*	98.6%	*(95.1-99.8%)*
Validation	100%	*(92.1-100%)*	98.0%	*(89.1-99.9%)*	100%	*(81.5-100%)*	99.0%	*(94.8-100%)*	100%	*(95.5-100%)*

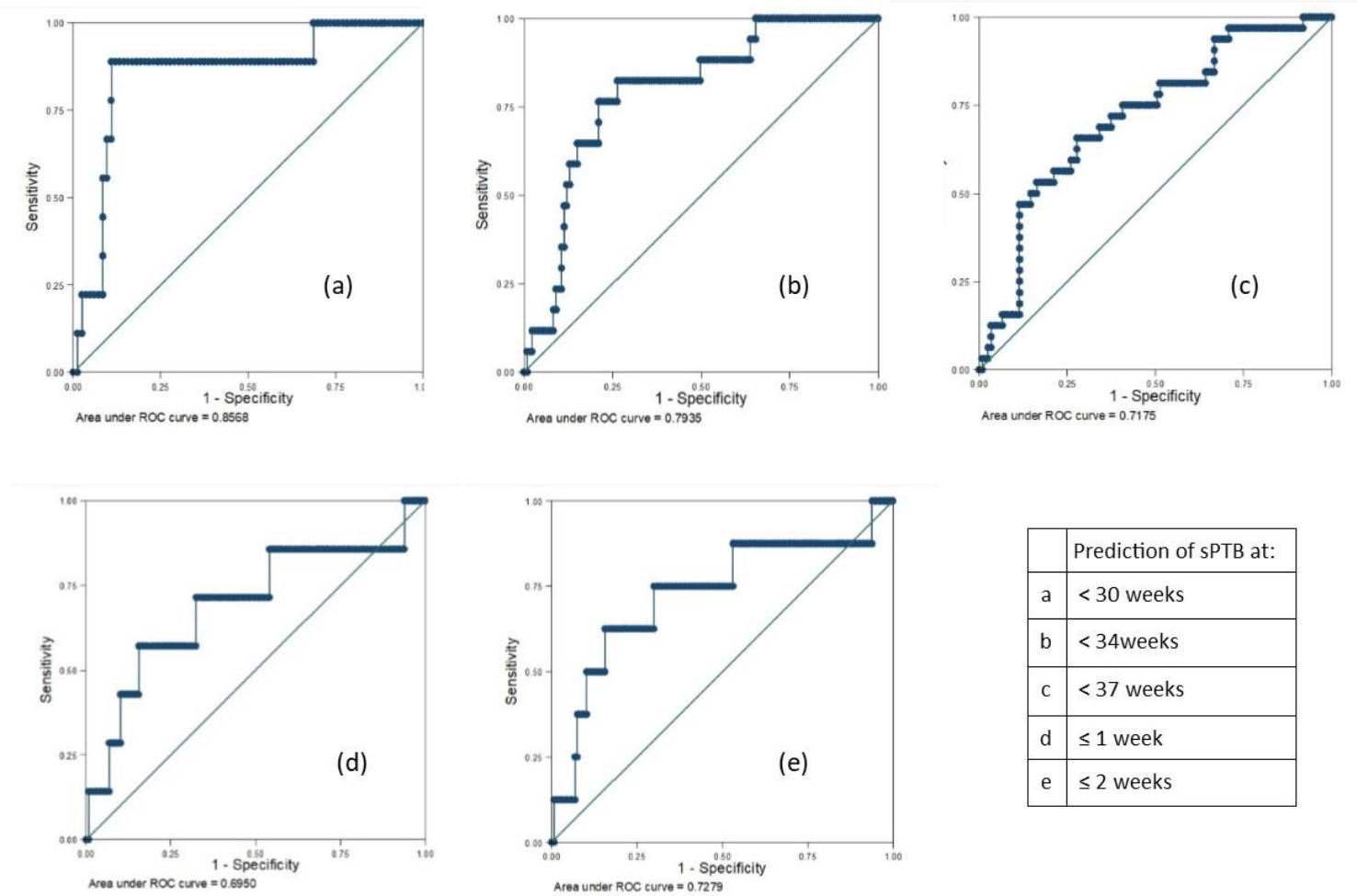
Tables 39 to 40 show a reasonable similarity between the training and validation sets at most outcome time points and for each of the test (fFN, CL, fFN+CL) groups. In the fFN group (the largest group) the ability of the algorithms to predict sPTB at less than 30 weeks' gestation appears to be most impressive with, in the validation set, a sensitivity of 90.0%, specificity of 90.8%, a positive likelihood ratio (LR+) of 9.83, a negative likelihood ratio (LR-) of 0.11, positive predictive value (PPV) of 27.3% and a negative predictive value (NPV) of 99.6%.

While the balanced accuracy statistics noted in Tables 39 to 40 above reflect the balance of sensitivity and specificity using the 5% risk cut off, the ROC curves shown in Figures 23, 24 and 25 indicate overall test performance, using validation set only, at all percentage risks (i.e. without using 5% as a cut off for positive test).



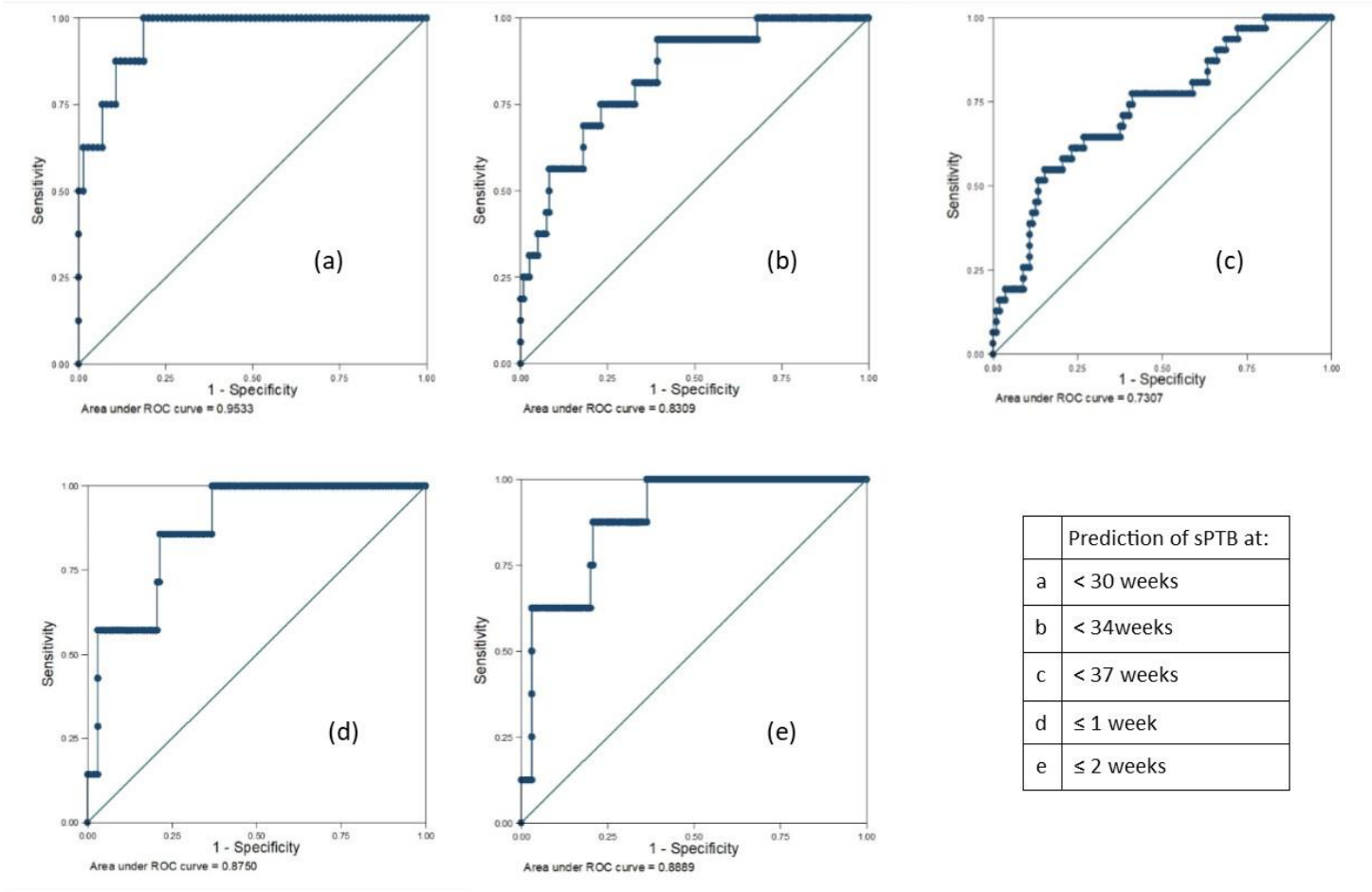
	Prediction of sPTB at:
a	< 30 weeks
b	< 34weeks
c	< 37 weeks
d	≤ 1 week
e	≤ 2 weeks

Figure 23. ROC curves showing QUIPP app prediction of spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with fetal fibronectin (fFN) test results in the validation set.



	Prediction of sPTB at:
a	< 30 weeks
b	< 34weeks
c	< 37 weeks
d	≤ 1 week
e	≤ 2 weeks

Figure 24. ROC curves showing QUIPP app prediction of spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with cervical length (CL) in the validation set.



	Prediction of sPTB at:
a	< 30 weeks
b	< 34weeks
c	< 37 weeks
d	≤ 1 week
e	≤ 2 weeks

Figure 25. ROC curves showing QUIPP app prediction of spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with both fetal fibronectin (fFN) and cervical length (CL) in the validation set.

For the fFN test group, the AUC for predicting sPTB at less than 30 weeks' indicates good prediction, at 0.9634, with similarly impressive AUCs for predicting sPTB at less than 1 week and 2 weeks post-test. Confidence intervals here are also relatively narrow which means it is very likely that similar results would be seen in a similar population (Tables 41).

Table 41. ROC curve statistics table showing QUIPP app prediction of spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with fetal fibronectin (fFN) test in the validation set.

fFN test group				
Prediction of sPTB	n	AUC	Std Err	*95%CI*
<30 weeks	272	0.9634	0.0128	*(0.93821-0.98851)*
<34 weeks	520	0.8500	0.0353	*(0.78069-0.91925)*
<37 weeks	576	0.7711	0.0307	*(0.71088-0.83127)*
<1 week	576	0.9147	0.0224	*(0.87080-0.95869)*
<2 weeks	576	0.9190	0.0222	*(0.87541-0.96250)*

The risk prediction algorithm using cervical length appears to perform best at prediction of sPTB < 30 weeks, but this is inferior to the fFN test (Table 42).

Table 42. ROC curve statistics table showing QUIPP app prediction of spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with cervical length (CL) in the validation set.

CL group				
Prediction of sPTB	n	AUC	Std Err	*95%CI*
<30 weeks	92	0.8568	0.0731	*(0.71357-0.99995)*
<34 weeks	150	0.7935	0.0534	*(0.68885-0.89805)*
<37 weeks	155	0.7175	0.0503	*(0.61894-0.81602)*
<1 week	155	0.6950	0.1274	*(0.44531-0.94465)*
<2 weeks	155	0.7279	0.1137	*(0.50505-0.95073)*

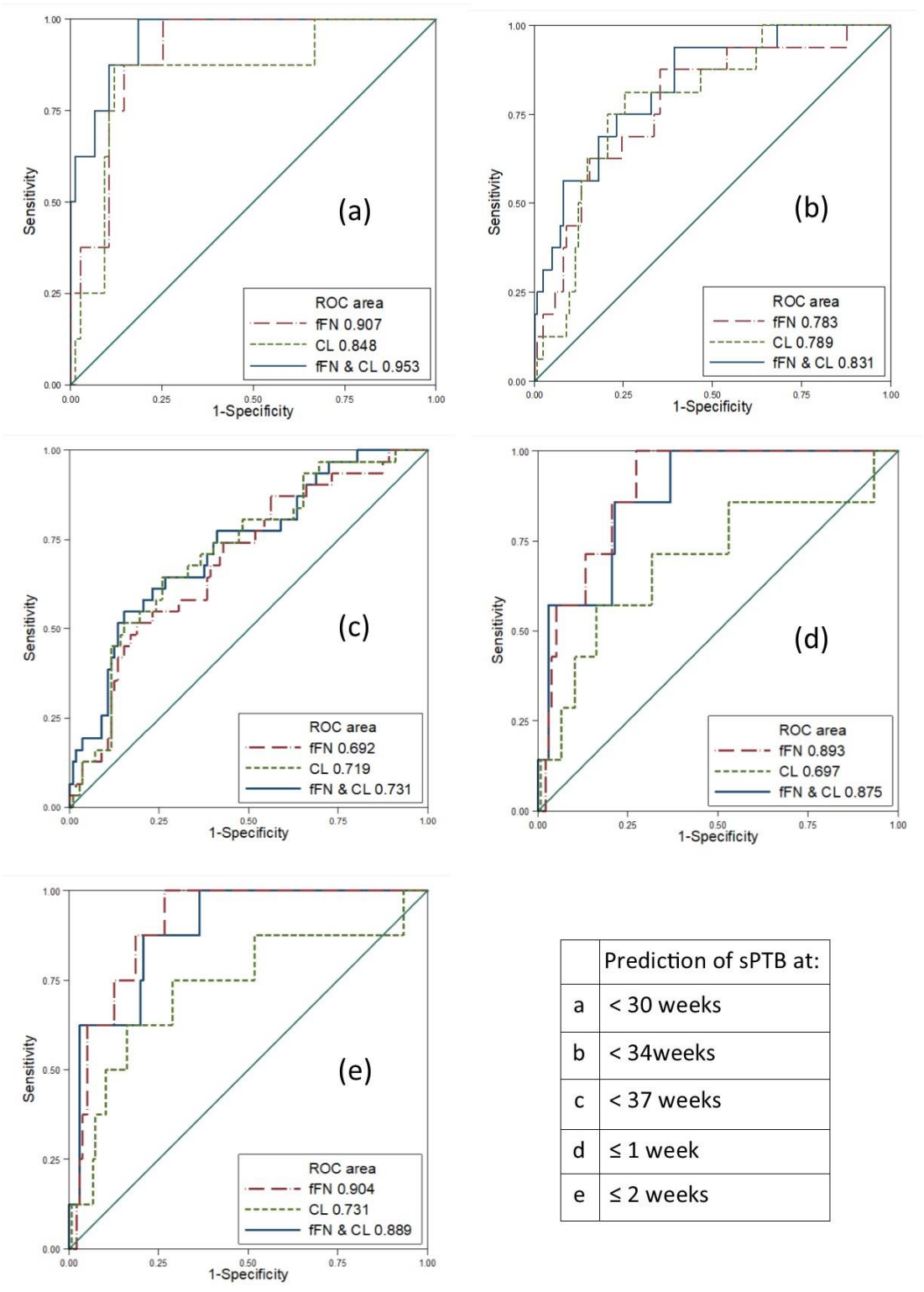
When both test results are combined, the prediction improves, but is inferior to fFN alone at all time points (Table 43).

Table 43. ROC curve statistics table showing QUIPP app prediction of spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with both fetal fibronectin (fFN) and cervical length (CL) in the validation set.

fFN test + CL group				
Prediction of sPTB	n	AUC	Std Err	*95%CI*
<30 weeks	83	0.9533	0.0276	*(0.89914-1.00000)*
<34 weeks	138	0.8309	0.0520	*(0.72912-0.93277)*
<37 weeks	143	0.7307	0.0512	*(0.63040-0.83101)*
<1 week	143	0.8750	0.0555	*(0.76623-0.98377)*
<2 weeks	143	0.8889	0.0491	*(0.79264-0.98514)*

8.7.4. Risk prediction using results of fFN test alone, CL alone and both test results

In addition to development of the risk assessment tool, a primary aim of the PETRA study, further objectives included exploring the added value of CL in a UK setting. This was investigated by creating ROC curves and comparing areas under the curve (AUC) in the validation set of women who had had both tests for difference outcomes, i.e. sPTB at less than 30, 34 and 37 weeks' gestation, and at 1 and 2 weeks following the test (Figure 26 and Tables 44 to 48).



	Prediction of sPTB at:
a	< 30 weeks
b	< 34weeks
c	< 37 weeks
d	≤ 1 week
e	≤ 2 weeks

Figure 26. ROC curves showing ability of QUIPP app to predict spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with both fetal fibronectin (fFN) and cervical length (CL) in the validation set, based on fFN alone, CL alone, or combination of both tests.

Table 44. Significance test comparing area under the ROC curve (AUC) between QUIPP prediction of spontaneous preterm birth (sPTB) at less than 30 weeks' gestation, using fetal fibronectin (fFN) test alone, cervical length (CL) alone, and both tests.

Area under ROC for prediction of sPTB < 30 weeks (n=83*)				
	AUC	Std Err	*95%CI*	*Pr>chi² ***
Both fFN & CL	0.9533	0.0276	*(0.89914-1.00000)*	*standard*
fFN alone	0.9067	0.0384	*(0.83148-0.98185)*	*0.1437*
CL alone	0.8483	0.0791	*(0.69327-1.00000)*	*0.1714*

*number of observations. Some women were recruited at later gestations.
** Pr>chi2 test of significance

Table 45. Significance test comparing area under the ROC curve (AUC) between QUIPP prediction of spontaneous preterm birth (sPTB) at less than 34 weeks' gestation, using fetal fibronectin (fFN) test alone, cervical length (CL) alone, and both tests.

Area under ROC for prediction of sPTB < 34 weeks (n=138*)				
	AUC	Std Err	*95%CI*	*Pr>chi² ***
Both fFN & CL	0.8309	0.0520	*(0.72912-0.93277)*	*standard*
fFN alone	0.7833	0.0622	*(0.66146-0.90514)*	*0.0945*
CL alone	0.7894	0.0545	*(0.68266-0.89623)*	*0.3534*

*number of observations. Some women were recruited at later gestations.
**Pr>chi2 test of significance

Table 46. Significance test comparing area under the ROC curve (AUC) between QUIPP prediction of spontaneous preterm birth (sPTB) at less than 37 weeks' gestation, using fetal fibronectin (fFN) test alone, cervical length (CL) alone, and both tests.

Area under ROC for prediction of sPTB < 37 weeks (n=143)				
	AUC	Std Err	*95%CI*	*Pr>chi²**
Both fFN & CL	0.7307	0.0512	*(0.63040-0.83101)*	*standard*
fFN alone	0.6921	0.0528	*(0.58859-0.79563)*	*0.2406*
CL alone	0.7189	0.0509	*(0.61911-0.81867)*	*0.7446*

* Pr>chi2 test of significance

Table 47. Significance test comparing area under the ROC curve (AUC) between QUIPP prediction of spontaneous preterm birth (sPTB) within one week of testing, using fetal fibronectin (fFN) test alone, cervical length (CL) alone, and both tests.

Area under ROC for prediction of sPTB < 1 week (n=143)				
	AUC	Std Err	*95%CI*	*Pr>chi²**
Both fFN & CL	0.8750	0.0555	*(0.76623-0.98377)*	*standard*
fFN alone	0.8929	0.0418	*(0.81089-0.97483)*	*0.6475*
CL alone	0.6975	0.1262	*(0.45017-0.94479)*	*0.0199*

*Pr>chi2 test of significance

Table 48. Significance test comparing area under the ROC curve (AUC) between QUIPP prediction of spontaneous preterm birth (sPTB) within two weeks of testing, using fetal fibronectin (fFN) test alone, cervical length (CL) alone, and both tests.

Area under ROC for prediction of sPTB < 2 weeks (n=143)				
	AUC	Std Err	*95%CI*	*Pr>chi²**
Both fFN & CL	0.8889	0.0491	*(0.79264-0.98514)*	*standard*
fFN alone	0.9037	0.0362	*(0.83266-0.97475)*	*0.6687*
CL alone	0.7306	0.1126	*(0.50978-0.95133)*	*0.0219*

* Pr>chi2 test of significance

Although the addition of CL to fFN appears to be useful, the significance tests as shown in Tables 44 to 46, indicate there is no difference between the tests or combination of both tests for predicting sPTB at 30, 34 or 37 weeks. However, at 1 and 2 weeks post-test, fFN alone appears to be the best predictor although not statistically different from combined fFN and CL. CL alone, however, has reduced ability to predict sPTB, with AUCs of 0.6975 and 0.7306, respectively (Tables 47 and 48). The number of women in this cohort having both tests was small (particularly so for prediction of sPTB at less than 30 weeks) so these results must be interpreted with caution.

8.7.5. Review of PETRA cohort participants with sPTB < 30 weeks

The ROC curves demonstrating the QUIPP app's ability to predict sPTB < 30 weeks appear to be particularly useful, both the in fFN group validation set (AUC 0.963, 95% CI 0.938-0.989) and the fFN+CL group (AUC 0.953, 95% CI 0.899-1.000). In order to confirm these findings, a review of all PETRA cohort participants with sPTB < 30 weeks was carried out, including individual calculation of their % risk of delivery using the QUIPP app. Table 49 shows the results of this investigation.

Seventeen women in the full PETRA cohort had sPTB < 30 weeks. The QUIPP app predicted risk of sPTB <30 weeks to be ≥5% in all cases. In two cases (5766 and 7132) fFN was <50 ng/ml, the commonly accepted threshold under which reassurance is given. However, in both cases, the CL was short, and the risk of delivery was calculated at over 5% for delivery at less than 30 weeks and within four weeks. This means that using the app to guide practice, using a threshold of 5% for recommending intervention, would be safe and unlikely to result in false reassurance.

Three women (5193, 5740 and 6928) delivered within one week with a QUIPP % risk of less than 5% within one week, but over 5% within two weeks. In one of these cases (6928) a CL of 29 mm was recorded alongside an fFN of 465 ng/ml. In this case, QUIPP % risk calculated with the fFN alone increased the risk to 6.6% for sPTB <1 week. This demonstrates the importance of maintaining clinical judgement in the final decision and perhaps considering the % risk for sPTB <2 weeks, rather than one week, at these earlier gestations.

Table 49. Individual QUIPP % risk calculations for PETRA cohort participants with spontaneous preterm birth (sPTB) at less than 30 weeks' gestation, including risk status, test results, interventions, gestation at, and interval to, delivery with QUIPP % risk scores for prediction of sPTB at < 30 weeks' gestation and within 1, 2 and 4 weeks of testing.

ID	High Risk*	Gestation at visit		qfFN ng/ml	CL mm	Outcome of visit	Tocolysis	Steroids	Gestation at delivery		Visit to del. interval		QUIPP app % risk of sPTB at			
		weeks	days						weeks	days	weeks	days	< 30 wks	< 1 wk	< 2 wks	< 4 wks
4020	Yes	26	0	104	0	*Admitted*	χ	√	29	1	3	1	41.9	10.1	20.7	41.9
4239	Yes	27	3	290	5	*Admitted*	χ	√	29	4	2	1	44.1	18.9	35.7	61.8
4770	No	25	4	431	0	*Admitted*	χ	√	29	5	4	1	62.5	16.7	32.2	58.0
4843	Yes	28	0	51	8	*Home with follow up*	χ	√	29	2	1	2	15.6	7.4	15.6	33.0
5193	No	28	3	269	*not done*	*Admitted*	χ	√	29	1	0	5	5.3	3.2	7.0	15.7
5543	Yes	29	4	500	0	*Admitted*	√	√	29	6	0	2	17.1	35.8	59.5	84.5
5694	Yes	24	1	419	0	*Admitted*	χ	√	27	3	3	2	84.4	22.6	41.7	69.4
5740	No	25	5	332	*not done*	*Admitted*	χ	√	26	1	0	3	17.7	3.2	7.0	16.2
5766	Yes	24	2	43	4	*Admitted*	√	√	28	6	4	4	33.8	3.7	8.5	21.0
5879	No	25	3	294	8	*Admitted*	χ	√	25	5	0	2	34.7	6.1	13.3	29.8
6551	No	27	4	464	*not done*	*Admitted*	√	√	27	6	0	2	24.6	10.3	20.4	39.3
6627	No	23	1	389	8	*Admitted*	χ	√	24	0	0	6	55.2	5.9	13.0	29.9
6699	Yes	26	1	*not done*	17	*Admitted*	χ	√	28	6	2	5	16.5	3.5	7.6	17.6
6901	No	24	4	306	3	*Home with follow up*	χ	√	27	3	2	6	47.4	7.3	15.7	34.1
6928	No	24	1	465	29	*Admitted*	χ	√	24	4	0	3	28.4	2.6	6.2	16.2
7132	Yes	23	6	31	18	*Home with follow up*	χ	√	29	1	5	2	13.4	0.7	1.9	5.9
7148	No	24	1	105	6	*Admitted*	χ	√	26	4	2	3	17.0	1.2	3.0	8.8

**High risk=history of preterm birth or prelabour preterm ruptured membranes at less than 37 weeks' gestation, or late miscarriage in previous pregnancy, or cervical surgery*

9. Results 2: QUIPP app users study

Findings from the QUIPP app users study, where clinicians were asked to express their views, are presented below.

9.1. Participant characteristics

Ten QUIPP app users agreed to be interviewed. Participant characteristics are shown Table 50). Of the 10 participants, 7 were Consultant Obstetricians, one described their grade as ST5 and two were ST4. All were members of the UK Preterm Clinical Network. Years of experience making management decisions in respect of women at risk of preterm birth ranged from 3 to 23 years (median 13 years), and the number of months using the QUIPP app ranged from 9 to 28 (median 18 months). The majority used the app every week in managing the care of selected women.

Table 50. Participant characteristics of PETRA QUIPP app users study.

Study ID.	Grade	Years making PTB management decisions?	Months using the QUIPP app?	How often do you use the app?
CQ001	ST4	3	18	Every week, selected women
CQ002	ST5	5	18	Every week, selected women
CQ003	Consultant	20	18	Once a month, selected women
CQ004	Consultant	19	9	2-3 times a month
CQ005	ST4	5	28	Every week, selected women
CQ006	Consultant	8	18	Every week, selected women
CQ007	Consultant	6	14	Every week, selected women
CQ008	Consultant	23	18	Every week, selected women
CQ009	Consultant	18	28	Every week, selected women
CQ010	Consultant	20	28	Every week, selected women

9.2. Positive elements identified by users

All participants said they had, and would continue to recommend, the QUIPP app to colleagues. The themes emerging from data relating to questioning as to what they liked about, or saw as positive attributes of the app, included: reassurance for women,

clinical management assistance and how the app provides both objective and simplified risk assessment.

9.2.1. Reassurance for women

Many users spoke about how they found the app very useful in reassuring women who were very anxious. In addition, being able to show her the % risk based on her test results made it easier to explain and reassurance was more readily accepted.

[do you think that helps them to accept what you're saying to them?]..."yeah, and I think it gives them confidence… and that's why I do it 4 weeks before the earliest [previous] delivery, because at the time when women are really starting to worry, and they come in, and we risk assess them, and let them know, you know, and I think they find it very reassuring. I know they find it very reassuring." [CQ009]

"… it's another instrument to help inform the conversation between yourself and the women who may be very worried about things." [CQ003]

"I guess the things that I use it for mostly are just straight off reassurance for the woman…it allows me to reassure women in a number of ways ... some women will just be really anxious about getting past 30 weeks because they had a baby at 29 weeks. So therefore I look at the app and say 'ok, actually 90% of women will deliver more than 30 weeks' and then they feel happy." [CQ001]

"I think it's fairly reassuring [to see something simple]. Most women are reassured even if it's …even if they are quite high risk actually. Actually even quite high risk women normally the risk is only around 5% or something like that, that actually puts it into perspective." [CQ002]

9.2.2. Clinical management assistance

Users found that using the app helped them with making clinical management decisions, and this could reassure them that intervening at this point was unnecessary.

"… I think it has two benefits. Firstly by helping the doctor make difficult decisions, but also for explaining risk, and I think those two aren't necessarily the same thing." [CQ002]

"The woman can see either before the weekly threshold or … weeks in pregnancy, or weeks from the test. There's quite a lot that you can point to that is reassuring, and avoids the need for hospitalisation or steroids, or you know, other sort of interventions that one is keen not to use." [CQ003]

"I think it stops doctors overreacting." [CQ002]

"…and it makes me think about management decisions in a way that you maybe wouldn't before, because , you know, what's a percentage risk of giving birth rather than, you know, what's their fibronectin level. It makes me think about what percentage risk, would I want to do X, Y or Z." [CQ005]

9.2.3. Objective risk assessment

Participants described how the felt the app provided risk assessment that supported their clinical judgement in more objective way.

"…it's useful I think for women to actually see it on an objective calculator rather than just, you know, me telling them. I think it makes it more believable." [CQ005]

"…and also with the confidence that that is based on something, rather than the clinician on the day saying 'I'm worried' or the patients really worried, because actually it is our responsibility really to be worried or not worried and not be guided … not be fully guided by the patient's worry." [CQ001]

"…it lends weight to your clinical judgement, and that's … your clinical judgement is from the woman's point of a view a qualitative subjective expert assessment, but something that states in black and white an absolute percentage tends to reinforce that or it tends to incarnate that sentiment… [something solid?]... Yes that's right." [CQ003]

9.2.4. Simplified risk assessment

Another benefit participants spoke about was the way the risk assessment tool reduces the combination of risk factors and test results into a simple % individual risk.

"there are a number of different factors going on here … continuous variables and that sort of thing … fetal fibronectin and the length of the cervix as well… Yeah, so it puts it in to the one thing to take home the message". [CQ002]

"…with the serial ones [women having repeat appointments] they can see that's going up or down more easily." [CQ006]

"I think it's excellent because it actually gives you … it integrates fetal fibronectin with cervical length." [CQ007]

9.2.5. Simple and easy to use

A number of users commented that a very positive feature was the app's simplicity and ease of use:

"Very simple. Really, really simple and really quick." [CQ008]

"…it's very easy to use because you just plug in the details and it gives you an immediate risk." [CQ007]

"The main thing I like is it's easy. So it's not that many clicks and it gives you a number". [CQ004]

9.3. Limitations and suggestions for improvement

9.3.1. More definition of risk factors

Some users stated that they thought the risk factors could be more specific. For example, they would like to be able to denote how many previous preterm births a woman had experienced, and at what gestations, as a woman who had had a number of early preterm births was likely to be at a greater risk than one who had had one previous preterm birth at 35 weeks. One participant pointed out the range of different invasive cervical surgery methods and that it may be useful to be able to stipulate this.

"…if we could expand on the risk factors a bit more it might be more useful… how many previous preterm and what was the earliest, or what were the gestations … I suppose the statisticians will have to see whether or not it turns out to be important." [CQ009]

"It doesn't take into account more than one preterm birth…the other thing is, it doesn't distinguish between different forms of cervical surgery." [CQ009]

9.3.2. More options for entering single or combined test results

Several users highlighted the fact that not all preterm clinics are able to use qfFN testing with all women, so they would like the app to be more flexible and be able to give results based on either qfFN or TVS CL alone, or a combination of both.

> *"Most preterm clinics I think all do a cervical length but they don't all use fetal fibronectin, so it would be useful if they could just go on cervical length." [CQ001]*

> *"We tend to use transvaginal scans as our primary screening test. The use of fibronectin is generally restricted to women beyond 24 weeks [so being able to use it with CL only would be useful] …." [CQ003]*

Although one participant was concerned that restricting the algorithm to one test might undermine the predictive value:

> *" …you could do the app with just cervical length, [but] your margins of error are going to be huge and I think that would play on the good name of the app." [CQ008]*

9.3.3. Comparison with background risk

One user thought it was important to be able to contextualise the woman's individual % risk with the background risk and that this would help the high risk woman to put her situation into perspective.

> *"I think for women it's quite useful for them if you can just eyeball it and say 'well this would be a background risk in a population who don't have risk factors for preterm labour, where your risk relative to this is this'." [CQ007]*

9.3.4. Access to validation information

A number of users said they would find it reassuring if they were able to instantly access, through the app, information about the validation.

> *"It would be quite useful to maybe have a page somewhere where or button for information or something that you could press so that you could see what that validated data is just to give you extra confidence." [CQ009]*

> *"[I would like it to show] just how many women are in the database that forms that data". [CQ008]*

> *"It would be good if we had a bit more information on it about how it's been validated and what, you know, how many …I'm not really, really brilliant at keeping up with, um, all the literature so I wouldn't know how often it's been updated from the point of view of how many patients are in at the back end." [CQ004]*

9.3.5. Links to management guidelines

Several users felt the app could be used to provide guidance, dependent on results, or at least links to other sources of information, such as NICE guidelines.

> *"…if we had some sort of protocol for management pathways and, you know, even just links to, you know, NICE guidelines or our sort of protocols in prem clinic according to risk." [CQ005]*

> *"It would just be a flag… So you know how for example… if you put 'bulging membranes' a thing pops up that says 'are you going to consider a rescue stitch in the patient?'…or you could have something that said 'given the gestation of this patient are you going to consider …?… [or]…think about this and talk to the consultant'." [CQ001]*

Not everyone agreed with this, however:

> *"I think [building in management guidance] is an option but I think you need to leave it up to clinicians and women, because I think it depends on their situation. Because a 4% risk to one lady in one context is different to [another's]… I'm not sure that's necessary." [CQ002]*

9.3.6. Ability to provide feedback on the app.

The current version of the app does not allow users to provide feedback, and this was noted by one participant as a potential improvement.

> *"I think it is really important that the new version should have feedback… feedback of people who are using it." [CQ002]*

9.3.7. Availability for android devices

It was noted that the availability of app would be improved if it was available for android phones and not just through the Apple store.

> *"Interestingly one of my colleagues actually phoned me because they …were struggling to download it. I don't know why they were struggling, but they basically just gave me the measurements and I put it into my version of the app…[we are working on it being on android if that was the problem]… I think that might have been the issue." [CQ007]*

> *"I think that your android version is a bit needed though." [CQ001]*

9.3.8. Additional information on interventions and outcomes

One participant said he would like to be able to note whether a woman had undergone an intervention to reduce her risk of preterm birth, such as cervical cerclage or progesterone therapy, which might affect her risk. Another suggested that the app could be used to collect information on outcomes, possibly even by the women themselves who could be given access to complete them. This extra data could be used for further revisions to the predictive algorithms.

9.4. Visual illustrations of risk

All users indicated that their preferred risk illustration was, by far, the icon array with women (card A, Figure 14, page 135). Where they expressed further preferences the icon array with dots (card C) came in second place with one clinician stating the donut chart (card B) would be their second choice.

All were happy using percentages themselves but some indicated that they felt that not all women found them easy to understand and that they often converted the percentage risk into number in 100, or another denominator that they felt the woman would be most likely to understand (e.g. out of the number in your class, on a bus, chances of winning the lottery etc.).

Many indicated they would individualise the way they described the risk to the woman and this may depend on her background risk, previous history and anxiety levels.

Data collected in the women's experience study suggests that the women also favour the icon array with women (card A) the most, followed by the percentage (card E) and

the donut chart (card B). The clinicians, however, seemed to favour the icon array-women only, and felt that if the women were struggling to understand a percentage, the other "mathematical" charts would not help.

10. Results 3: Women's experience study

10.1. Participants

Data saturation was achieved after 19 women had been interviewed. Eleven were low risk for preterm birth, while eight were high risk (e.g. with a history of preterm birth or late miscarriage). Seven of the eight high risk women had experienced previous preterm birth or late miscarriage, and one had a twin pregnancy. Eleven women were admitted because of their symptoms and test results. A summary of participant characteristics is shown in Table 51 while individual participant profiles are shown in Table 52.

Table 51. Summary of PETRA qualitative study showing number of participants by age group, ethnicity, parity, risk status and whether admitted for threatened preterm labour (TPTL) (n=19).

Age Range		
> 20	1	5%
20-24	1	5%
25-29	3	16%
30-34	4	21%
35-39	7	37%
40-44	1	5%
45+	2	11%
Ethnicity		
Black African	7	37%
Black Caribbean	2	11%
White British	7	37%
White Other European	3	16%
Parity		
Multiparous	7	37%
Primiparous	12	63%
Risk status		
No risk factors	11	58%
Other risk factors	1	5%
Previous PTB/late misc.	7	37%
Admitted for TPTL		
No	8	42%
Yes	11	58%

Table 52. Profiles of PETRA qualitative study participants showing admission for threatened preterm labour (TPTL), age group, ethnicity, location of interview, parity and risk status.

Study ID	Admitted for TPTL	Age group	Ethnicity	Interview Location	Parity	Risk Status
01_4020	Yes	19 and below	White British	Hospital - inpatient	Multiparous	Previous preterm birth or late miscarriage
02_4355	No	35 to 39	White Other European	Home	Multiparous	No risk factors for PTB
03_4410	Yes	25 to 29	Black African	Hospital - inpatient	Multiparous	Previous preterm birth or late miscarriage
04_4492	Yes	30 to 34	White Other European	Hospital - inpatient	Primiparous	No risk factors for PTB
05_4258	No	40 to 44	White British	Hospital - outpatient	Primiparous	No risk factors for PTB
06_4658	No	30 to 34	White British	Hospital - outpatient	Primiparous	No risk factors for PTB
07_4789	Yes	30 to 34	Black Caribbean	Hospital - inpatient	Primiparous	No risk factors for PTB
08_4770	Yes	30 to 34	Black African	Hospital - inpatient	Primiparous	No risk factors for PTB
09_5222Q	No	20 to 24	White British	Hospital - outpatient	Primiparous	No risk factors for PTB
10_5864Q	Yes	35 to 39	Black African	Hospital - inpatient	Primiparous	No risk factors for PTB
11_6237	Yes	45 and over	White British	Hospital - outpatient	Primiparous	Other risk factors - twins
12_6239	No	25 to 29	Black African	Home	Primiparous	No risk factors for PTB
13_6253	No	35 to 39	White Other European	Home	Primiparous	No risk factors for PTB
14_6317	Yes	35 to 39	White British	Home	Multiparous	Previous preterm birth or late miscarriage
15_5991	Yes	25 to 29	Black African	Hospital - inpatient	Primiparous	Previous preterm birth or late miscarriage
16_6382	No	45 and over	White British	Home	Primiparous	No risk factors for PTB
17_6338	No	35 to 39	Black African	Hospital - outpatient	Multiparous	Previous preterm birth or late miscarriage
18_6174	Yes	35 to 39	Black Caribbean	Home	Multiparous	Previous preterm birth or late miscarriage
19_6322	Yes	35 to 39	Black African	Hospital - outpatient	Multiparous	Previous preterm birth or late miscarriage

10.2. Themes

Four main themes were identified, two of which captured the women's experience of threatened preterm labour, "Coping with Uncertainty" and "Dealing with Conflicts" and two which elucidated elements of care which had an important effect on the experience, "Aspects of Care" and "Interactions with Professionals" (Figure 27). Findings in relation to the specific questions about risk illustration are dealt with separately.

Figure 27. Thematic overview of findings from the qualitative study, showing main themes and subthemes.

10.2.1. Theme 1: Coping with Uncertainty

Threatened preterm labour is a state of uncertainty, where women experience symptoms that may, or may not be early preterm labour. The sense of unease that comes with this state is evident from the data gathered in this study. The whole of pregnancy itself, particularly for primiparous women, can be a time of great anxiety, caused largely from simply not-knowing what is currently going on and what is going to

happen in the near future. For those with experience of pregnancy and preterm birth or late miscarriage, the possibility that it could happen again can cause great anxiety. Data from this study suggests that women, both worried first time mothers and women with a history of preterm birth, will initially try to make sense of the symptoms they are experiencing, go on to seek reassurance and then try to maintain a sense of control over this unpredictable state as they "try to hold it together".

10.2.1.1. Trying to make sense of the symptoms

Many women appeared to have spent some time trying to rationalise their symptoms as something other than PTL, although this was less likely in women with a history of PTB:

> *"… I had a kidney infection as well five weeks ago, and the pain I was feeling seemed similar to that." [10_5864]*

> *"...but I guess with the pain it might be something surgical." [07_4789]*

> *""... the pains are still coming, the cramping is still coming, and I'm kind of confused because I don't think it's labour but I know it's not Braxton Hicks either." [18_6174]*

There was also a sense that some women were worried that the symptoms had been caused by something they had done, for example, activity, sex or not resting enough, and they felt responsible.

> *"... I felt like after sex I would feel more of the tightness of the tummy…but I am wondering if it is something about the anatomy and the physicality of it, or if it has to do with the semen or something like that..." [04_4492]*

"... I thought it was maybe because I was feeling a little bit upset and panicked." [06_4658]

"Maybe because I was walking a lot more than usual … I don't know." [12_6239]

Where symptoms remained unexplained, some women accepted that sometimes there are no answers. However, others were not happy, and felt "shrugged off" by the health care professionals, which could also diminish their trust in the doctors.

" …it's quite scary actually, especially when I get …tightening, and sometimes it's kind of painful. It's just … I just feel I'm everywhere right now. I don't know what's going on." [15_5991]

"... if there was anything that needed attention the midwife would have said 'you need to see a doctor', and because they didn't I just assumed 'well that's fine', but clearly it's not fine, not for me…" [05_4258]

10.2.1.2. Seeking reassurance

Most women were aware that symptoms may have indicated TPTL and seemed happy to approach their midwife, or call for advice, and knew how to do this.

"…and I sort of thought 'oh, this is sounding a little bit like what they told us in NCT classes, could be your early stages of labour'…and so we decided to ring the midwife number that is on the medical notes." [06_4658]

"… Sunday [the pain] was still there and was getting worse now, spreading to my lower abdomen. And so I thought 'well, I better just call the labour ward just in case'." [10_5864]

The low risk primiparous women, however, usually took some time to consider what might be happening before doing so, more time trying to make sense of their symptoms, while those with a history of preterm birth or late miscarriage were more certain and accessed help more quickly.

Most found the fFN and cervical length test results helpful and that they reduced anxiety. This was particularly so with the high risk women who were already aware of, and trusted the tests, having had experience of them in the preterm clinic.

> *"...But the fibronectin test is actually very reassuring because I know it's still … it's still signs and probabilities, but together with the cervical length and the fibronectin test kind of puts your mind at ease..." [17_6338]*

> *"... [I had] the transvaginal scan which was another good thing because …we weren't just relying on I suppose the midwife looking at my cervix and saying 'oh yes, it's good'..." [04_4492]*

If the symptoms continued, however, the reassurance was only temporary.

> *"... they reassured me I wasn't in labour …because that was my main worry. Then afterwards you think 'ok, why am I going through … what is going on?'." [12_6239]*

> *"... I think what is difficult is that you can only ever get a diagnosis or you know somebody explain what is happening now and then, so I can be reassured walking out of the ADU Unit and I'm kind of like 'brilliant', twelve hours later still experiencing the same symptoms and you are back to square one again." [05_4258]*

"... if there was anything that needed attention the Midwife would have said 'you need to see a Doctor', and because they didn't I just assumed 'well that's fine', but clearly it's not fine, not for me…" [05_4258]

" … it's quite scary actually, especially when I get …tightening, and sometimes it's kind of painful. It's just … I just feel I'm everywhere right now. I don't know what's going on." [15_5991]

Women with a history of preterm birth were aware that their previous experience had a great influence on how their perceived their symptoms, and how this affected their need for reassurance.

"… before I was admitted I used to go to the ADU a lot… just because of my experience with the previous one I am a bit more cautious." [15_5991]

Another woman, although she knew she was not at high risk for preterm birth, was very anxious which she perceived to be a result of her previous history of early miscarriages and difficulty conceiving with IVF treatment. She also found it very difficult to accept the reassurance she craved.

"I think I have to just learn that when somebody reassures you that you just take it… You know… don't try to create another story…. when you have had previous experiences so you are coming from quite a negative place to start with it is quite hard to see how there could actually be a positive outcome …." [05_4258]

10.2.1.3. Trying to hold it together

Those that were hospitalised appeared to be attempting to "hold it together", trying to stay calm, as they felt anxiety was not good for them or the baby.

> *"… my husband stayed quite calm actually which was quite good and I calmed myself down. I gave myself a minute to calm myself down with some breathing techniques that I used. I was like 'it's not going to help me, I need to sort my bag out'..." [14_6317]*

Many spoke about how they tried to stay positive, or to distract themselves from thinking about it. This could be quite difficult, particularly when other things happened on the ward.

> *" … I try to think positive. I try to, um, to have a look at the facts and not try to anticipate something that probably will not happen." [13_6253]*

> *"... just try to think about what is on the other side as well and about being a parent." [05_4258]*

> *"...when I am not being stressed I am focused on the baby, on her dancing and what she is doing, and I am not so much thinking about how I felt when I lost the first baby again." [03_4410]*

Midwives tried to address women's anxiety, sometimes by providing more information. This was not always welcome. One woman who had been given a book on neonatal unit care could not read it as it interfered with her trying to stay positive.

> *"... I didn't read it... [information book]… I wanted to read it but every time I opened it I went to the bad side... because you always sort of read what could happen … worst case scenarios … so I just sort of left it." [08_4770]*

Some women dealt with their anxiety by getting through from one day to the next, or one week to the next.

"... it is almost like I look forward to Monday as I know Monday is the start of a new week in the pregnancy, and then usually anxiety starts to rise probably about, yeah, Wednesday, you know, Thursday towards the end of that week, and then if I have completed the week and nothing has happened I kind of have a sort of mini celebration almost myself and think 'great, that's another week, brilliant'." [05_4258]

"… I was just sort of counting the days until I reached twenty six weeks, counting the days until I reached twenty seven weeks, and then, you know, sort of counting, and counting and counting." [08_4770]

Some women found comfort in prayer and sometimes resolved that, providing everything had been done that could have been done, they were prepared to accept what happened.

"... I believe in God, I have a personal relationship with him … that helps me. I trust that he is going to see us through... I study my bible and read positive and encouraging scriptures... I have a lot of people praying for me as well. It's encouraging." [10_5864]

"...as far as I am concerned everything that could be done has been done…the medicine that the doctors have blessed me with have done all that they could already, so then they have kind of like left it up to [God] now, for him to decide what happens." [03_4410]

10.2.2. Theme 2: Dealing with conflicts

Women experiencing TPTL have to deal with a number of conflicts. The unsettling experience of TPTL, its risk assessment and management can be exacerbated by conflicting information and advice, which may have come about from clinician

uncertainty. Hospitalised women may also be trying to deal with balancing the conflicting responsibilities of, for example, having to rest or be in hospital in order to protect their unborn baby, and the need to care for other children at home. All this uncertainty and conflict can result in an emotional rollercoaster of conflicting feelings.

10.2.2.1. Conflicting advice

As PTL is very difficult to diagnose in its early stages, it is unsurprising that women can hear many differing opinions as to what may be causing the symptoms. This was clearly an issue for several women in this study:

> *"...different answers from different people. I was told it was ligament pain, I was told it was fibroids, I was told it was a UTI, you know, all in the space of five days." [07_4789].*

> *"…having continuity of care with the same doctor or consultant I think probably is something that I would have benefitted …, because every time I come in …you see somebody different, and everyone has slightly different views." [05_4258].*

> *"The doctor did tell me I can increase my activity level. The midwife said 'no, go back to bed'. So I am sticking to the midwife." [08_4770].*

10.2.2.2. Conflicting responsibilities

Anxiety caused by being separated from other children appeared to be the most significant issue for women who were admitted to the antenatal ward. They felt they were being pulled emotionally between their need to care for them and protecting their unborn baby.

"…the last time she came she said quietly …'look, mummy, they are not looking, let's leave now'". [ID. 4020].

Women described how they felt the need to protect current children from the potential pain of loss, but also wanted to be positive, both for themselves and their children, some of whom had borne witness to the grief and loss of earlier pregnancies.

"…we want her to be positive and want to talk to her about it but we don't know how much to say because we don't want her to be really upset if it all goes wrong again." [01_4020]

Although women felt sad and guilty for not being able to care for older children, they often talked about how they saw this time as an investment, and that the longer they stayed in hospital and the baby stayed inside, the less likely the baby would have problems when it was born.

"I was quite happy [to be admitted] because I know that at the end of this my son would be a lot happier to have a sibling because I know that is what he really wants." [03_4410]

For those women without other children at home there was some concern about work responsibilities, but most felt it was important to reduce stress for the sake of this baby. Some expressed concerned that they were not able to do their job properly, and one that her job was at risk if she had time off.

"...it's the added pressures of wanting to be able to, you know, do well at work, obviously have a healthy pregnancy, you know... wanting to be able to do it all basically... commuting in and out of work, not have any problems etc. etc." [05_4258]

"Sickness is a big thing and you can just get replaced so easily. So um, yeah, I just done myself a favour and [went on maternity leave] early." [09_5222]

10.2.2.3. Conflicting emotions

Women felt very anxious but tried hard to be positive and stay calm. This was sometimes very difficult and could result in them feeling like they were swaying between calmness and confusion.

"… I was waking up every hour to see if I had lost any water… And then it didn't happen again for the next couple of days and I sort of got a bit relaxed and thought this isn't going to happen... um, I'm calm now." [08_4770]

"At first they just said everything's fine so I thought I am having a nice pregnancy, but now sort of you get told certain information and … obviously you're worrying so the baby is obviously feeling all your worry … so you just have to try and be calm and just take every day as it comes." [09_5222]

They could feel reassured for a time, but then would experience a rising anxiety again, as the reassurance subsides if the pain continued, or fears that the baby could come early continued to haunt them.

"...it is almost like I look forward to Monday as I know Monday is the start of a new week…and then usually anxiety starts to rise probably about, yeah, Wednesday, you know, Thursday towards the end of that week…" [05_4258]

10.2.3. Theme 3: Aspects of care

What happens when a woman with symptoms of TPTL seeks maternity care can affect her experience, both positively and negatively. This theme elucidates the aspects of

care which appeared to be important to the participants of this study, and is presented as sub-themes: organisation of care; clinical procedures and relationships with other patients. A significant aspect of maternity care is, of course, the interaction with healthcare professionals, however, as this is such an important topic, with its own sub-categories, it is discussed separately.

10.2.4. Organisation of care

Overall, the women in this study appeared to be knowledgeable about how and when to contact a midwife for advice, and found it reassuring that they were able to do so at any time.

> *"That has really put my mind at ease, knowing that you have that point of contact there, anytime day or night." [06_4658]*

> *"… I feel so much more confident now that, were something to panic me again, I know that I can contact the midwives and they're there, and they really don't mind." [06_4658]*

Easy access to information and advice from a trusted health professional was highly valued by women who were known to the specialist preterm clinic.

> *"… It is really easy to get hold of her. When I had my stitch done she informed them to let me know that they were in a conference and it was really good that I could get hold of her even though she wasn't there." [03_4410]*

Several women spoke about the importance of continuity of carer, and how this could enhance relationships and trust, as well as making care potentially more efficient and safer. Continuity of carer also helps with easy access to advice, knowing who and how to call, and feeling comfortable doing so.

> *"… I think it is because when you have a midwife you build up a rapport and a relationship so you are much more likely and willing to have discussions, whereas if you are seeing different people all the time …" [05_4258]*

> *"… the fact that I can see the same [professionals]. It almost feels that when I come in I don't have to repeat myself anymore…." [03_4410]*

Women appreciated it when midwives reorganised the bays according to the care needs of the women, for example, women admitted for induction of labour were moved to a different room from those with TPTL.

> *"And we have two others that are just crying because they want to get their babies out. I am crying and thinking 'please God we don't have the same problems' - I am trying to keep it in, they are trying to get it out." [03_4410]*

One women recalled a previous experience and how she could hear other babies crying while she was left holding her stillborn baby:

> *"…I've been in that situation before. It's kind of surreal because you are sitting there with your child which you are going to send back, for intents and purposes, to a fridge, and then you can hear women with their children crying less than a few doors away and you are like 'why would you put us here?'." [18_6174]*

Waiting and delays were an important aspect of care that affected women's experience. Many had to wait a long time to be seen in the day assessment unit, however, most understood and were prepared for this. They felt that it was worth it for the reassurance it would bring in the end.

> *"… [it might be] a very long wait yeah, but it's better to be at peace than worry yourself and not know what is going on really." [15_5991]*

Waiting for interventions to be administered once they had been prescribed, however, was a different matter. One woman was told how important it was that she had steroids but then had to wait a long time before she was given them:

> *"...By then that had been an hour and a half, so he [her partner] got very upset because in his mind it was like 'take these injections now if we have decided'…" [04_4492]*

Another had a long wait for ambulance for in utero transfer after being told it was vital the baby was born in a hospital with adequate neonatal care.

> *"… they said 'oh, the ambulance will come soon'…and you keep on asking and they say 'well, it's on its way'… You've been told it's extremely urgent … and there is a six hour wait." [08_4770]*

One women recalled having her planned cervical cerclage cancelled and delayed on a number of occasions. She understood, to a degree, because she knew they are carried out on the labour ward where emergencies constantly disrupt the elective procedures, but found it very difficult.

> *"…I got to the point where I just said 'you know what, if I'm going to lose it I don't want nobody to get my hopes up anymore …I said 'if you are not going to operate then don't string me along for so long'." [03_4410]*

Women also talked about how getting test results quickly was very important to them.

"… the fact that we can get that test result back quick is a bonus. Yes, definitely, because you do feel quite anxious at the beginning." [06_4658]

The issue of discharge was an area of discussion that appeared to be important to the women who had been hospitalised and this could produce strong and mixed feelings.

Although they really wanted to go home, particularly if they had other children, women generally felt they were in the right place, and sometimes wanted to stay in longer than the doctors thought necessary.

> *"… and then I thought 'ok, I will go home on the Monday', and they told me Wednesday… and my heart sunk... and I went through it all over again…I kind of made my peace, by Monday, then it turned out to be Wednesday... And actually when it was time to go I wanted to cry." [18_6174]*

> *" …the doctor was saying as well, because I am out of the catchment area in case something would happen they don't want me in an ambulance with a premi baby, or even having a premi baby at home… so I would rather stay here till thirty weeks…" [08_4770]*

Having to wait a long time to be discharged once the decision had been made was a problem for some women. They were aware that this not only led to anxiety for them, but also that they were effectively "blocking" the bed for someone else who might need it.

> *"Every single person on that ward knew it was my son's birthday… I was bugging them slightly so I could go.… You sort of feel like you are taking care away, not in a bad way, but I was like 'I don't need to be here, I feel absolutely fine'..." [14_6317]*

Delay to discharge was often caused by waiting for medications to be ready. One woman spoke of a "deal" she made with the midwife who let her go on the condition that she would return the following day to collect her anticoagulant medication.

> *"…a midwife who said to me 'do you know what, generally we don't do this, the reason you are still here is because of your extremely high risk to develop a blood clot, and you're supposed to be being taught and sent home with*

medicines'. So she said 'I will do your tonight one for you if you promise to come back tomorrow and collect your medication'." [18_6174].

10.2.4.1. Clinical procedures

Women spoke about their experiences of both the clinical assessment procedures and also interventions they had relating to preterm birth risk. Clinical assessment included CTG monitoring, speculum examination, fFN testing and TVS CL.

The women found CTG monitoring reassuring, both because it reassured them of the baby's wellbeing, but also for some, because it "proved" they were having contractions.

"… she put me on the monitor and, you know, it was quite reassuring. I could see that the heartbeat and everything was fine. I could see that I was having contractions." [06_4658]

Although speculum examinations were often noted as unpleasant, women were prepared to tolerate them and found it very reassuring when they were told their cervix was closed.

"As soon as the doctor had said my cervix was closed I felt really reassured because I felt that maybe I was worried the sharp pain that I was getting was perhaps the beginning of my cervix opening. … I didn't know what was causing that pain." [06_4658]

"…So when she told me my cervix was closed, I thought, 'well I'm not having the baby tonight'." [14_6317]

Women were reassured by low fFN results, and appreciated the fact the results came quickly.

"…when my fibronectin is very low and they put it in the app [risk assessment tool] and they show in one week, 0.0%, that makes me feel better, like 'ok, I'm definitely maybe safe for a week, hopefully'." [15_5991]

However, they were often shocked and, unsurprisingly, worried by high results. Some felt that the way they had been told the results could have been better if they had been presented in a less worrying way.

"When I saw that amount… because she said before [low risk] was 50, I saw 200 and I started to cry because I was like 'oh my god, it's not 51 or 52 it's like 200'." [04_4492]

The women who had cervical length scans found them acceptable and valued the extra information. They felt it was more reassuring to actually see the cervix themselves, and, of course, they always appreciated the opportunity to see their baby.

"... [I had] the transvaginal scan which was another good thing because …the cervix was a good size, so it meant that we weren't just relying on I suppose the midwife looking at my cervix and saying 'oh yes, it's good'..." [04_4492]

"..so I think having a test, the fibronectin test…is great, but equally that only gives you an indication of what is happening from the outside , whereas ...on the inside there could be pressure effects from baby starting to change things in the cervix." [05_4258]

Some women spoke about the interventions intended to reduce the risks associated with preterm birth. These included hospital admission for observation and bed rest, steroid administration for fetal lung maturation and IUT.

Those admitted to hospital generally felt they were in the right place, and sometimes appeared to be very pleased because they knew they would not be able to rest properly at home, particularly with other children around.

> *"… so I think just being on bed rest made a difference … and I would love to stay on bed rest, because I know if I go home …." [08_4770]*

For those who had steroids, there was unanimous agreement that this is a very painful procedure. All understood the reasons and accepted the intervention, and most said that they preferred to be warned about the pain, however, so they could prepare themselves.

> *"I remember the first jab and I said to my husband 'that was worse than these pelvic contractions'. It's stingy and you don't get anything nice at the end of it. With labour you've got a baby'." [14_6317].*

With IUT, there were problems with waiting for ambulances and worries that it would have to be a long way from home.

> *"… the next day they said because a lady just gave birth to twins at 23 weeks there is no bed available so they would have to transfer me out, and they mentioned Brighton…but that means I would never see my husband." [08_4770]*

10.2.4.2. Relationships with other patients

Being with, and relating to other patients on the ward could both help and hinder women's ability to cope with the experience. Developing relationships could be helpful, resulting in a sense of shared experience, and also helping them to put their own worries into perspective.

> *"… we've had to come in for some reason, whether it was because we had contractions or our waters had started leaking … whatever the reason is we are all there for, you know, the same purpose." [18_6174]*

"…you become sort of kindred spirits in that, and there is something supportive and bonding about it... I think there's something grounding about being with other people who have … circumstances that are more fortuitous than yours and some that aren't." [11_6237]

However, being witness to emergencies on the ward could be extremely alarming, particularly when it happened to women they had developed relationships with, and especially if they were in for the same reason, i.e. in danger of preterm birth. This made it very difficult for them to stay positive.

"… this morning I woke up very early 'cause the emergency bell went off… … I know when I see baby doctors they have a blue bag, a very big bag, so I had a clue that ok, something not so good was going on… … straight away in my mind I said 'oh my God, please just save the baby'… it was so frightening and I just started crying in the toilet." [15_5991]

"…in hospital you are just wondering when you hear someone's buzzer go off you don't know if you are the one next." [15_5991]

"...one minute you can just be laughing and going to the toilet normal, having a shower, and next minute something else can happen [emergency on the AN ward] - it always makes me get on the edge like." [15_5991]

10.2.5. Theme 4: Interactions with professionals

Arguably the most important aspect of care is interaction with health professionals. The issues that emerged from this study were the attitude of the clinician, communication and trust in the professionals.

10.2.5.1. Attitudes of clinicians

It is reassuring that most of the women in this study felt the staff were very caring and supportive and this had a positive effect on their experience.

> *"The midwives … are always smiling, always friendly, introduce themselves, asking do you need anything, just offering that care and that help. I think it makes a huge difference in a situation like this..." [10_5864]*

> *" ...the midwives were all lovely, all of them. They were really great. I felt really well cared for in there…" [14_6317]*

10.2.5.2. Communication with clinicians

Communication was, on the whole, good. Most women appeared to be comfortable in asking for further explanation if they did not understand, and this was provided on most occasions.

> *"...so he, he stayed with me for a little while. He explained everything that needed explaining basically... and he did make sure I understood everything that was going to happen." [14_6317]*

> *"Sometimes I can't express myself properly. They could see that we come from other country, but they explained everything…. If I didn't understand something I could ask it and they explained it another way." [02_4355]*

The women who had quick access to specialist advice and continuity of carer seemed most likely to have confidence in the health professionals.

10.2.5.3. Confidence and trust in clinicians

Overall, most women seemed to trust the health professionals caring for them and were prepared to take their advice.

> *"… I trust them, so I go with trust." [18_6174]*

Feeling that the professional was confident in their own knowledge was important, unsurprisingly. This was not always the case, however, and when there was uncertainty as to the diagnosis confidence was undermined.

> *"…sometimes they said there's nothing but I'm getting these pains but they don't know why. They said 'it could just be your stomach getting bigger' but I don't really think they are that sure themselves." [09_5222Q]*

> *" … I know there are different people. They all have different opinions on everything. Like on the issues of steroids ... Some will say I will get it, some are saying I won't get another one, which is confusing. So what's the plan if something actually happens?" [15_5991]*

One woman was not happy to immediately accept the advice to have steroids and as she was not convinced the doctor advising her knew enough about it, first wanted to speak to her aunt who was a paediatrician.

> *"I spoke to my aunt and she said straight away: 'Oh no, there is no doubt, take the steroids. There is absolutely no question.' And once she said that I said 'ok', because although she didn't give me a lot of scientific explanation she is someone I trust very much." [04_4492]*

This may have been due to the uncertainty displayed which undermined her confidence in the doctor who was assessing her.

10.3. Women's views on illustrations of risk

10.3.1. Participant characteristics

The characteristics of all the women who took part in the second part of PETRA are presented in Section 10.1. Of the last ten, who also expressed their views on the risk illustration cards, five had experience of preterm birth or late miscarriage, one had a twin pregnancy and four were low risk for preterm birth. Six were of Black ethnic origin while four were White European. Of the ten, six had been admitted to hospital for their TPTL symptoms.

10.3.2. Risk illustration preferences

Participants were asked to consider the risk illustration cards (Figure 14, page 135) and to express their preferences. They were also prompted to give an explanation for their answers and encouraged to expand on how a risk of preterm birth should to be explained to women. The most popular illustration was Card A, an icon array with female figures. The simple percentage (Card E) appeared to be the second most popular. Figure 28 illustrates first and second preferences along with least preferred options. Table 53 shows these by individual participant.

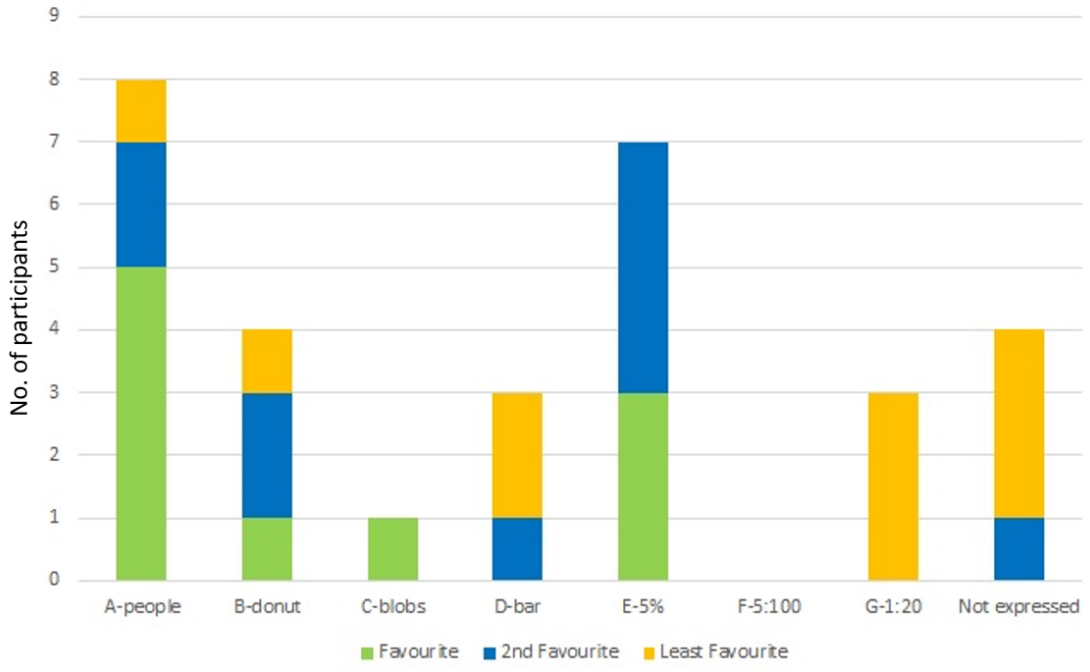


Figure 28. PETRA qualitative study participants' favourite (green), second favourite (blue) and least favourite (yellow) risk illustrations.

Table 53. Individual participant preferences of risk illustration with parity and risk status.

Study ID	Parity / Risk status	Favourite	2nd favourite	Least favourite
10_5864	***Primiparous No risk factors for PTB***	B-donut	D-bar	G-1:20 ratio
11_6237	***Primiparous Other risk factors for PTB***	E-%	A- female	G-1:20
12_6239	***Primiparous No risk factors for PTB***	E-%	A- female	B-donut
13_6253	***Primiparous No risk factors for PTB***	A-female	B-donut	D-bar
14_6317	***Multiparous Previous PTB or late miscarriage***	A-female	B-donut	D-bar
15_5991	***Primiparous; Previous PTB or late miscarriage***	E-%	No 2nd	A- female/C-blobs
16_6382	***Primiparous No risk factors for PTB***	A-female	E-%	*No clear least favourite*
17_6338	***Multiparous Previous PTB or late miscarriage***	A- female	E-%	*No clear least favourite*
18_6174	***Multiparous Previous PTB or late miscarriage***	A- female	E-%	G-1:20 ratio
19_6322	***Multiparous Previous PTB or late miscarriage***	C-blobs	E-%	*No clear least favourite*

10.3.3. Key issues arising from discussion of risk illustrations

In order to explore the women's views in more depth, a qualitative analysis of the data was undertaken and revealed a number of key issues. These were the variation in preference, the use of numbers versus pictorial representations of risk and the importance of the denominator.

10.3.3.1. Variation in preferences

In a small qualitative study, it is not possible to generalise results, however, the icon arrays, particularly those with the female shapes, appeared to be most popular (6/10 first and 2/10 second preference).

> *"…this one you see some people so maybe it's more representative of … you're talking about a child… I would say is more question of a feeling, of emotion…because it's a picture of people… makes it more real." [13_6253]*

> *"Because it's visual and it's done with people rather than blobs, so you relate to the people more as yourself." [11_6237]*

> *"I really, really like these little people. The ones that are highlighted with the amount. I think that gives a really nice visual aid to show that actually most people don't have preterm deliveries, just a small number." [14_6317]*

Most women said they felt comfortable with percentages (3/10 first and 4/10 second preference).

> *"I mean without explaining, I can quickly grab what 5% means." [15_5991]*

> *"… figures and charts no, percentages are fine." [18_6174]*

> *"I have done a lot of statistics … I am perhaps not your typical person that might be having this data presented to them, so I am perfectly comfortable with this [percentage]". [11_6237]*

The donut chart (Card B) was also popular, and much preferred to the bar chart (Card D).

"I think this one is the best because it tells you exactly. So without speaking to anyone I could immediately tell what the graph is about." [10_5864]

"…Because on this graph you see the 95%, you see that it's big and you are in the low 5% which is small compared to the other one [B]." [13_6253]

This variation in the way people preferred risk presented to them is in line with current advice on presentation of risk as discussed in Section 1.7.3.

10.3.3.2. The use of numbers versus pictorial illustrations of risk

Although most women said they found percentages easy to understand, one woman spoke about how difficult she found it when she was asked to consider the ratio cards F and G:

"… when I'm talking about risks of preterm… one minute I'm here and I'm thinking preterm, and then you're throwing me figures of 5 out of 100 or 1 in 20 …….taking me somewhere else and asking me to concentrate, sort of like a maths lesson." [18_6174]

Many appeared to prefer the pictorial illustrations:

"I think this is a bit better. There's obviously the thing, how it's going to be received by that person, especially when they are going to moments of anxiety and not really thinking clearly, and so visually this looks better." [17_6338]

"I certainly prefer those. I feel you get more information, because when you had that one I thought was the least helpful I thought '1/20, what does that mean'." [10_5864]

It appears that using visual illustrations can aid understanding, particularly if women are very anxious. As the majority of women with TPTL symptoms will be low risk and not go on to birth their babies prematurely, using this method could provide speedy reassurance for many.

10.3.3.3. The importance of the denominator

One woman was comfortable with the different numerical illustrations and, as a scientist herself, did not see any difference between 5%, 5:100 and 1:20. However, other women did, and spoke about how they "preferred" 5:100 rather than 1:20 because it felt more reassuring. They didn't "like" the 1:20, because it felt like the risk was higher:

> *"… I would need it explained to me more… Like 1/20 people which is quite high to me. Like 1 in every 20 people there's a possibility - that's how I read it. [Interviewer: That seems higher than 5/100?]… Yes definitely."* [15_5991]

> *"I am more willing to take the treatment if it was 1/20 than 5/100. Less likely to do it 5%, because you are so used to hearing it. 5% is nothing. You need to think about it a bit more." [12_6239]*

> *"I can imagine someone being more worried by 1/20 than 5/100… Maybe they can think of 20 women that they know that are pregnant or in labour, and think of the fact that one of those might have it early."* [14_6317]

The chosen denominator appears to affect women's perception of risk, and whether they will accept, or decline, advice and intervention. It is important, then, that clinicians are mindful of this and take care not to inadvertently pressurise women into compliance.

10.4. Summary of findings

In this study, women spoke about unsettling feelings of uncertainty and conflict associated with TPTL and how these affected their ability to cope. They also talked, largely positively, about the care they received and interactions with the professionals providing that care. An analysis of women's opinions on how useful they perceived a number of visual illustrations of risk demonstrated that icon arrays with female symbols and simple percentages were the most popular.

11. Discussion

This PhD project sought to address two issues: i) improving risk assessment in TPTL by developing a clinical decision support tool, the QUIPP app and ii) understanding the experience of TPTL from the woman's perspective and identifying areas of TPTL management that could be improved. In this chapter, these issues are considered in relation to the findings of the three parts of the PETRA study along with, and in the context of, other literature and current clinical practice.

11.1. PETRA cohort study and development of the QUIPP app.

11.1.1. Prediction of sPTB

PETRA is the largest prospective cohort, to date, of UK women with symptoms of TPTL whose clinical assessment included qfFN plus or minus TVS CL. Although many investigators have previously found associations between a plethora of factors and preterm birth, including demographic and lifestyle characteristics, the only factors identified in this cohort to be predictive of sPTB at <34 and <37 weeks were the major risk factors, such as previous preterm birth or cervical surgery, as shown in Section 8.4.2. Creation and validation of the prediction models also found no association with demographic or other risk factors, so they were subsequently not included in the risk prediction algorithms. This apparent lack of effect was possibly due to the heterogeneity of mechanisms leading to PTB, sample size and low event rates in this population. Therefore, perhaps a larger, more varied cohort would produce different results.

Prediction based on qfFN and CL category, and that the likelihood of sPTB increases with rising fFN and shortening CL is no surprise, and is concordant with a large amount of literature on the subject (Section 1.4). To compare and contrast all research findings in this area is difficult, partly because investigators use different thresholds of fFN concentration and cervical length for what they deem a "positive" test. For example, some will use a CL of <15mm and a fFN of 50 ng/ml (Tsoi *et al*., 2006), while others choose CL ≤20 mm and/or fFN of 20 ng/ml (Levine *et al*., 2018) or even an fFN ≤ 5 ng/ml (Jwala *et al*., 2016). The aim of this project was not to demonstrate the ability of fFN or CL in predicting sPTB but it is interesting to compare results with previous research carried out in the same hospital and therefore with a similar population. An earlier prospective study with a cohort of 300 symptomatic women, published by our group (Abbott *et al*., 2013), investigated the ability of qfFN to predict sPTB at <34 weeks and within 2 weeks of testing. We found the relative risk of sPTB at less than 34 weeks' increased in each category when compared with the lowest category (<10 ng/ml): fFN 10-49 ng/ml, 5.6 (95% CI,1.05–29.57; P<0.01); 50-199 ng/ml, 7.9 (95% CI, 1.38–45.0; P<0.01); fFN 200-499 ng/ml, 22.8 (95% CI, 3.84–135.5; P<0.01); and fFN ≥500 ng/ml, 51.3 (95% CI, 12.49–211.2; P<0.01). These findings are similar in the PETRA cohort for the categories: 50-199 ng/ml, 7.4 (95% CI, 2.8-19.5) and fFN 200-499 ng/ml, 20.5 (95% CI, 8.8-47.8). However, there was not a significant difference for sPTB at <34 weeks, (or at <37 weeks or within one or two weeks of testing) between the lowest and second lowest category (10-49 ng/ml) with a RR of 2.1 (95% CI, 0.7-6.6). Additionally, in the highest category, fFN ≥500 ng/ml, the risk ratio was lower than the second highest for sPTB < 34 weeks, 8.9 (95% CI, 1.2-65.9). Abbott *et al*. (2013) did

not report any data on CL measurements because this was not standard practice in TPTL assessment in the UK at that time.

It is also useful to compare the PETRA findings with another from our group, (Kuhrt *et al*., 2016a), where we reported the creation and validation of the predictive algorithm for symptomatic women used in the first version of the QUIPP app. This study included data on 382 women (190 training set, 192 validation set) with qfFN test results. We reported predictive statistics demonstrating the ability of our prediction model to predict sPTB at <30, <34 and <37 weeks, and at within 2 and 4 weeks, using a threshold of >10% as a positive result.

In the PETRA study, prediction was investigated for sPTB at <30, <34 and <37 weeks, and within 1 and 2 weeks, using a threshold of ≥5% as a positive result, with a substantially larger cohort (1173 training set and 576 validation set). Comparison can only be made with the fFN group predictive statistics as CL measurements were not available in the earlier study. Comparable prediction statistics for validation sets of Kuhrt and PETRA data are summarised in Appendix 17.6. PETRA findings demonstrate a significant increase in sensitivity, the test's ability to correctly predict sPTB, at all times points. The specificity, however, is reduced, but not by as much. These differences are likely due to the reduction in risk threshold for a positive test from 10% to 5% Positive predictive values (PPV), the probability that a women with a positive test (in this case, a ≥ 5 or 10% risk of sPTB) are lower in the PETRA cohort while the negative predictive values (NPV), the probability that a women with a negative test (% risk < 5% or 10%) will not have sPTB, is similar to the Kuhrt cohort. Unlike sensitivity and specificity, PPV and NPV are dependent on prevalence, and NPV will always be

high where the prevalence is low. In Kuhrt's study, the prevalence of sPTB was higher at all time points, so it is not surprising that the PPV is higher than in the PETRA cohort validation set.

The area under the ROC curves (AUC), which demonstrate the predictive ability of the QUIPP algorithms at different thresholds, can also be compared with Kuhrt *et al*.'s findings in Appendix 17.6. In that study, we found AUCs of 0.88, 0.83, 0.77, 0.77 and 0.78, for prediction of sPTB at <30, <34, <37 week's gestation and within two and four weeks of testing, respectively. This represented an overall improvement compared to an earlier systematic review of fFN for predicting sPTB (Honest *et al*., 2002). Honest *et al*.'s review included data from forty studies and 26,876 women, in which ROC curves ranging from 0.71 to 0.77 demonstrated the ability of fFN to predict sPTB at < 34 and <37 weeks' respectively. In the PETRA validation set, AUCs were, therefore, higher than previously reported (Honest *et al*., 2002; Kuhrt *et al*., 2016a) in all but the < 37 weeks' time point: 0.96 (<30 weeks); 0.85 (<34 weeks); 0.77 (<37 weeks); 0.91 (<1 week) and 0.92 (<2 weeks).

Comparison of the predictive statistics with our earlier work (Kuhrt *et al*., 2016a) demonstrate improved prediction but are based on algorithm developed for qfFN only. For the 2nd version of QUIPP algorithms for predicting sPTB using qfFN alone, TVS CL alone or a combination of both tests were created and validated. The ability of the new version of the QUIPP app to predict risk of sPTB using risk factors and either, or both, tests, increases its utility as the app has the flexibility to be used by clinicians where fFN testing is not available, and TVS CL is likely to become more common as more clinicians are trained.

11.1.2. Administration of steroids in PETRA cohort

In the PETRA cohort, whether steroids had been administered or not, was known in 1024 cases. Of these, over 30% had steroids on at least one occasion. Considering that only 12.1% of women overall had sPTB this appears high. However, this rate is substantially lower than reported in previous similar cohorts where often more than 50% of women received steroids (Freeman *et al.*, 2015). In one study over two thirds of women with TPTL who delivered after 34 weeks had received an unnecessary course (Sanya *et al*., 2014). The lower rate in our cohort, compared to earlier studies, might suggest that identification of women who really need them is improving, with over 76% of the women who delivered at term not receiving them. This may be due to an increased confidence of clinicians, over time, in the value of fFN as a rule out test. All the hospitals participating in this study used fFN in TPTL assessment as part of standard care.

There were few repeated courses, which again could reflect more appropriate targeting of this intervention. It is reassuring to note that, in the small number of women delivering within 7 days, the optimal window for steroid administration, 90% (18/20) had received them. The two that did not receive steroids were at 32^{+3} and 34^{+6} weeks' gestation, so it is possible that in at least one of these cases steroids were deliberately withheld as the gestation was over 33+6, and inside a range within which NICE (2015) recommends "considering" rather than definitively "offering" them (Figure 2).

11.1.3. Discussion of QUIPP App users study findings in relation to other literature.

The literature review on mobile apps for clinical decision support (Chapter 2) highlighted the importance of mobile app users being involved in development and evaluation, both for informing further developments and maximising the likelihood of the tool being used in practice. Part 3 of the PETRA study investigated clinical users' views of the first version of the QUIPP app with the intention of incorporating ideas for improvements and addressing negative issues ahead of the 2nd version development.

In terms of acceptability and ease of use, respondents were generally very positive. This was particularly in respect of its simplicity, both in ease of use, and how it combined separate factors (i.e. background risk, gestation and test results) into a simple percentage figure. No users reported problems with downloading the app or it closing unexpectedly. No training had been provided but this was not highlighted as a problem.

Suggestions for improvements included increasing flexibility by including the option to use QUIPP with either or both test results. In the first version of the app, the user was required to enter both qfFN and CL results for the high risk asymptomatic women. It was only possible, however, to enter qfFN for symptomatic women. This was because there were insufficient data on CL from women with TPTL symptoms when the first algorithms were created and validated.

Another suggestion for improvement was increasing the specificity of background risk factors, and use of preventative interventions, e.g. stipulating the number, and gestations, of previous preterm births and whether the women had had a preventative intervention, such as cerclage or progesterone. This was considered when the new algorithms were developed, but there were insufficient numbers to detect differences between these sub-groups. Future revisions with larger cohorts may allow incorporation of these elements.

Multifunctionality was an element apparently prized by the clinicians involved in the studies included in the literature review on mobile apps for clinical decision support (Chapter 2). In PETRA, clinicians suggested increasing the functionality of the app by including information or links to current clinical guidelines and using the tool to collect data on outcomes, which could later be used in future algorithm development. It was not possible to include these suggestions in the 2nd version of QUIPP due to time and budget restraints but they have been noted and may be incorporated in future versions.

11.1.4. QUIPP app users' and women's views in relation to presentation of risk

The variety in the views and preferences of the women participants of this study confirmed findings from previous research and literature which reports wide differences in risk perception (Brewer *et al*., 2007; Herxheimer, 2005; Lee *et al*., 2012). It is reassuring that the clinician participants understood the value of individualising their approach to communicating risk and of using illustrations to explain it, both of which are consistent with best practice evidence and current guidelines (David and

Akintomide, 2016; Fagerlin *et al*., 2011; Royal College of Obstetricians and Gynaecologists, 2007; Lipkus *et al*., 1999; Spiegelhalter 2008).

The women in this study did not favour the ratio illustrations and tended to feel more negatively, because they perceived the risk to be higher, when the denominator was lower, i.e. 1:20 as opposed to 5:100. This is concordant with Schapira and colleagues (2001) who undertook a qualitative study of how women's perception of breast cancer risk varied depending on the way the risk was presented. They found that icon arrays with larger denominators were perceived as representing lower risks. This contrasts, however, with earlier studies which suggest participants perceive risk to be higher when the denominator was higher, the so-called "ratio bias" effect (Reyna and Brainerd, 2008).

Most of the clinicians and women participants preferred pictorial illustrations of risk, particularly the icon array with female symbols, which was the favourite with the donut chart being second pictorial preference for the women. Goodyear-Smith and colleagues (2008) also found a preference amongst patients for visual illustrations of risk. They interviewed 100 patients with cardiovascular disease and found that 57% of those who expressed a preference of one method over others said they preferred graphical presentation of risk. This was significantly greater than those who chose the next popular option which was relative risk (19%, p=<0.001).

All clinicians and most women in the PETRA study also felt comfortable with percentages, although some clinicians said they sometimes converted the % risk into a

number in a hundred and tried to adapt the way they explained it on an individual basis.

As a result of the PETRA findings a visual illustration of risk was included in 2nd version of the QUIPP app. Although the icon array was the most popular amongst both the women and the clinician QUIPP app users, the image detail did not display well on a typically sized mobile phone screen. Additionally, a % risk of less than one is commonly calculated (e.g. 0.1%), which means a denominator of 1000 would be necessary. A decision was taken, therefore, to use the women's next most popular pictorial preference, which was the donut chart, and place the percentage, their overall second preference, within it (Figure 29).

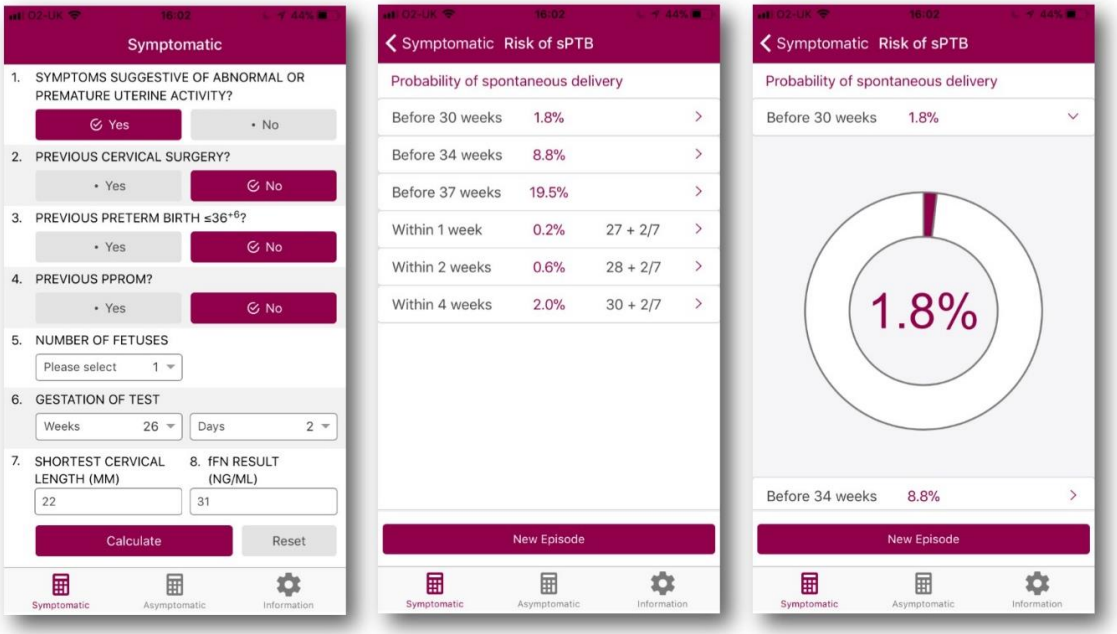


Figure 29. Screen shots of 2nd version of QUIPP. User indicates risk factors and enters gestation and test results on first screen. % risks are revealed on second screen. User clicks arrow to reveal visual illustration of risk on third screen.

Although an icon array is not included in the 2nd version of QUIPP, the findings have changed practice in our preterm surveillance clinic at GSTfT. A4 sized laminated cards with icon arrays illustrating risks of 1 in 100 on one side, and 1 in 1000 on the other, are now being utilized when a clinician feels they will help a woman to understand her % risk as calculated by the app.

11.2. Women's experience of TPTL

In this section, the main themes identified in this qualitative study, as well as potential areas for improvement in care, one of the research objectives, will be discussed in relation to other research, policy and practice.

11.2.1. Uncertainty and conflict in threatened preterm labour

The very nature of threatened preterm labour is one of uncertainty. Preterm labour is very difficult to diagnose in its early stages, so it is not surprising that women in our study experienced a great deal of uncertainty and, at times, conflicting opinions as to what may be causing their symptoms. TPTL symptoms can have many potential causes, some requiring urgent treatment, for example urine infections, while others need less urgent treatment, e.g. pelvic girdle pain and constipation. Other causes of pain, such as fibroid degeneration, are usually managed with pain relief and reassurance. Most of the time TPTL symptoms are transient and resolve on their own, but as a diagnostic test for very early preterm labour does not exist, clinicians are likely to be uncertain and must consider the possibility of labour, whilst not ruling out other, sometimes potentially serious, causes for the symptoms that may be unrelated to the pregnancy.

Women too are uncertain as to the causes of their symptoms and participants in this study were no exception. They appeared to undergo a process which included trying to make sense of their symptoms before seeking reassurance or medical help, and this echoed findings reported in other studies (Patterson *et al.,* 1992; Coster-Shultz and Mackey, 1998; Barlow *et al.,* 2007; Weiss *et al.,* 2001). This process appeared to be more prolonged in primiparous women in this study, however, and women with previous experience of preterm birth were quicker to seek help and less concerned about being seen as over-reacting, which is also reported by the high risk women in O'Brien *et al.,*'s study (2010).

The uncertainty of clinicians around TPTL can lead to increased anxiety caused by conflicting advice and information, and this was reported by several study participants. Conflicting advice and information appeared to be an important theme in our study and although mentioned by Barlow *et al.,* (2007) does not feature prominently in the studies identified in the literature review. Although evidence on how best to deal with uncertainty in clinical practice remains unclear (Politi *et al.,* 2007; David and Akintomide, 2016) failing to acknowledge it can cause further problems (Politi, 2015). Clinicians may try to minimize uncertainty for the benefit of their patients, but if they give the impression of confidence in a diagnosis, particularly without reliable test results, the woman whose symptoms persist may hear a different diagnosis from another very soon afterwards.

Although a recurring theme, it was noticeable that the high risk women in our study tended to get less conflicting advice than the low risk mothers. This was possibly because the hospital where this study took place has a dedicated specialist preterm team. Newly admitted women, including those transferred from other units, will be quickly referred to the team and a management plan made. The hospital staff have confidence in this well-established team, and therefore the likelihood of advice and information being inconsistent is lower. It is also possible that clinicians may be more inclined to recommend interventions at lower thresholds for high risk women.

The emotional stress of conflicting responsibilities, the need to care for other children as well as their unborn baby, was also apparent in the women in our study, and has

been reported previously. Those who remained under threat of preterm birth appeared to be trying to "hold it together", and employed a range of coping mechanisms as they dealt with the sometimes intense anxiety and the recommended, albeit temporary, life changes such as hospitalisation or restriction of activity. This also resonates with findings from earlier studies (Adler and Zarchin, 2002; Mackinnon, 2006; Höglund and Dykes, 2013).

11.2.2. Anxiety in threatened preterm labour

There is a possibility that the uncertainty and conflict associated with TPTL and its resulting anxiety could even increase the risk of preterm birth (Section 1.3). It would appear sensible, then, to seek to address the modifiable causes of anxiety in women at risk of preterm birth, including those with symptoms of TPTL. Simple interventions, such as using reliable predictive tests (e.g. fFN and CL measurement) could reduce uncertainty, at least in those women with reassuring results, who make up the majority of women with TPTL symptoms.

Interventions designed to directly address stress and anxiety in women at risk of preterm birth have been investigated. Jallo *et al.,* (2017) examined the use of a mobile app which provided women with information and guided imagery and compared stress levels (Perceived Stress Scale (PSS), Visual Analog Stress Scale (VASS) scores, Coping Self-efficacy (CSES)) in 15 women hospitalised for TPTL. They found a significant difference ($p<0.0001$) in VASS scores, but not PSS or CSES, which suggests that immediate stress, at least, was relieved by the intervention. In another study

(Chuang *et al.,* 2012) researchers found that a relaxation training programme improved the immediate psychological and physiological stress responses in women with TPTL. They also found that, although numbers were too small to prove effect on outcomes (n=129), fewer women in the experimental group gave birth within one week of study entry (16% vs 30%), and within two weeks of study entry (7% vs 19%).

Another intervention, an internet-based cognitive behavioural self-management training programme (IB-CBSM), was tested in 93 women with TPTL (Scherer *et al.,* 2016). The researchers found the control group, who had been given alternative exercises, such as Sudoku, riddles and writing stories, experienced the same reduction in stress and anxiety as the intervention group. This suggests that distraction itself could be useful, and several women in our study appeared to be using distraction as coping mechanism. Other studies have found distraction to have beneficial effects on stress in both preterm labour (van Zuuren, 1998) and other stressful conditions (Priem and Solomon, 2009; Ram *et al.,* 2010).

Women who were trying to stay positive and using distraction in coping with their anxiety did not always feel the staff understood when they declined offers of information and books about what might happen if the baby was born early and needed neonatal admission. This finding echoes those of Gaucher and colleagues (2016) who surveyed women about their experience of neonatal specialist consultation when they had been hospitalised for TPTL. Of the 229 women who responded, 90% indicated they had had a positive experience, although 39% felt they had received too much information.

11.2.3. Aspects of care and interactions with professionals

The organisation of maternity care and interactions with healthcare professionals can have a profound effect of women's experience of TPTL. Several women in this study spoke about the importance of continuity of carer, and how this could enhance relationships and trust, as well as potentially making care more efficient and safer. Knowing who, and how, to call, and feeling comfortable doing so, makes speedy access to information, another important issue for women in this study, and reassurance easier. Continuity of care models have been shown to be safe and effective in reducing interventions, preterm birth and fetal loss (Sandall *et al.,* 2016), although the actual mechanisms involved remain unclear. The women in our study who had quick access to specialist advice and continuity of carer appeared to be most likely to have confidence in the health professionals.

Most of the women in this study who were considered to be particularly at risk of preterm birth, either because of their obstetric history or the severity of their symptoms, were known to the specialist preterm team. They appeared to trust the clinicians advising them, who were less likely to display uncertainty, and they spoke less of receiving conflicting advice. Specialist preterm clinics and teams that can quickly identify risk and instigate timely interventions are not currently established in all maternity services. However, numbers are increasing (Carter *et al.,* 2018a) and they have been identified as a useful mechanism in achieving the UK government's target to reduce the preterm birth rate from 8 to 6% by 2025 (Department of Health, 2017).

Evidence on the effectiveness of specialist preterm services is, however, limited. A systematic review of the effectiveness of specialist preterm clinics in reducing preterm birth and its consequences found mixed results (Malouf and Renshaw, 2017). Findings from randomised controlled trials, all of which were carried out before 1990, showed no benefit, however later cohort studies reported a reduction in preterm birth. As cohort studies are regarded as low quality evidence the authors recommend caution when interpreting the results, but acknowledge that the lack of recent RCT evidence is likely to continue due to the difficulties of conducting randomised trials which deny women a valued service. The women attending a specialist preterm clinic in O'Brien *et al.,*'s (2010) qualitative study appreciated the regular reassurance and support they obtained at these clinics and reported feeling that other health professionals did not always understand their particular worries. The high risk women in this study expressed similar views. Women known to the specialist preterm team often spoke of how they felt comfortable accessing the team for the reassurance they frequently required.

Fernandez Turienzo *et al.,* (2016) in their systematic review and meta-analysis of models of antenatal care designed to reduce and prevent preterm birth found that while "alternative" models of care (i.e. midwife-led continuity of care and specialised care) reduce preterm birth, conclusions on the relative benefits of the two models could not be drawn.

The findings from this study suggest that these two models share at least two elements: 1. quick and easy access to advice from a known and trusted clinician and 2.

continuity of carers who know the woman and how best to support her in her coping mechanisms, whether that be providing more information or helping her to be positive, and giving, in most cases, speedy reassurance. As anxiety is highly associated with preterm birth risk, perhaps one of the most important factors is the reduction of anxiety that comes with quick access and continuity of carer.

12. Limitations

A number of limitations must be taken into consideration when reviewing the PETRA study findings. Nearly half of the participants in the cohort study, and all in the qualitative study, were recruited from one inner-city teaching hospital with a specialist preterm surveillance clinic which is directed by an internationally renowned expert in preterm birth. Care of women with symptoms of TPTL may not be representative of care in other hospitals, many of which do not currently offer these specialist services, and local guidelines and policies may differ from those elsewhere. Clinicians working in this hospital may also have greater confidence in one of the tests used, i.e. fetal fibronectin, because much of the research that validated its use in the UK was carried out at this hospital.

Similar to other studies of TPTL, the prevalence of preterm birth was low. This was particularly so in respect of delivery within 7 days, where the numbers were very small with only 15 cases in the training set, and 13 in the validation set. This is an important interval for risk prediction as it is the optimal window for administration of steroids. Confidence in QUIPP's ability to accurately predict sPTB <1 week of testing would be increased with a larger cohort. One of the reasons the prevalence was low was because the prospective cohort study design meant women had to be consented before delivery. Many women whose TPTL symptoms progressed quickly into established labour could have been missed because research staff were unable to approach them before they delivered. Other study designs which allow more

comprehensive data collection, such as retrospective cohort studies, might capture these important cases, but would be vulnerable to selection bias.

Another limitation was the smaller than expected number of cases with both fFN and TVS CL. This was despite efforts to increase the availability of ultrasound vaginal probes and the encouragement of staff training. There was, nevertheless, sufficient data available to create and validate predictive algorithms for TVS CL in the 2nd version of QUIPP, but these could be further refined with a larger dataset. For this reason, ethical approval for an extension, focusing on recruitment of women with TVS CL, was sought and achieved, as outlined in section 5.4.

The women's experience study was, as is common in qualitative research, small, so the findings are not necessarily representative of all women who have experienced TPTL. Even in respect of the local population the experience and views of the women who agreed to participate may not be the same as those who did not. Some of the participants were known to be high risk for PTB and had been reviewed by members of the specialist team and their experience of this and these women's knowledge of the tests may have influenced their experience when they presented with symptoms. Additionally, interpretation of the findings will have been influenced by the researcher's experience, as a woman, a mother, a midwife, and a midwife with a long experience of caring for women at risk of preterm birth.

13. Implications for practice

13.1. Ongoing improvements in PTB risk prediction

The NICE guideline (NICE, 2015) recommends that, when established labour has been ruled out during the clinical assessment of women over 30 weeks' gestation, TVS CL should be offered, followed by fFN testing, only if TVS CL is unavailable or unacceptable. NICE do not recommend using a combination of both tests, based on a paucity of evidence to support its value and cost effectiveness. While some investigators have found added value in combining tests, others have not, as discussed in section 1.4.4. In PETRA, the effect of combining CL with qfFN on predictive ability was examined. Results indicated that it did not improve prediction and, in fact, that TVS CL alone was inferior in predicting sPTB within 1 or 2 weeks (AUC 0.698 vs 0.875, sPTB < 1 week, p=0.02; AUC 0.730 vs 0.889, sPTB < 2 weeks, p=0.02). This suggests that fFN has superior predictive ability, and that, based on these findings, fFN should be first choice of test in TPTL over TVS CL.

The PETRA study findings support use of 15mm as a cut-off for the NICE guideline, as the majority of women in this study were recruited after 30 weeks and CL category 15-24 mm appears to have the same rate of sPTB as CL >24 mm (Table 24), with risk ratios of only 1.1 (95% CI 0.2-5.6) and 1.8 (95% CI 0.9-3.4) for sPTB <34 and <37 respectively. Similarly, analysis of fFN by category in this study confirmed a threshold of 50 ng/ml was appropriate as there was no difference in accuracy of prediction between the 0-9 and 10-49 ng/ml categories.

In the PETRA cohort, 85% of women were treated according to the fFN and CL thresholds recommended in the NICE guideline: 87.4% (181/207) of those with an fFN of >50 ng/ml or CL of ≤ 15 mm received steroids appropriately, 84.3% (689/817) with longer cervix or lower fetal fibronectin did not receive steroids. However, PETRA study recruitment commenced before the NICE guideline was published so it is unclear to what extent the guideline influenced practice.

Findings from our Delphi consensus of preterm experts (Carter *et al*., 2016) suggest that NICE's treat-all strategy for women under <30 weeks without reference to either TVS CL or fFN may not be universally accepted. If fully implemented it is likely to lead to a significant increase in unnecessary intervention (Watson *et al*., 2017b). Validation of the predictive algorithms developed in this PhD project for the 2nd version of QUIPP show excellent prediction for sPTB <30 weeks as well as within 1 and 2 weeks (Section 8.7). The value and safety of QUIPP for decision support in TPTL are currently being evaluated in practice in the EQUIPTT study. The results of that study may provide evidence for this recommendation to be reviewed.

The findings from the PETRA study will contribute to the ongoing quest to find more accurate methods in predicting preterm birth. Use of the QUIPP app in practice could lead to an increased confidence and better targeting of interventions for both reducing preterm birth and its associated morbidities, as well as unnecessary intervention. The excellent prediction of sPTB at less than 30 weeks has particular importance and may inform a review of the NICE recommendation to treat all women with TPTL under 30 weeks without even testing with qfFN or TVS CL. Nevertheless, however accurate

QUIPP is, whether its use influences practice is yet to be determined and results of the EQUIPTT study are eagerly anticipated.

13.2. Developments in specialist PTB care provision

Findings from the qualitative study suggest that continuity of carer is a significant issue for women at risk of preterm birth and the importance of continuity in preterm birth reduction has been acknowledged by the UK Department of Health (Department of Health, 2017). Since publication of "Changing Childbirth" in 1993, continuity of carer has been virtually enshrined in UK maternity policy (Expert Maternity Group & Cumberlege, 1993; Department of Health, 2004; Department of Health, 2007; NHS England, 2016), yet this model of care remains unavailable to most women (Redshaw and Henderson, 2015). There is new impetus, however, since the Better Births Maternity Review Report (NHS England, 2016) and the NHS England's Maternity Transformation Programme which is working towards implementing the recommendations.

The establishment of national guidance on referral to specialist preterm services, currently in development, could lead to a reduction in conflicting advice and information for women at risk, as well as the targeting of interventions that reduce preterm birth and the risks associated with it. Additionally, utilizing reliable tests such as qfFN and/or TVS CL, which have high negative predictive values, could reduce the number of unnecessary interventions, at least in women where risk of delivery is low. Reducing unnecessary hospitalisation, treatments and the *in utero* transfers

which result in women being sometimes long distances from their families would undoubtedly reduce concomitant anxiety.

Increased awareness of the issues important to women with symptoms of TPTL will help to improve their experience and, potentially, pregnancy outcomes. Where risk remains high and reassurance cannot be given, clinicians must take care to acknowledge uncertainty, minimize delays and conflicting advice and take time to assess the woman's individual coping strategies. Providing detailed information may be important for some, but this is not necessarily the case for women who are coping by distracting themselves and trying to stay positive.

14. Recommendations for further research

As previously noted, the PETRA study was extended beyond its original recruitment period for continued collection of TVS CL data. This is particularly important because NICE recommends this as the test of first choice in TPTL and because more clinicians are being trained in practice. Additionally, there is a need to evaluate the QUIPP app in practice and it is hoped that the findings of the ongoing EQUIPTT study will provide the necessary answers.

Recently published systematic reviews on the effect of TVS CL and fFN on management and outcomes reached the conclusion that use of TVS CL for assessment of women with TPTL appears to reduce sPTB while fFN does not (Berghella and Saccone, 2016; Berghella *et al.*, 2017). However, more research is needed in this area because most of the studies included in these reviews were carried out before fFN was an established and trusted test. Future studies and systematic reviews may come to different conclusions. Findings from PETRA suggest that confidence in fFN testing may have increased and better targeting of intervention is already underway.

Research into other biomarkers for predicting sPTB continues. The ongoing QUIDS 2 study (ISRCTN trial registry number: ISRCTN41598423) is evaluating two bedside tests, Actim Partus and Partosure, alongside side qfFN. If these two biomarkers prove to be as valuable as fetal fibronectin, it may be possible to include them in future developments of QUIPP, increasing its flexibility further.

In PETRA, only major obstetric risk factors, such as previous preterm birth or cervical surgery influenced, and were therefore included in, the predictive algorithms. Other factors that have previously been associated with sPTB, such as age, ethnicity, history of urinary tract and Group B Streptococcal infection did not influence prediction in our cohort, but this may have been due to the sample size. It is important, therefore, that data collection is ongoing so that, if effects are noted in larger cohorts, they can be included in future refinements of QUIPP. Other research projects, clinical registries and databases, such as the Preterm Clinical Network Database (Carter *et al*., 2018a), have the potential to provide high quality prospectively collected data for this purpose.

Further research into the relationship between anxiety and preterm birth and anxiety reducing interventions is needed. This is a promising area and more needs to be done to explore how stress management interventions can be utilised to help women at risk of preterm birth.

Research into continuity models for high risk women would also be useful. One such project is ongoing. The POPPIE study (ISRCTN trial registry number: ISRCTN37733900) is an RCT investigating potential improvements in experience and outcomes of women at risk of preterm birth between women allocated to either specialist preterm midwifery team care or standard care.

15. Summary and conclusion

This PhD project sought to develop a risk assessment tool for predicting preterm birth in women with symptoms of TPTL. This, along with establishing an understanding of women's experience and the aspects of care that effected it, would ultimately inform future improvements in care. Findings from all three parts of PETRA were utilized in development of the 2nd version of QUIPP. This new version appears to be superior in predicting sPTB in women with symptoms of TPTL when compared with previously reported findings on prediction using fFN, TVS CL or the first QUIPP algorithms. Whether its use in practice leads to more appropriate management will remain unknown until the EQUIPTT study is complete. As the largest cohort study of women with TPTL in the UK to date, it also throws some light on current use of interventions intended to reduce sPTB and its associated risks.

The women's experience study was the first exploring women's experience of TPTL in a UK hospital with a specialist preterm service. The findings provide insight into the experience of both low and high risk women with symptoms of TPTL and further supports the need for women of all risk groups to have timely access to advice and information, and continuity of care. These findings have already been published (Carter *et al*., 2018b) and are, therefore, available to interested clinicians and those involved in the development of clinical management guidelines.

In conclusion, then, the research questions addressed by this PhD thesis have been successfully answered and all the specific objectives have been met; these findings will go on to inform future research and clinical practice.

16. References

Abbott, D., Smout, E., Foster, C., Seed, P.T. & Shennan, A.H. 2011, "The development and validation of a predictive tool for spontaneous preterm birth incorporating fetal fibronectin and cervical length." *Blair Bell RCOG Annual Academic Conference*, December 2011.

Abbott, D.S., Radford, S.K., Seed, P.T., Tribe, R.M. & Shennan, A.H. 2013, "Evaluation of a quantitative fetal fibronectin test for spontaneous preterm birth in symptomatic women." *American Journal of Obstetrics and Gynecology,* vol. 208, no. 2, pp. 122. e1-122. e6.

ACOG Committee on Obstetric Practice, 2017. American College of Obstetricians and Gynecologists Committee Opinion No. 713: *Antenatal corticosteroid therapy for fetal maturation*. August 2017 [online] available at: https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co713.pdf?dmc=1&ts=20180927T1214475515. Accessed: 17th August 2018.

Adler, C.L. & Zarchin, Y.R. 2002, "The “Virtual Focus Group”: Using the Internet to Reach Pregnant Women on Home Bed Rest." *Journal of Obstetric, Gynecologic, & Neonatal Nursing,* vol. 31, no. 4, pp. 418-427.

Ahmed, H., Naik, G., Willoughby, H. & Edwards, A.G. 2012, "Communicating risk." *BMJ (Clinical research ed.),* vol. 344, pp. e3996.

Altman, D.G. & Royston, P. 2000, "What do we mean by validating a prognostic model?", *Statistics in Medicine,* vol. 19, no. 4, pp. 453-473.

Amoakoh-Coleman, M., Borgstein, A.B., Sondaal, S.F., Grobbee, D.E., Miltenburg, A.S., Verwijs, M., Ansah, E.K., Browne, J.L. & Klipstein-Grobusch, K. 2016, "Effectiveness of mHealth Interventions Targeting Health Care Workers to Improve Pregnancy Outcomes in Low- and Middle-Income Countries: A Systematic Review." *Journal of Medical Internet Research,* vol. 18, no. 8, pp. e226.

Arbour, M.W. & Stec, M.A. 2018, "Mobile Applications for Women's Health and Midwifery Care: A Pocket Reference for the 21st Century." *Journal of Midwifery & Women's Health,* vol. 63, no.3, pp.330-334.

Asztalos, E., Willan, A., Murphy, K., Matthews, S., Ohlsson, A., Saigal, S., Armson, A., Kelly, E., Delisle, M. & Gafni, A. 2014, "Association between gestational age at birth, antenatal corticosteroids, and outcomes at 5 years: multiple courses of antenatal corticosteroids for preterm birth study at 5 years of age (MACS-5)." *BMC Pregnancy and Childbirth,* vol. 14, no. 1, pp. 272.

Badgery-Parker, T., Ford, J.B., Jenkins, M.G., Morris, J.M. & Roberts, C.L. 2012, "Patterns and outcomes of preterm hospital admissions during pregnancy in NSW, 2001-2008." *Medical Journal of Australia,* vol. 196, no. 4, pp. 261-265.

Banta, D. 2003, "What is the efficacy/effectiveness of antenatal care and the financial and organizational implications." *Copenhagen: WHO Regional Office for Europe (Health Evidence Network report)*.

Barlow, J.H., Hainsworth, J.M. & Thornton, S. 2007, "An exploratory, descriptive study of women's experiences of hospital admission during pre-term labor." *Acta Obstetricia et Gynecologica Scandinavica,* vol. 86, no. 4, pp. 429-434.

Basak, S. & Babbur, V. 2012, "Audit of in-utero transfers following introduction of rapid fetal fibronectin test for assessment of preterm labour in a district general hospital in United Kingdom." *International Journal of Gynecology and Obstetrics,* vol. 119, pp. S291.

Battle, J.D., Farrow, L., Tibaijuka, J. & Mitchell, M. 2015, "mHealth for Safer Deliveries: A mixed methods evaluation of the effect of an integrated mobile health intervention on maternal care utilization." *Healthcare,* vol. 3, no. 4, pp. 180-184.

Berghella, V., Palacio, M., Ness, A., Alfirevic, Z., Nicolaides, K. & Saccone, G. 2017, "Cervical length screening for prevention of preterm birth in singleton pregnancy with threatened preterm labor: systematic review and meta-analysis of randomized controlled trials using individual patient-level data." *Ultrasound in Obstetrics & Gynecology,* vol. 49, no. 3, pp. 322-329.

Berghella, V. & Saccone, G. 2016, "Fetal fibronectin testing for prevention of preterm birth in singleton pregnancies with threatened preterm labor: a systematic review and metaanalysis of randomized controlled trials." *American Journal of Obstetrics and Gynecology,* vol. 215, no. 4, pp. 431-438.

Berghella, V., Baxter, J.K. & Hendrix, N.W. 2009, "Cervical assessment by ultrasound for preventing preterm delivery." *Cochrane Database of Systematic Reviews,* no. 3, pp. 007235.

Berretta, R., Gizzo, S., Dall'Asta, A., Mazzone, E., Monica, M., Franchi, L., Peri, F., Patrelli, T.S. & Bacchi Modena, A. 2013, "Risk of preterm delivery associated with prior treatment of cervical precancerous lesion according to the depth of the cone." *Disease markers,* vol. 35, no. 6, pp. 721-726.

Bertin, M., Chevrier, C., Serrano, T., Monfort, C., Rouget, F., Cordier, S. & Viel, J. 2015, "Association between prenatal exposure to traffic-related air pollution and preterm birth in the PELAGIE mother–child cohort, Brittany, France. Does the urban–rural context matter?" *Environmental Research,* vol. 142, pp. 17-24.

Bierbrier, R., Lo, V. & Wu, R.C. 2014, "Evaluation of the accuracy of smartphone medical calculation apps." *Journal of Medical Internet Research,* vol. 16, no. 2, pp. e32.

Blencowe, H., Cousens, S., Chou, D., Oestergaard, M., Say, L., Moller, A., Kinney, M. & Lawn, J. 2013, "Born too soon: the global epidemiology of 15 million preterm births", *Reproductive Health,* vol. 10, no. 1, pp. S2.

Boesveld, M., Heida, K.Y., Oudijk, M.A., Brouwers, H.A.A., Koenen, S.V. & Kwee, A. 2014, "Evaluation of antenatal corticosteroid prescribing patterns among 984 women at risk for preterm delivery." *J Matern Fetal Neonatal Med,* vol. 27, no. 5, pp. 516-519.

Bolt, L.A., Chandiramani, M., De Greeff, A., Seed, P.T., Kurtzman, J. and Shennan, A.H., 2011. The value of combined cervical length measurement and fetal fibronectin testing to predict spontaneous preterm birth in asymptomatic high-risk women. *The Journal of Maternal-Fetal & Neonatal Medicine*, 24(7), pp.928-932.

Bourgeault, I., Dingwall, R. & De Vries, R. 2010, *The SAGE Handbook of Qualitative Methods in Health Research,* London*:*Sage.

Braun, V. & Clarke, V. 2006, "Using thematic analysis in psychology." *Qualitative Research in Psychology,* vol. 3, no. 2, pp. 77-101.

Brewer, N.T., Chapman, G.B., Gibbons, F.X., Gerrard, M., McCaul, K.D. & Weinstein, N.D. 2007, "Meta-analysis of the relationship between risk perception and health behavior: the example of vaccination." *Health Psychology,* vol. 26, no. 2, pp. 136.

Bruijn, M.M., Vis, J., Wilms, F.F., Oudijk, M., Kwee, A., Porath, M.M., Oei, G., Scheepers, H., Spaanderman, M.E. & Bloemenkamp, K. 2016, "Quantitative fetal fibronectin testing in combination with cervical length measurement in the prediction of spontaneous preterm delivery in symptomatic women." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 123, no. 12, pp. 1965-1971.

Bush, J., Barlow, D.E., Echols, J., Wilkerson, J. & Bellevin, K. 2017, "Impact of a Mobile Health Application on User Engagement and Pregnancy Outcomes Among Wyoming Medicaid Members." *Telemedicine Journal & E-Health,* vol. 23, no. 11, pp. 891-898.

Cadwalladr, C. & Graham-Harrison, E. 2018, "Revealed: 50 million Facebook profiles harvested for Cambridge Analytica in major data breach", *The Guardian*, vol. 17. March 18, 2018

Carter, J., Tribe, R., Watson, H. & Shennan, A. 2016, "Threatened preterm labour management: results of a Delphi consensus on best practice." *BJOG: An International Journal of Obstetrics and Gynaecology,* vol. 123, pp. 100-101.

Carter, J., Tribe, R.M., Sandall, J. & Shennan, A.H. 2018a, "The Preterm Clinical Network (PCN) Database: a web-based systematic method of collecting data on the care of women at risk of preterm birth." *BMC Pregnancy and Childbirth,* vol. 18, no. 1, pp. 335.

Carter, J., Tribe, R.M., Shennan, A.H. & Sandall, J. 2018b, "Threatened preterm labour: women's experiences of risk and care management: a qualitative study." *Midwifery,* vol. 64 pp.85-92.

Chao, T.T., Bloom, S.L., Mitchell, J.S., McIntire, D.D. & Leveno, K.J. 2011, "The diagnosis and natural history of false preterm labor." *Obstetrics and Gynecology,* vol. 118, no. 6, pp. 1301-1308.

Chen, H., Chai, Y., Dong, L., Niu, W. & Zhang, P. 2018, "Effectiveness and Appropriateness of mHealth Interventions for Maternal and Child Health: Systematic Review." *JMIR mHealth and uHealth,* vol. 6, no. 1, pp. e7.

Christian, L.M. 2012, "Psychoneuroimmunology in pregnancy: Immune pathways linking stress with maternal health, adverse birth outcomes, and fetal development." *Neuroscience & Biobehavioral Reviews,* vol. 36, no. 1, pp. 350-361.

Chuang L.L., Lin L.C., Cheng P.J., Chen C.H., Wu S.C. & Chang, C.L. 2012, "Effects of a relaxation training programme on immediate and prolonged stress responses in women with preterm labour." *Journal of Advanced Nursing,* vol. 68, no. 1, pp. 170-180.

Constantine, M.M., Weiner, S.J. & Shriver, E.K. 2009, "(NICHD) Maternal-Fetal Medicine Units Network (MFMU). Effects of antenatal exposure to magnesium sulphate on neuroprotection and mortality in preterm infants: a meta-analysis." *Obstetrics & Gynecology,* vol. 114, pp. 354-364.

Copper, R.L., Goldenberg, R.L., Davis, R.O., Cutter, G.R., DuBard, M.B., Corliss, D.K. & Andrews, J.B. 1990, "Warning symptoms, uterine contractions, and cervical examination findings in women at risk of preterm delivery." *American Journal of Obstetrics and Gynecology,* vol. 162, no. 3, pp. 748-754.

Coster-Schulz, M.A. & Mackey, M.C. 1998, "The preterm labor experience: A balancing act." *Clinical Nursing Research,* vol. 7, no. 4, pp. 335-359.

Coulter, A., Stilwell, D., Kryworuchko, J., Mullen, P.D., Ng, C.J. & van der Weijden, T. 2013, "A systematic development process for patient decision aids." *BMC Medical Informatics and Decision Making,* vol. 13, no. 2, pp. S2.

Coxon, K. 2014, *Birth place decisions: Information for women and partners on planning where to give birth,* London:King's College, London.

Crane, J.M.G., Van den Hof, M., Armson, B.A. & Liston, R. 1997, "Transvaginal Ultrasound in the Prediction of Preterm Delivery: Singleton and Twin Gestations." *Obstetrics & Gynecology,* vol. 90, no. 3, pp. 357-363.

Crowther, C.A., Brown, J., McKinlay, C.J.D., Middleton, P. 2014 "Magnesium sulphate for preventing preterm birth in threatened preterm labour." *Cochrane Database of Systematic Reviews*, Issue 8. Art. No.: CD001060. DOI: 10.1002/14651858.CD001060.pub2.

Davey, M., Watson, L., Rayner, J.A. & Rowlands, S. 2015, "Risk-scoring systems for predicting preterm birth with the aim of reducing associated adverse outcomes." *Cochrane Database of Systematic Reviews,* vol. 10, pp. 004902.

David, A.L. & Akintomide, H. 2016, "Presenting risk information in sexual and reproductive health care." *The Journal of Family Planning and Reproductive Health Care,* vol. 42, no. 3, pp. 213-219.

DeFranco, E.A., Lewis, D.F. & Odibo, A.O. 2013, "Improving the screening accuracy for preterm labor: is the combination of fetal fibronectin and cervical length in symptomatic patients a useful predictor of preterm birth? A systematic review." *American Journal of Obstetrics & Gynecology,* vol. 208, no. 3, pp. 233.e1-233.e6.

Department of Health 2004, *National service framework for children, young people and maternity services*, London:Department of Health.

Department of Health 2007, *Maternity matters: choice, access and continuity of care in a safe service,* London:Department of Health.

Department of Health 2017, "Safer Maternity Care - The National Maternity Safety Strategy - Progress and Next Steps." [online] Available at: https://www.gov.uk/government/publications/safer-maternity-care-progress-and-next-steps Last accessed: 17th August 2018.

Deshpande, S.N., van Asselt, A.D., Tomini, F., Armstrong, N., Allen, A., Noake, C., Khan, K., Severens, J.L., Kleijnen, J. & Westwood, M.E. 2013, "Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis." *Health Technology Assessment (Winchester, England),* vol. 17, no. 40, pp. 1-138.

Dew, P.C., Guillory, V.J., Okah, F.A., Cai, J. & Hoff, G.L. 2007, "The effect of health compromising behaviors on preterm births", *Maternal and Child Health Journal,* vol. 11, no. 3, pp. 227-233.

Dhawale, T., Steuten, L.M. & Deeg, H.J. 2017, "Uncertainty of Physicians and Patients in Medical Decision Making." *Biology of Blood and Marrow Transplantation,* vol. 23, no. 6, pp. 865-869.

Di Renzo, G.C., Giardina, I., Rosati, A., Clerici, G., Torricelli, M. & Petraglia, F. 2011a, "Maternal risk factors for preterm birth: a country-based population analysis." *European Journal of Obstetrics & Gynecology and Reproductive Biology,* vol. 159, no. 2, pp. 342-346.

Di Renzo, G.C., Roura, L.C., Facchinetti, F., Antsaklis, A., Breborowicz, G., Gratacos, E., Husslein, P., Lamont, R., Mikhailov, A. & Montenegro, N. 2011b, "Guidelines for the management of spontaneous preterm labor: identification of spontaneous preterm labor, diagnosis of preterm premature rupture of membranes, and preventive tools for preterm birth." *The Journal of Maternal-Fetal & Neonatal Medicine,* vol. 24, no. 5, pp. 659-667.

Dixon-Woods, M., Shaw, R.L., Agarwal, S. & Smith, J.A. 2004, "The problem of appraising qualitative research." *Quality & Safety in Health Care,* vol. 13, no. 3, pp. 223-225.

Dixon-Woods, M., Cavers, D., Agarwal, S., Annandale, E., Arthur, A., Harvey, J., Hsu, R., Katbamna, S., Olsen, R. & Smith, L. 2006, "Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups." *BMC Medical Research Methodology,* vol. 6, no. 1, pp. 35.

Dole, N., Savitz, D.A., Hertz-Picciotto, I., Siega-Riz, A.M., McMahon, M.J. & Buekens, P. 2003, "Maternal Stress and Preterm Birth." *American Journal of Epidemiology,* vol. 157, no. 1, pp. 14-24.

Dunsmuir, D.T., Payne, B.A., Cloete, G., Petersen, C.L., Gorges, M., Lim, J., von Dadelszen, P., Dumont, G.A. & Ansermino, J.M. 2014, "Development of mHealth applications for pre-eclampsia triage." *IEEE Journal of Biomedical & Health Informatics,* vol. 18, no. 6, pp. 1857-1864.

Duthie, L. & Reynolds, R.M. 2013, "Changes in the maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: influences on maternal and fetal outcomes." *Neuroendocrinology,* vol. 98, no. 2, pp. 106-115.

Edwards, A., Elwyn, G. & Gwyn, R. 1999, "General practice registrar responses to the use of different risk communication tools in simulated consultations: a focus group study." *BMJ (Clinical Research ed.),* vol. 319, no. 7212, pp. 749-752.

Edwards, A.G., Naik, G., Ahmed, H., Elwyn, G.J., Pickles, T., Hood, K. & Playle, R. 2013, "Personalised risk communication for informed decision making about taking screening tests." *The Cochrane Database of Systematic Reviews,* vol. (2):CD001865. doi, no. 2, pp. CD001865.

Ehsanipoor, R.M., Swank, M.L., Jwa, S.C., Wing, D.A., Tarabulsi, G. & Blakemore, K.J. 2016, "Placental α-microglobulin-1 in vaginal secretions of women with evidence of preterm labor." *American Journal of Perinatology,* vol. 33, no. 02, pp. 208-213.

Elwyn, G., O'Connor, A., Stacey, D., Volk, R., Edwards, A.G., Coulter, A., Thomas, R., Barratt, A., Barry, M. & Bernstein, S. 2006, "International Patient Decision Aids Standards (IPDAS) collaboration. Developing a quality criteria framework for patient decision aid: online international Delphi consensus process." *British Medical Journal,* vol. 333, no. 7565, pp. 417-419.

Epstein, F.H., Parry, S. & Strauss, J.F. 1998, "Premature rupture of the fetal membranes." *New England Journal of Medicine,* vol. 338, no. 10, pp. 663-670.

Expert Maternity Group & Cumberlege, B.J. 1993, *Changing Childbirth: Report of the Expert Maternity Group,* HM Stationery Office.

Fagerlin, A., Zikmund-Fisher, B.J. & Ubel, P.A. 2011, "Helping patients decide: ten steps to better risk communication." *Journal of the National Cancer Institute,* vol. 103, no. 19, pp. 1436-1443.

Fernandez Turienzo, C., Sandall, J. & Peacock, J.L. 2016, "Models of antenatal care to reduce and prevent preterm birth: a systematic review and meta-analysis." *BMJ Open,* vol. 6, no. 1.

Ferrero, D.M., Larson, J., Jacobsson, B., Di Renzo, G.C., Norman, J.E., Martin Jr, J.N., D'Alton, M., Castelazo, E., Howson, C.P. & Sengpiel, V. 2016, "Cross-country individual participant analysis of 4.1 million singleton births in 5 countries with very high human development index confirms known associations but provides no biologic explanation for 2/3 of all preterm births." *PLoS One,* vol. 11, no. 9, pp. e0162506.

Finlay, L. 2002, ""“Outing” the researcher: The provenance, process, and practice of reflexivity." *Qualitative Health Research,* vol. 12, no. 4, pp. 531-545.

Fisk, N.M. & Bruce Storey, G. 1988, "Fetal outcome in obstetric cholestasis." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 95, no. 11, pp. 1137-1143.

Food and Drug Administration, 2015, “Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff” [online] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf Accessed: 17th August 2018

Foster, C. & Shennan, A.H. 2014, "Fetal fibronectin as a biomarker of preterm labor: a review of the literature and advances in its clinical use." *Biomarkers in Medicine,* vol. 8, no. 4, pp. 471-484.

Freeman, C.I., Hezelgrave, N.L. & Shennan, A.H. 2015, "Antenatal steroids for fetal lung maturity: Time to target more frequent doses to fewer women?" *Obstetric Medicine,* vol. 8, no. 4, pp. 172-176.

Fuchs, I.B., Henrich, W., Osthues, K. & Dudenhausen, J.W. 2004, "Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor." *Ultrasound in Obstetrics and Gynecology,* vol. 24, no. 5, pp. 554-557.

Gale C, Hay A, Philipp C, Khan R, Santhakumaran S & Ratnavel N 2012, "In-utero transfer is too difficult: results from a prospective study." *Early Human Development,* vol. 88, no. 3, pp. 147-150.

Galesic, M., Garcia-Retamero, R. & Gigerenzer, G. 2009, "Using icon arrays to communicate medical risks: overcoming low numeracy." *Health Psychology,* vol. 28, no. 2, pp. 210.

Gaucher, N., Nadeau, S., Barbier, A., Janvier, A. & Payot, A. 2016, "Personalized Antenatal Consultations for Preterm Labor: Responding to Mothers' Expectations." *Journal of Pediatrics,* vol. 178, pp. 130-134.e7.

Gigerenzer, G. & Edwards, A. 2003, "Simple tools for understanding risks: from innumeracy to insight." *BMJ (Clinical Research ed.),* vol. 327, no. 7417, pp. 741-744.

Godolphin, W. 2009, "Shared decision-making", *Healthcare Quarterly,* vol. 12 (Sp).

Goel, M.K., Khanna, P. & Kishore, J. 2010, "Understanding survival analysis: Kaplan-Meier estimate." *International Journal of Ayurveda Research,* vol. 1, no. 4, pp. 274-278.

Goldenberg, R.L., Culhane, J.F., Iams, J.D. & Romero, R. 2008, "Epidemiology and causes of preterm birth." *The Lancet,* vol. 371, no. 9606, pp. 75-84.

Gomez, R., Romero, R., Medina, L., Nien, J.K., Chaiworapongsa, T., Carstens, M., Gonzalez, R., Espinoza, J., Iams, J.D., Edwin, S. & Rojas, I. 2005, "Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes." *American Journal of Obstetrics & Gynecology,* vol. 192, no. 2, pp. 350-359.

Goodyear-Smith, F., Arroll, B., Chan, L., Jackson, R., Wells, S. & Kenealy, T. 2008, "Patients prefer pictures to numbers to express cardiovascular benefit from treatment." *Annals of Family Medicine,* vol. 6, no. 3, pp. 213-217.

Grimbizis, G.F., Camus, M., Tarlatzis, B.C., Bontis, J.N. & Devroey, P. 2001, "Clinical implications of uterine malformations and hysteroscopic treatment results." *Human Reproduction Update,* vol. 7, no. 2, pp. 161-174.

Gyetvai, K., Hannah, M.E., Hodnett, E.D. & Ohlsson, A. 1999, "Tocolytics for preterm labor: a systematic review." *Obstetrics & Gynecology,* vol. 94, no. 5, pp. 869-877.

Haas, D.M., Golichowski, A.M., Imperiale, T.F., Kirkpatrick, P.R., Zollinger, T.W. & Klein, R.W. 2009, "Tocolytic therapy: a meta-analysis and decision analysis." *Obstetrics & Gynecology,* vol. 114, no. 1, pp. 171.

Han, P.K. 2013, "Conceptual, methodological, and ethical problems in communicating uncertainty in clinical evidence", *Medical Care Research and Review,* vol. 70, no. 1_suppl, pp. 14S-36S.

Haram, K., Mortensen, J.H.S. & Morrison, J.C. 2015, "Tocolysis for acute preterm labor: does anything work", *The Journal of Maternal-Fetal & Neonatal Medicine,* vol. 28, no. 4, pp. 371-378.

Hart, C. 2018, *Doing a Literature Review: Releasing the Research Imagination,* London*:*Sage.

Heath, V.C.F., Southall, T.R., Souka, A.P., Elisseou, A. & Nicolaides, K.H. 1998, "Cervical length at 23 weeks of gestation: prediction of spontaneous preterm delivery." *Ultrasound in Obstetrics and Gynecology,* vol. 12, no. 5, pp. 312-317.

Herxheimer, A. 2005, "Communicating with patients about harms and risks." *PLoS medicine,* vol. 2, no. 2, pp. e42.

Hoffman, J.R. & Cooper, R.J. 2012, "Overdiagnosis of disease: a modern epidemic." *Archives of Internal Medicine,* vol. 172, no. 15, pp. 1123-1124.

Höglund, E. & Dykes, A. 2013, "Living with uncertainty: A Swedish qualitative interview study of women at home on sick leave due to premature labour." *Midwifery,* vol. 29, no. 5, pp. 468-473.

Hollowell, J., Puddicombe, D., Rowe, R., Linsell, L., Hardy, P., Stewart, M., Newburn, M., McCourt, C., Sandall, J., Macfarlane, A., Silverton, L. and Brocklehurst, P. 2011, "The Birthplace national prospective cohort study: perinatal and maternal outcomes by planned place of birth Birthplace in England research programme." (Report No. Final report part 4). Southampton: HMSO.

Hologic Inc. 2018 “Fetal Fibronectin Specimen Collection” [online] available at: http://ffntest.com/hcp/professional-resources/specimen-collection Last accessed: 17th August 2018.

Honest H, Bachmann LM, Coomarasamy A, Gupta JK, Kleijnen J & Khan KS 2002, "Accuracy of cervical transvaginal sonography in predicting preterm birth: a systematic review." *Ultrasound in Obstetrics & Gynecology,* vol. 22, no. 3, pp. 305-322.

Husserl, E. 1982, *Ideas Pertaining to a Pure Phenomenology and to a Phenomenological Philosophy*, The Hague:Kersten*.*

Iams, J.D., Casal, D., McGregor, J.A., Goodwin, T.M., Kreaden, U.S., Lowensohn, R. & Lockitch, G. 1995, "Fetal fibronectin improves the accuracy of diagnosis of preterm labor." *American Journal of Obstetrics and Gynecology,* vol. 173, no. 1, pp. 141-145.

Iams, J.D., Goldenberg, R.L., Meis, P.J., Mercer, B.M., Moawad, A., Das, A., Thom, E., McNellis, D., Copper, R.L. & Johnson, F. 1996, "The length of the cervix and the risk of spontaneous premature delivery." *New England Journal of Medicine,* vol. 334, no. 9, pp. 567-573.

Iams, J.D., Newman, R.B., Thom, E.A., Goldenberg, R.L., Mueller-Heubach, E., Moawad, A., Sibai, B.M., Caritis, S.N., Miodovnik, M. & Paul, R.H. 2002, "Frequency of uterine contractions and the risk of spontaneous preterm delivery." *New England Journal of Medicine,* vol. 346, no. 4, pp. 250-255.

Information Services Division, 2017, *Births in Scottish Hospitals: year ending 31st March 2017.* [online] Available at: https://www.isdscotland.org/Health-Topics/Maternity-and-Births/Publications/2017-11-28/2017-11-28-Births-Report.pdf Accessed: 17th August 2018

Jallo, N., Thacker, L.R.I., Menzies, V., Stojanovic, P. & Svikis, D.S. 2017, "A stress coping app for hospitalized pregnant women at risk for preterm birth." *MCN: The American Journal of Maternal/Child Nursing,* vol. 42, no. 5, pp. 257-262.

Jeon, E., Park, H., Jo, S., Kang, H., Lee, J.Y. 2016, "Mobile apps providing tailored nursing interventions for patients with metabolic syndrome." *Stud Health Technol Inform,* vol. 225, pp. 510-514.

Jonas, S.M., Deserno, T.M., Buhimschi, C.S., Makin, J., Choma, M.A. & Buhimschi, I.A. 2016, "Smartphone-based diagnostic for preeclampsia: an mHealth solution for administering the Congo Red Dot (CRD) test in settings with limited resources." *Journal of the American Medical Informatics Association,* vol. 23, no. 1, pp. 166-173.

Jwala, S., Tran, T.L., Terenna, C., McGregor, A., Andrel, J., Leiby, B.E., Baxter, J.K. & Berghella, V. 2016, "Evaluation of additive effect of quantitative fetal fibronectin to cervical length for prediction of spontaneous preterm birth among asymptomatic low-risk women." *Acta Obstetricia et Gynecologica Scandinavica,* vol. 95, no. 8, pp. 948-955.

Kay, M., Santos, J. & Takane, M. 2011, "mHealth: New horizons for health through mobile technologies." *World Health Organization,* vol. 64, no. 7, pp. 66-71.

Kiefer, D.G. & Vintzileos, A.M. 2008, "The utility of fetal fibronectin in the prediction and prevention of spontaneous preterm birth." *Reviews in Obstetrics & Gynecology,* vol. 1, no. 3, pp. 106-112.

Kleinbaum, D.G. and Klein, M., 2010. *Survival analysis (Vol. 3*). New York: Springer.

Kuhrt, K., Hezelgrave, N., Foster, C., Seed, P.T. & Shennan, A.H. 2016a, "Development and validation of a tool incorporating quantitative fetal fibronectin to predict spontaneous preterm birth in symptomatic women." *Ultrasound in Obstetrics & Gynecology,* vol. 47, no. 2, pp. 210-216.

Kuhrt, K., Smout, E., Hezelgrave, N., Seed, P.T., Carter, J. & Shennan, A.H. 2016b, "Development and validation of a tool incorporating cervical length and quantitative fetal fibronectin to predict spontaneous preterm birth in asymptomatic high-risk women." *Ultrasound in Obstetrics & Gynecology,* vol. 47, no. 1, pp. 104-109.

Latendresse, G. 2009, "The Interaction between Chronic Stress and Pregnancy: Preterm Birth from A Biobehavioral Perspective." *Journal of Midwifery and Women's Health,* vol. 54, no. 1, pp. 8-17.

Lee, S., Ayers, S. & Holden, D. 2012, "Risk perception of women during high risk pregnancy: A systematic review." *Health, Risk & Society,* vol. 14, no. 6, pp. 511-531.

Leitich, H., Brunbauer, M., Kaider, A., Egarter, C. & Husslein, P. 1999a, "Cervical length and dilatation of the internal cervical os detected by vaginal ultrasonography as markers for preterm delivery: A systematic review." *American Journal of Obstetrics and Gynecology,* vol. 181, no. 6, pp. 1465-1472.

Leitich, H., Egarter, C., Kaider, A., Hohlagschwandtner, M., Berghammer, P. & Husslein, P. 1999b, "Cervicovaginal fetal fibronectin as a marker for preterm delivery: a meta-analysis." *American Journal of Obstetrics and Gynecology,* vol. 180, no. 5, pp. 1169-1176.

Leung, L. 2015, "Validity, reliability, and generalizability in qualitative research." *Journal of Family Medicine and Primary Care,* vol. 4, no. 3, pp. 324-327.

Levin, H., Ananth, C., Benjamin-Boamah, C., Siddiq, Z., Son, M. & Friedman, A. 2016, "Clinical indication and timing of antenatal corticosteroid administration at a single centre." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 123, no. 3, pp. 409-414.

Levine, L.D., Downes, K.L., Romero, J.A., Pappas, H. & Elovitz, M.A. 2018, "Quantitative fetal fibronectin and cervical length in symptomatic women: results from a prospective blinded cohort study." *The Journal of Maternal-Fetal & Neonatal Medicine.* pp. 1-9.

Liberati, E.G., Ruggiero, F., Galuppo, L., Gorli, M., González-Lorenzo, M., Maraldi, M., Ruggieri, P., Friz, H.P., Scaratti, G. & Kwag, K.H. 2017, "What hinders the uptake of

computerized decision support systems in hospitals? A qualitative study and framework for implementation." *Implementation Science,* vol. 12, no. 1, pp. 113.

Lim, J., Cloete, G., Dunsmuir, D.T., Payne, B.A., Scheffer, C., von Dadelszen, P., Dumont, G.A. & Ansermino, J.M. 2015, "Usability and Feasibility of PIERS on the Move: An mHealth App for Pre-Eclampsia Triage." *JMIR mHealth and uHealth,* vol. 3, no. 2, pp. e37.

Lim, K., Butt, K. & Crane, J.M. 2011, "SOGC Clinical Practice Guideline. Ultrasonographic cervical length assessment in predicting preterm birth in singleton pregnancies." *Journal of Obstetrics & Gynaecology Canada: JOGC,* vol. 33, no. 5, pp. 486-499.

Lin, D.Y. & Wei, L. 1989, "The robust inference for the Cox proportional hazards model", *Journal of the American Statistical Association*, vol. 84, no. 408, pp. 1074-1078.

Liong, S., Di Quinzio, M.K., Fleming, G., Permezel, M., Rice, G.E. & Georgiou, H.M. 2015, "New biomarkers for the prediction of spontaneous preterm labour in symptomatic pregnant women: a comparison with fetal fibronectin." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 122, no. 3, pp. 370-379.

Lipkus, I.M., Samsa, G. & Rimer, B.K. 2001, "General performance on a numeracy scale among highly educated samples." *Medical Decision Making,* vol. 21, no. 1, pp. 37-44.

Lipkus, I.M. & Hollands, J.G. 1999, "The visual communication of risk." *Journal of the National Cancer Institute.Monographs,* vol. 25, no. 25, pp. 149-163.

Lloyd, A., Hayes, P., Bell, P.R. & Naylor, A.R. 2001, "The role of risk and benefit perception in informed consent for surgery." *Medical Decision Making,* vol. 21, no. 2, pp. 141-149.

Lobel, M., Cannella, D. L., Graham, J. E., DeVincent, C., Schneider, J., & Meyer, B. A. 2008, "Pregnancy-specific stress, prenatal health behaviors, and birth outcomes." *Health Psychology,* vol. 27, no. 5, pp. 604-615.

Lockwood, C.J., Senyei, A.E., Dische, M.R., Casal, D., Shah, K.D., Thung, S.N., Jones, L., Deligdisgh, L. & Garite, T.J. 1991, "Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery." *New England Journal of Medicine,* vol. 325, no. 10, pp. 669-674.

Lowenkron, A.H. 1999, "Coping with the Stress of Premature Labor." *Health Care for Women International,* vol. 20, no. 6, pp. 547-561.

Lucaroni, F., Morciano, L., Rizzo, G., D'Antonio, F., Buonuomo, E., Palombi, L. & Arduini, D. 2018, "Biomarkers for predicting spontaneous preterm birth: an umbrella systematic review", *The Journal of Maternal-Fetal & Neonatal Medicine,* vol. 31, no. 6, pp. 726-734.

Lucovnik, M., Chambliss, L.R. & Garfield, R.E. 2013, "Costs of unnecessary admissions and treatments for "threatened preterm labor." *American Journal of Obstetrics and Gynecology,* vol. 209, no. 3, pp. 217.e1-217.e3.

Mackey, M.C. & Coster-Schulz, M.A. 1992, "Women's views of the preterm labor experience." *Clinical Nursing Research,* vol. 1, no. 4, pp. 366-384.

Mackillop, L., Loerup, L., Bartlett, K., Farmer, A., Gibson, O.J., Hirst, J.E., Kenworthy, Y., Kevat, D.A., Levy, J.C. & Tarassenko, L. 2014, "Development of a real-time smartphone solution for the management of women with or at high risk of gestational diabetes." *Journal of Diabetes Science & Technology,* vol. 8, no. 6, pp. 1105-1114.

MacKinnon, K. 2006, "Living with the threat of preterm labor: Women's work of keeping the baby in." *JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing,* vol. 35, no. 6, pp. 700-708.

Maloni, J.A. 2010, "Antepartum Bed Rest for Pregnancy Complications: Efficacy and Safety for Preventing Preterm Birth." *Biological Research for Nursing,* vol. 12, no. 2, pp. 106-124.

Malouf, R. & Redshaw, M. 2017, "Specialist antenatal clinics for women at high risk of preterm birth: A systematic review of qualitative and quantitative research." *BMC Pregnancy and Childbirth,* vol. 17, no. 1.

Mangham, L.J., Petrou, S., Doyle, L.W., Draper, E.S. & Marlow, N. 2009, "The cost of preterm birth throughout childhood in England and Wales." *Pediatrics,* vol. 123, no. 2, pp. e312-27.

Marko, K.I., Krapf, J.M., Meltzer, A.C., Oh, J., Ganju, N., Martinez, A.G., Sheth, S.G. & Gaba, N.D. 2016, "Testing the Feasibility of Remote Patient Monitoring in Prenatal Care Using a Mobile App and Connected Devices: A Prospective Observational Trial." *JMIR Research Protocols,* vol. 5, no. 4, pp. e200.

Marlow, N., Bennett, C., Draper, E.S., Hennessy, E.M., Morgan, A.S. & Costeloe, K.L. 2014, "Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study." *Archives of Disease in Childhood.Fetal and Neonatal edition,* vol. 99, no. 3, pp. F181-8.

Matsuura, H., Takio, K., Titani, K., Greene, T., Levery, S.B., Salyan, M.E. & Hakomori, S. 1988, "The oncofetal structure of human fibronectin defined by monoclonal antibody FDC-6. Unique structural requirement for the antigenic specificity

provided by a glycosylhexapeptide." *The Journal of Biological Chemistry,* vol. 263, no. 7, pp. 3314-3322.

McKinlay, C.J., Crowther, C.A., Middleton, P. & Harding, J.E. 2012, "Repeat antenatal glucocorticoids for women at risk of preterm birth: a Cochrane Systematic Review." *American Journal of Obstetrics and Gynecology,* vol. 206, no. 3, pp. 187-194.

McPheeters, M.L., Miller, W.C., Hartmann, K.E., Savitz, D.A., Kaufman, J.S., Garrett, J.M. & Thorp, J.M. 2005, "The epidemiology of threatened preterm labor: a prospective cohort study." *American Journal of Obstetrics and Gynecology,* vol. 192, no. 4, pp. 1325-1329.

Medicines and Healthcare products Regulatory Agency 2018, "Guidance: Medical device stand-alone software including apps (including IVDMDs)." [online] https://www.gov.uk/government/publications/medical-devices-software-applications-apps Accessed: 17th August 2018.

Mercer, B.M., Goldenberg, R.L., Das, A., Moawad, A.H., Iams, J.D., Meis, P.J., Copper, R.L., Johnson, F., Thom, E., McNellis, D., Miodovnik, M., Menard, M.K., Caritis, S.N., Thurnau, G.R., Bottoms, S.F. & Roberts, J. 1996, "The preterm prediction study: A clinical risk assessment system." *American Journal of Obstetrics and Gynecology,* vol. 174, no. 6, pp. 1885-1895.

Milne, J. & Oberle, K. 2005, "Enhancing rigor in qualitative description." *Journal of Wound Ostomy & Continence Nursing,* vol. 32, no. 6, pp. 413-420.

Mozurkewich, E.L., Naglie, G., Krahn, M.D. & Hayashi, R.H. 2000, "Predicting preterm birth: a cost-effectiveness analysis." *American Journal of Obstetrics & Gynecology,* vol. 182, no. 6, pp. 1589-1598.

Murphy, K.E., Hannah, M.E., Willan, A.R., Hewson, S.A., Ohlsson, A., Kelly, E.N., Matthews, S.G., Saigal, S., Asztalos, E. & Ross, S. 2008, "Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial." *The Lancet,* vol. 372, no. 9656, pp. 2143-2151.

National Institute for Health and Care Excellence, 2015, *Preterm labour and birth*. NICE guideline (NG25)

Neergaard, M., Olesen, F., Andersen, R. & Sondergaard, J. 2009, "Qualitative description - the poor cousin of health research?" *BMC Medical Research Methodology,* vol. 9, no. 1, pp. 52.

Ness, A., Visintine, J., Ricci, E. & Berghella, V. 2007, "Does knowledge of cervical length and fetal fibronectin affect management of women with threatened preterm labor? A randomized trial." *American Journal of Obstetrics & Gynecology,* vol. 197, no. 4, pp. 426.e1-426.e7.

Ngo, T.T.M., Moufarrej, M.N., Rasmussen, M.H., Camunas-Soler, J., Pan, W., Okamoto, J., Neff, N.F., Liu, K., Wong, R.J., Downes, K., Tibshirani, R., Shaw, G.M., Skotte, L., Stevenson, D.K., Biggio, J.R., Elovitz, M.A., Melbye, M. & Quake, S.R. 2018, "Noninvasive blood tests for fetal development predict gestational age and preterm delivery." *Science (New York, N.Y.),* vol. 360, no. 6393, pp. 1133-1136.

NHS England, 2016, "National Maternity Review. Better Births; Improving Outcomes of Maternity Services in England." *NHS England, London.*

NHS England (2018). *NHS RightCare » Shared Decision Making programme*. [Online] Available at: https://www.england.nhs.uk/rightcare/shared-decision-making/ Accessed: 17th August 2018.

Nikolova, T., Bayev, O., Nikolova, N. & Di Renzo, G.C. 2014, "Evaluation of a novel placental alpha microglobulin-1 (PAMG-1) test to predict spontaneous preterm delivery." *Journal of Perinatal Medicine,* vol. 42, no. 4, pp. 473-477.

Nilsson, C., Lundgren, I., Smith, V., Vehvilainen-Julkunen, K., Nicoletti, J., Devane, D., Bernloehr, A., van Limbeek, E., Lalor, J. & Begley, C. 2015, "Women-centred interventions to increase vaginal birth after caesarean section (VBAC): A systematic review." *Midwifery,* vol. 31, no. 7, pp. 657-663.

Norberg, H., Stålnacke, J., Nordenström, A. & Norman, M. 2013, "Repeat Antenatal Steroid Exposure and Later Blood Pressure, Arterial Stiffness, and Metabolic Profile." *The Journal of Pediatrics,* vol. 163, no. 3, pp. 711-716.

Norberg, H., Kowalski, J., Maršál, K. & Norman, M. 2017, "Timing of antenatal corticosteroid administration and survival in extremely preterm infants: a national population-based cohort study." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 124, no. 10, pp. 1567-1574.

O'Brien, E.T., Quenby, S. & Lavender, T. 2010, "Women's views of high risk pregnancy under threat of preterm birth." *Sexual and Reproductive Healthcare,* vol. 1, no. 3, pp. 79-84.

O'Connor, A.M., Drake, E.R., Fiset, V., Graham, I.D., Laupacis, A. & Tugwell, P. 1999, "The Ottawa patient decision aids." *Effective Clinical Practice : ECP,* vol. 2, no. 4, pp. 163-170.

Office for National Statistics 2015, *Gestation specific infant mortality in England and Wales. Statistical bulletin,* London:ONS.

Owen, J., Iams, J.D. & National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network 2003, "What we have learned about cervical ultrasound." *Seminars in Perinatology,* vol. 27, no. 3, pp. 194-203.

Paling, J. 2003, "Strategies to help patients understand risks." *BMJ (Clinical Research ed.),* vol. 327, no. 7417, pp. 745-748.

Patterson, E.T., Douglas, A.B., Patterson, P.M. & Bradle, J.B. 1992, "Symptoms of preterm labor and self-diagnostic confusion." *Nursing Research,* vol. 41, no. 6 pp. 367-72.

Palmer, L. & Carty, E. 2006, "Deciding When It's Labor: The Experience of Women Who Have Received Antepartum Care at Home for Preterm Labor." *Journal of Obstetric, Gynecologic, & Neonatal Nursing,* vol. 35, no. 4, pp. 509-515.

Pathirana, T., Clark, J. & Moynihan, R. 2017, "Mapping the drivers of overdiagnosis to potential solutions." *BMJ (Clinical Research ed.),* vol. 358, pp. j3879.

Patterson, E.T., Douglas, A.B., Patterson, P.M. & Bradle, J.B. 1992, "Symptoms of Preterm Labor and Self-Diagnostic Confusion." *Nursing Research,* vol. 41, no. 6, pp. 367-373.

Patton, M.Q. 2005, *Qualitative research,* Encyclopedia of Statistics in Behavioral Science edn, Wiley Online Library.

Payne, K.F.B., Wharrad, H. & Watts, K. 2012, "Smartphone and medical related App use among medical students and junior doctors in the United Kingdom (UK): a regional survey", *BMC Medical Informatics and Decision Making*, vol. 12, no. 1, pp. 121.

Peaceman, A.M., Andrews, W.W., Thorp, J.M., Cliver, S.P., Lukes, A., Iams, J.D., Coultrip, L., Eriksen, N., Holbrook, R.H., Elliott, J., Ingardia, C. & Pietrantoni, M. 1997, "Fetal fibronectin as a predictor of preterm birth in patients with symptoms: A multicenter trial." *American Journal of Obstetrics and Gynecology,* vol. 177, no. 1, pp. 13-18.

Peleg, M., Shahar, Y., Quaglini, S., Broens, T., Budasu, R., Fung, N., Fux, A., García-Sáez, G., Goldstein, A. & González-Ferrer, A. 2017, "Assessment of a personalized and distributed patient guidance system." *International Journal of Medical Informatics,* vol. 101, pp. 108-130.

Perera, C. 2012, "The evolution of E-Health–mobile technology and mHealth." *Journal of Mobile Technology in Medicine,* vol. 1, no. 1, pp. 1-2.

Perry, R., Burns, R. & SimonFreeman, R. 2017, "A survey of mobile app use among california obstetrics and gynecology residents." 65th Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists, ACOG 2017. United States. 129 (Supplement 1) (pp 95S); W.B. Saunders, Obstetrics and Gynecology. Conference.

Peterson, W.E., Sprague, A.E., Reszel, J., Walker, M., Fell, D.B., Perkins, S.L., Dunn, S.I. & Johnson, M. 2014, "Women's perspectives of the fetal fibronectin testing

process: A qualitative descriptive study." *BMC Pregnancy and Childbirth,* vol. 14, no. 1.

Politi, M. 2015, "Stories of medical decision making: Helping patients and clinicians manage uncertainty during clinical care." *Health Literacy and Communication Faculty Publications. Paper 4.*
pp. http://digitalcommons.wustl.edu/healthlit_pubs/4.

Politi, M.C., Clark, M.A., Ombao, H., Dizon, D. & Elwyn, G. 2011, "Communicating uncertainty can lead to less decision satisfaction: a necessary cost of involving patients in shared decision making?" *Health Expectations,* vol. 14, no. 1, pp. 84-91.

Politi, M.C., Han, P.K. & Col, N.F. 2007, "Communicating the uncertainty of harms and benefits of medical interventions." *Medical Decision Making:an International Journal of the Society for Medical Decision Making,* vol. 27, no. 5, pp. 681-695.

Porcellato, L., Masson, G., O'mahony, F., Jenkinson, S., Vanner, T., Cheshire, K. & Perkins, E. 2015, "'It's something you have to put up with'—service users' experiences of in utero transfer: a qualitative study." *BJOG: An International Journal of Obstetrics & Gynaecology,* vol. 122, no. 13, pp. 1825-1832.

Preterm Birth Studies Database 2018 [online]. Available: www.medscinet.net/ptbstudies Accessed: 17th August 2018.

Priem, J.S. & Solomon, D.H. 2009, "Comforting apprehensive communicators: The effects of reappraisal and distraction on cortisol levels among students in a public speaking class." *Communication Quarterly,* vol. 57, no. 3, pp. 259-281.

Ram, D., Shapira, J., Holan, G., Magora, F., Cohen, S. & Davidovich, E. 2010, "Audiovisual video eyeglass distraction during dental treatment in children." *Quintessence International,* pp. 673.

Redshaw, M. & Henderson, J. 2015, *Safely delivered: a national survey of women's experience of maternity care 2014*, Oxford:National Perinatal Epidemiology Unit.

Reeves, S., Albert, M., Kuper, A. & Hodges, B.D. 2008, "Why use theories in qualitative research." *BMJ,* vol. 337, no. 7670, pp. 631-634.

Reyna, V.F. & Brainerd, C.J. 2008, "Numeracy, ratio bias, and denominator neglect in judgments of risk and probability." *Learning and Individual Differences,* vol. 18, no. 1, pp. 89-107.

Rich-Edwards, J.W. & Grizzard, T.A. 2005, "Psychosocial stress and neuroendocrine mechanisms in preterm delivery." *American Journal of Obstetrics and Gynecology,* vol. 192, no. 5, pp. S30-S35.

Riessman, C.K. 1993 *Narrative Analysis*. Newbury Park, CA:Sage

Ritchie, J. & Spencer, L. 1994, "Qualitative data analysis for applied policy research." in Bryman, A. and Burgess, R.G., (eds) *Analysing Qualitative Data,* London:Routledge.

Romero, R., Espinoza, J., Kusanovic, J.P., Gotsch, F., Hassan, S., Erez, O., Chaiworapongsa, T. & Mazor, M. 2006, "The preterm parturition syndrome." *BJOG: An International Journal of Obstetrics and Gynaecology,* vol. 113, no. SUPPL. 3, pp. 17-42.

Royal College of Obstetricians and Gynaecologists 2008, *Presenting Information on Risk (Clinical Governance Advice No.7)*, London:RCOG.

Royal College of Obstetricians and Gynaecologists 2010, *Antenatal Corticosteroids to Reduce Neonatal Morbidity (Green-top Guideline No. 7),* London:RCOG.

Royal College of Obstetricians and Gynaecologists 2011, *Tocolysis for women in preterm labour (Green-top guideline No.1b),* London:RCOG.

Royston, P. & Sauerbrei, W. 2008, *Multivariable model-building: a pragmatic approach to regression anaylsis based on fractional polynomials for modelling continuous variables,* London:John Wiley & Sons.

Ruiz, R.J., Fullerton, J. & Dudley, D.J. 2003, "The interrelationship of maternal stress, endocrine factors and inflammation on gestational length." *Obstetrical & Gynecological Survey,* vol. 58, no. 6, pp. 415-428.

Sandall, J., Soltani, H., Gates, S., Shennan, A., Devane, D. 2016 “Midwife-led continuity models versus other models of care for childbearing women.” *Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD004667. DOI: 10.1002/14651858.CD004667.pub5.

Sandelowski, M. 2000, "Whatever happened to qualitative description?" *Res Nurs Health,* vol. 23, pp. 334-340.

Sanya, R., Al Naggar, E., Gasim, M. & Ahmed, B.I. 2014, "Use or overuse of antenatal corticosteroids for suspected preterm birth." *The Journal of Maternal-Fetal & Neonatal Medicine,* vol. 27, no. 14, pp. 1454-1456.

Schapira, M.M., Nattinger, A.B. & McHorney, C.A. 2001, "Frequency or probability? A qualitative study of risk communication formats used in health care." *Medical Decision Making,* vol. 21, no. 6, pp. 459-467.

Scherer, S., Alder, J., Gaab, J., Berger, T., Ihde, K. & Urech, C. 2016, “Patient satisfaction and psychological well-being after internet-based cognitive behavioral stress management (IB-CBSM) for women with preterm labor: A randomized controlled trial.” *Journal of Psychosomatic Research,* vol. 80, pp. 37-43.

Sciscione, A.C. 2010, "Maternal activity restriction and the prevention of preterm birth." *American Journal of Obstetrics and Gynecology,* vol. 202, no. 3, pp. 232.e1-232.e5.

Smith, J., Bekker, H. & Cheater, F. 2011, "Theoretical versus pragmatic design in qualitative research." *Nurse Researcher,* vol. 18, no. 2, pp. 39-51.

Smith, J. & Firth, J. 2011, "Qualitative data analysis: the framework approach." *Nurse Researcher,* vol. 18, no. 2, pp. 52-62.

Smith, V., Devane, D., Begley, C.M., Clarke, M. & Higgins, S. 2009, "A systematic review and quality assessment of systematic reviews of randomised trials of interventions for preventing and treating preterm birth." *European Journal of Obstetrics & Gynecology and Reproductive Biology,* vol. 142, no. 1, pp. 3-11.

Sondaal, S.F.V., Browne, J.L., Amoakoh-Coleman, M., Borgstein, A., Miltenburg, A.S., Verwijs, M. & Klipstein-Grobusch, K. 2016, "Assessing the Effect of mHealth Interventions in Improving Maternal and Neonatal Care in Low- and Middle-Income Countries: A Systematic Review." *PLoS ONE [Electronic Resource],* vol. 11, no. 5, pp. e0154664.

Sosa, C.G., Althabe, F., Belizán, J.M. & Bergel, E. 2015, "Bed rest in singleton pregnancies for preventing preterm birth." *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD003581. DOI: 10.1002/14651858.CD003581.pub3.

Sotiriadis, A., Papatheodorou, S., Kavvadias, A. & Makrydimas, G. 2010, "Transvaginal cervical length measurement for prediction of preterm birth in women with threatened preterm labor: a meta-analysis." *Ultrasound in Obstetrics & Gynecology,* vol. 35, no. 1, pp. 54-64.

Spiegelhalter, D.J. 2008, "Understanding uncertainty." *Annals of Family Medicine,* vol. 6, no. 3, pp. 196-197.

Stacey, D., Légaré, F., Lewis, K., Barry, M.J., Bennett, C.L., Eden, K.B., Holmes-Rovner, M., Llewellyn-Thomas, H., Lyddiatt, A., Thomson, R., Trevena, L. 2017, "Decision aids for people facing health treatment or screening decisions." [online]. Available from: DOI: 10.1002/14651858.CD001431.pub5. Accessed: 17th August 2018.

Stock, S.J., Morris, R.K., Chandiramani, M., Shennan, A.H. and Norman, J.E., 2015. "Variation in management of women with threatened preterm labour." *Archives of Disease in Childhood-Fetal and Neonatal Edition,* 100(3), pp.F276-F276.

Strauss, A. & Corbin, J. 1994, "Grounded theory methodology." *Handbook of Qualitative Research,* vol. 17, pp. 273-285.

Stroux, L., Martinez, B., Coyote Ixen, E., King, N., Hall-Clifford, R., Rohloff, P. & Clifford, G.D. 2016, "An mHealth monitoring system for traditional birth attendant-led

antenatal risk assessment in rural Guatemala." *Journal of Medical Engineering & Technology,* vol. 40, no. 7-8, pp. 356-371.

Trevena, L.J., Zikmund-Fisher, B.J., Edwards, A., Gaissmaier, W., Galesic, M., Han, P.K., King, J., Lawson, M.L., Linder, S.K. & Lipkus, I. 2013, "Presenting quantitative information about decision outcomes: a risk communication primer for patient decision aid developers." *BMC Medical Informatics and Decision Making,* vol. 13, no. 2, pp. S7.

Tsai, A.C., Tomlinson, M., Dewing, S., le Roux, I.M., Harwood, J.M., Chopra, M. & Rotheram-Borus, M.J. 2014, "Antenatal depression case finding by community health workers in South Africa: feasibility of a mobile phone application." *Archives of Women's Mental Health,* vol. 17, no. 5, pp. 423-431.

Tsoi, E., Fuchs, I., Rane, S., Geerts, L. & Nicolaides, K. 2005, "Sonographic measurement of cervical length in threatened preterm labor in singleton pregnancies with intact membranes." *Ultrasound in Obstetrics & Gynecology,* vol. 25, no. 4, pp. 353-356.

Tsoi, E., Akmal, S., Geerts, L., Jeffery, B. & Nicolaides, K. 2006, "Sonographic measurement of cervical length and fetal fibronectin testing in threatened preterm labor." *Ultrasound in Obstetrics and Gynecology,* vol. 27, no. 4, pp. 368-372.

van Baaren, G., Vis, J.Y., Grobman, W.A., Bossuyt, P.M., Opmeer, B.C. & Mol, B.W. 2013, "Cost-effectiveness analysis of cervical length measurement and fibronectin testing in women with threatened preterm labor." *American Journal of Obstetrics and Gynecology,* vol. 209, no. 5, pp. 436.e1-436.e8.

van Zuuren, F.J. 1998, "The effects of information, distraction and coping style on symptom reporting during preterm labor." *Psychology and Health,* vol. 13, no. 1, pp. 49-54.

Vélez, O., Okyere, P.B., Kanter, A.S. & Bakken, S. 2014, "A usability study of a mobile health application for rural Ghanaian midwives." *Journal of Midwifery & Women's Health,* vol. 59, no. 2, pp. 184-191.

Vis, J.Y., Kuin, R.A., Grobman, W.A., Mol, B.W., Bossuyt, P.M. & Opmeer, B.C. 2011, "Additional effects of the cervical length measurement in women with preterm contractions: a systematic review." *Archives of Gynecology & Obstetrics,* vol. 284, no. 3, pp. 521-526.

von Dadelszen, P., Magee, L.A., Payne, B.A., Dunsmuir, D.T., Drebit, S., Dumont, G.A., Miller, S., Norman, J., Pyne-Mercier, L., Shennan, A.H., Donnay, F., Bhutta, Z.A. & Ansermino, J.M. 2015, "Moving beyond silos: How do we provide distributed personalized medicine to pregnant women everywhere at scale? Insights from PRE-EMPT." *International Journal of Gynaecology & Obstetrics,* vol. 131, no. Suppl 1, pp. S10-S15.

Wadhwa, P.D., Culhane, J.F., Rauh, V., Barve, S.S., Hogan, V., Sandman, C.A., Hobel, C.J., Chicz-DeMet, A., Dunkel-Schetter, C. & Garite, T.J. 2001, "Stress, infection and preterm birth: a biobehavioural perspective." *Paediatric and Perinatal Epidemiology,* vol. 15, no. s2, pp. 17-29.

Watson, H.A., Carter, J., David, A.L., Seed, P.T. & Shennan, A.H. 2017a, "Full dilation cesarean section: a risk factor for recurrent second-trimester loss and preterm birth", *Acta Obstetricia et Gynecologica Scandinavica,* vol. 96, no. 9, pp.1100-1105.

Watson, H.A., Carter, J., Seed, P.T., Tribe, R.M. & Shennan, A.H. 2017b, "The QUiPP App: a safe alternative to a treat-all strategy for threatened preterm labor." *Ultrasound in Obstetrics & Gynecology,* vol. 50, no. 3, pp. 342-346.

Weiss, M.E., Saks, N.P. & Harris, S. 2002, "Resolving the uncertainty of preterm symptoms: Women's experiences with the onset of preterm labor." *Journal of Obstetric, Gynecologic, & Neonatal Nursing,* vol. 31, no. 1, pp. 66-76.

Whittemore, R., Chase, S.K. & Mandle, C.L. 2001, "Validity in qualitative research." *Qualitative Health Research,* vol. 11, no. 4, pp. 522-537.

Wing, D.A., Haeri, S., Silber, A.C., Roth, C.K., Weiner, C.P., Echebiri, N.C., Franco, A., Pappas, L.M., Yeast, J.D., Brebnor, A.A., Quirk, J.G., Murphy, A.M., Laurent, L.C., Field, N.T. & Norton, M.E. 2017, "Placental Alpha Microglobulin-1 Compared With Fetal Fibronectin to Predict Preterm Delivery in Symptomatic Women." *Obstetrics and Gynecology,* vol. 130, no. 6, pp. 1183-1191.

17. Appendices

17.1. Research Ethics Committee and Health Research Authority Approval Letters

NHS
Health Research Authority

NRES Committee London - South East
Bristol Research Ethics Committee Centre
Level 3, Block B
Whitefriars,
Lewins Mead,
Bristol
BS1 2NT

Telephone: 01173421386
Fax:01173420445

26 November 2014

Dr Rachel Tribe
Women's Health Academic Centre
10th Floor, North Wing
St Thomas' Hospital, London
SE1 7EH

Dear Dr Tribe

Study title: **Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management.**
REC reference: **14/LO/1988**
IRAS project ID: **111142**

The Research Ethics Committee reviewed the above application at the meeting held on 12 November 2014. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager Mr Rajat Khullar, nrescommittee.london-southeast@nhs.net.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

1. The Committee recommended that pictures should be revised in the PIS as discussed at the meeting.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on question 2 of the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee asked you at what stage the qualitative interviews will take place and how would the outcomes be collected. You explained that outcomes will be collected from the additional group of women. The interviews could take place when the women may still be in wards. Most of them would not go on to having their babies early but some of them will. You added that you did consider leaving the interviews to later as you did not want the final outcome on everyone, but later it was decided that it would be better to get the information as early as possible as you want to know about the opinion of the women up to that point. Therefore the majority of the interviews will be prenatal.

The Committee queried if the recruitment be done prenatally, or at least the women could be introduced to the study, in case they go in preterm labor. You explained that a lot of research is done in your department and most of the women that come are approached for participating in a research study. You added that you have to be very careful when consenting these women for taking part at this stage as they could be quite anxious given their condition. A lot of women may be contacted for the study and only a minority of them may actually become eligible later on, however the general idea of the study can be introduced.

The Committee noted that one part of the application mentions 20-30 interviews and another part mentions 30-40. The Committee queried if you will be able to achieve such a high number of interviews. You confirmed that there will be 30-40 interviews and as for the number of interviews you have been guided by the study supervisor to conduct these many interviews.

Recruitment arrangements and access to health information, and fair participant selection

The Committee asked you how and when you would approach the smaller group of women, with regards to the interviews. You explained that these women would be given PIS and consent form and at the time of that first approach they will be asked if they would be happy to be approached again for a short interview. You added that you will ask all the woman so you can get a good sample size of 30-40 and they do not have to be asked again.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee expressed concerns that the woman may be under stress and anxiety due to their condition. The Committee asked you if you have considered this and how would that be managed in terms of recruitment for this project. You explained that you would only approach women if their midwives or doctors have spoken to them and are happy for them to be approach for a research study and will make sure that they are comfortable to participate. You added that in terms of participation you will not ask them to do anything new or different. They will only be asked to provide information to create the risk assessment tool with permission to keep collecting the data and a follow up qualitative study.

Informed consent process and the adequacy and completeness of participant information

The Committee noted that the PIS has been designed to be quite appealing and attractive. Secondly there may be cultural bias in terms of the pictures in the PIS. You explained that in your experience a lot of women who are approached do not really read the PIS and therefore you have designed the PIS to be more attractive so they do read them. You agreed to consider revising the pictures in the PIS to make it more culturally neutral.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [PETRA Qualitative Interview Schedule]		20 October 2014
IRAS Checklist XML [Checklist_22102014]		22 October 2014
Letter from funder [NIHR letter of intent]		11 December 2013
Other [Summary CV for supervisor]		01 March 2014
Participant consent form [PETRA Consent cohort]	1	16 October 2014
Participant consent form [PETRA Consent qual]	1	16 October 2014
Participant information sheet (PIS) [PETRA PIS cohort]	1	16 October 2014
Participant information sheet (PIS) [PETRA PIS qual study]	1	16 October 2014
REC Application Form [REC_Form_22102014]		22 October 2014
Research protocol or project proposal [PETRA protocol]	1	16 October 2014
Summary CV for Chief Investigator (CI) [CV Dr Rachel Tribe]		20 October 2014
Summary CV for student [CV Jenny Carter Aug 2014]		11 August 2014
Summary CV for supervisor (student research) [CV Jane Sandall]		20 October 2014

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

There were no declarations on interest.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

NHS
Health Research Authority

NRES Committee London - South East
Bristol Research Ethics Committee Centre
Level 3, Block B
Whitefriars,
Lewins Mead,
Bristol
BS1 2NT

Telephone: (0117) 3421382

16 December 2014

Dr Rachel Tribe
Women's Health Academic Centre
10th Floor, North Wing
St Thomas' Hospital
London SE1 7EH

Dear Dr Tribe

Study title:	**Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management.**
REC reference:	**14/LO/1988**
IRAS project ID:	**111142**

Thank you for your letter of 10 December 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 26 November 2014

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Other [PETRA PIS v 2b qual_09 12 14]	2b	09 December 2014
Other [PETRA PIS v 2b qual_09 12 14]	2b	09 December 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [PETRA Qualitative Interview Schedule]		20 October 2014
IRAS Checklist XML [Checklist_22102014]		22 October 2014

Letter from funder [NIHR letter of intent]		11 December 2013
Other [Summary CV for supervisor]		01 March 2014
Other [PETRA PIS v 2b qual_09 12 14]	2b	09 December 2014
Other [PETRA PIS v 2b qual_09 12 14]	2b	09 December 2014
Participant consent form [PETRA Consent cohort]	1	16 October 2014
Participant consent form [PETRA Consent qual]	1	16 October 2014
Participant information sheet (PIS) [PETRA PIS cohort]	1	16 October 2014
Participant information sheet (PIS) [PETRA PIS qual study]	1	16 October 2014
Participant information sheet (PIS) [PETRA PIS]	2a cohort	09 December 2014
Participant information sheet (PIS) [PETRA PIS]	2b qual	09 December 2014
REC Application Form [REC_Form_22102014]		22 October 2014
Research protocol or project proposal [PETRA protocol]	1	16 October 2014
Summary CV for Chief Investigator (CI) [CV Dr Rachel Tribe]		20 October 2014
Summary CV for student [CV Jenny Carter Aug 2014]		11 August 2014
Summary CV for supervisor (student research) [CV Jane Sandall]		20 October 2014

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/LO/1988	Please quote this number on all correspondence

Yours sincerely

Mr Wai Yeung
Research Ethics Committee (REC) Assistant

E-mail: nrescommittee.london-southeast@nhs.net

Copy to: *Ms Barbara Dahill*
Mrs Karen Ignatian, Guy's & St Thomas' NHS Foundation Trust

A Research Ethics Committee established by the Health Research Authority

NHS
Health Research Authority
National Research Ethics Service

NRES Committee London - South East
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

17 June 2015
Modified 19 June 2015

Jenny Carter
NIHR Clinical Academic Training Fellow/Research Midwife
Division of Women's Health
King's College London
Women's Health Academic Centre KHP
10th Floor, North Wing
St. Thomas' Hospital
Westminster Bridge Road
London
SE1 7EH

Dear Jenny Carter

Study title:	**Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management.**
REC reference:	**14/LO/1988**
Amendment number:	**SA1**
Amendment date:	**28 May 2015**
IRAS project ID:	**111142**

The Substantial Amendment proposed to:
1. Add multiple pregnancies to the eligibility criteria
2. Identify and approach women who are assessed for TPTL when they attend for follow up appointments
3. Occasionally participants who have already consented experience further episodes of threatened preterm labour- the researchers wanted to capture data from these episodes and highlight this possibility in the participant information sheet, allowing them to withhold consent if preferred
4. Notified the Committee of the revised study start and end dates (03.03.2015-31.10.2017)

The above amendment was reviewed on 17 June 2015 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)		28 May 2015
Participant information sheet (PIS) [PETRA PIS]	3a- Tracked	28 May 2015
Research protocol or project proposal [PETRA protocol]	2.0- Tracked	28 May 2015

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/LO/1988:	**Please quote this number on all correspondence**

Yours sincerely

pp K. Southee

On behalf of Ms Stephanie Cooper
Vice Chair

E-mail: nrescommittee.london-southeast@nhs.net

Copy to: *Mrs Karen Ignatian, Guy's & St Thomas' NHS Foundation Trust*
Dr Rachel Tribe
Keith Brennan, King's College London

NRES Committee London - South East

Attendance at Sub-Committee of the REC meeting on 17 June 2015

Committee Members:

Name	*Profession*	*Present*	
Ms Stephanie Cooper	Retired Solicitor	Yes	
Ms Janelle Hill	Non medical lay member	Yes	

Also in attendance:

Name	*Position (or reason for attending)*	
Mrs Margaret Hutchinson	REC Manager	
Miss Katie Southeard	REC Assistant	

NHS
Health Research Authority
National Research Ethics Service

London - South East Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

25 November 2015

Jenny Carter
NIHR Clinical Academic Training Fellow/Research Midwife
Division of Women's Health
King's College London
Women's Health Academic Centre
10th Floor, North Wing
St Thomas' Hospital, London
SE1 7EH

Dear Jenny Carter

Study title:	**Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management.**
REC reference:	**14/LO/1988**
Amendment number:	**Two**
Amendment date:	**09 October 2015**
IRAS project ID:	**111142**

The Substantial Amendment proposed to:
1. Name of Sponsor's (Lead and Cosponsor) Representatives have been changed
2. There are currently no national guidelines on which tests should be used in the assessment of women with symptoms of threatened preterm labour (TPTL), and practice varies around the UK. Some maternity units offer fetal fibronectin (fFN) testing, some offer transvaginal ultrasound cervical length measurements (TVS CL), and some offer both. The researchers aim to validate the risk assessment tool using the results of fFN testing alone, TVS CL alone, and the combination of both tests. Currently, the eligibility criteria stipulates that the TPTL assessment must include fFN testing, with or without TVS CL. The proposed change will allow recruitment of participants who are assessed with either or both tests.

The above amendment was reviewed on 24 November 2015 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Two	09 October 2015
Participant information sheet (PIS) [PETRA PIS v 4a cohort]	4a- Tracked	09 October 2015
Research protocol or project proposal [PETRA protocol]	3- Tracked	09 October 2015

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/LO/1988:	**Please quote this number on all correspondence**

Yours sincerely

pp K. Southern

On behalf of Professor David Caplin
Chair

E-mail: nrescommittee.london-southeast@nhs.net

Copy to: *Mrs Karen Ignatian, Guy's & St Thomas' NHS Foundation Trust*
Keith Brennan, King's College London
Dr Rachel Tribe, Women's Health Academic Centre

London - South East Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 24 November 2015

Committee Members:

Name	*Profession*	*Present*	*Notes*
Professor David Caplin	Physicist	Yes	
Mr Guy Gardener	Retired Assistant Chief Constable	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Katie Southeard	REC Assistant

NHS
Health Research Authority

London - South East Research Ethics Committee

Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

02 November 2016

Dear Ms Carter

Study title:	**Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management.**
REC reference:	**14/LO/1988**
Amendment number:	**3**
Amendment date:	**11 July 2016**
IRAS project ID:	**111142**

1. Addition of New NHS Sites

2. Interview schedule asking women to consider cards showing different ways of illustrating risk and explain their views on them. Understanding women's views on the different illustrations of risk and how these may affect their perception of risk, will enable us to develop the risk assessment tool in ways that are most useful from the women's perspective.

3. Addition of Part 3:QUIPP app users' experience and views - a qualitative study exploring clinicians' use of the QUIPP app, a risk assessment tool for use in the management of women at risk of preterm birth. This app is already being used in practice in the care of women at risk, and the data from the PETRA study will be used to develop the prediction algorithm in relation to women with symptoms of threatened preterm labour. Understanding the users experience and views of the app to date will help us in the development of the app and ensure the tool and its results are presented in the most appropriate format.

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Interview schedules or topic guides for participants [PETRA Qualitative Interview schedule - Clean]	2	11 July 2016
Interview schedules or topic guides for participants [PETRA Qualitative Interview schedule - Tracked Changes]	2	11 July 2016
Interview schedules or topic guides for participants [PETRA Part 3 Interview schedule]	1	11 July 2016
Notice of Substantial Amendment (non-CTIMP) [Amendment Form]		11 July 2016
Other [Email of Amendment]		21 September 2016
Other [REC Form]		21 September 2016
Participant consent form [PETRA Part 3 Participant Consent Form]	3	11 July 2016
Participant information sheet (PIS) [PETRA Part 3 PIS]	3	11 July 2016
Research protocol or project proposal [PETRA Protocol - Clean]	4	11 July 2016
Research protocol or project proposal [PETRA Protocol - Tracked Changes]	4	11 July 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/LO/1988:	Please quote this number on all correspondence

Yours sincerely

Professor David Caplin
Chair

E-mail: nrescommittee.london-southeast@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mrs Karen Ignatian, Guy's & St Thomas' NHS Foundation Trust*
Dr Rachel Tribe , Keith Brennan, King's College London

London - South East Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 15 October 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Professor David Caplin	Physicist	Yes	
Mr Graham Smith	Business Consultant	Yes	

NHS
Health Research Authority

Dr Rachel Tribe
Women's Health Academic Centre
10th Floor, North Wing
St Thomas' Hospital, London
SE1 7EH

Email: hra.approval@nhs.net

07 December 2016

Dear Dr Tribe

Letter of HRA Approval for a study processed through pre-HRA Approval systems

Study title:	**Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management.**
IRAS project ID:	**111142**
Sponsor	**King's College London**

Thank you for your request for HRA Approval to be issued for the above referenced study.

I am pleased to confirm that the study has been given **HRA Approval.**. This has been issued on the basis of an existing assessment of regulatory compliance, which has confirmed that the study is compliant with the UK wide standards for research in the NHS.

The extension of HRA Approval to this study on this basis allows the sponsor and participating NHS organisations in England to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

If you have submitted an amendment to the HRA between 23 March 2016 and the date of this letter, this letter incorporates the HRA Approval for that amendment, which may be implemented in accordance with the amendment categorisation email (e.g. not prior to REC Favourable Opinion, MHRA Clinical Trial Authorisation etc., as applicable). If the submitted amendment included the addition of a new NHS organisation in England, the addition of the new NHS organisation is also approved and should be set up in accordance with HRA Approval processes (e.g. the organisation should be invited to assess and arrange its capacity and capability to deliver the study and confirm once it is ready to do so).

Participation of NHS Organisations in England

IRAS project ID	111142

Please note that full information to enable set up of participating NHS organisations in England is not provided in this letter, on the basis that activities to set up these NHS organisations is likely to be underway already.

The sponsor should provide a copy of this letter, together with the local document package and a list of the documents provided, to participating NHS organisations in England that are being set up in accordance with HRA Approval Processes. It is for the sponsor to ensure that any documents provided to participating organisations are the current, approved documents.

For non-commercial studies the local document package should include an appropriate Statement of Activities and HRA Schedule of Events. The sponsor should also provide the template agreement to be used in the study, where the sponsor is using an agreement in addition to the Statement of Activities. Participating NHS organisations in England should be aware that the Statement of Activities and HRA Schedule of Events for this study have not been assessed and validated by the HRA. Any changes that are appropriate to the content of the Statement of Activities and HRA Schedule of Events should be agreed in a pragmatic fashion as part of the process of assessing, arranging and confirming capacity and capability to deliver the study. If subsequent NHS organisations in England are added, an amendment should be submitted to the HRA..

For commercial studies the local document package should include a validated industry costing template and the template agreement to be used with participating NHS organisations in England.

It is critical that you involve both the research management function (e.g. R&D office and, if the study is on the NIHR portfolio, the LCRN) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

After HRA Approval

In addition to the document, *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC Favourable Opinion, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

IRAS project ID	111142

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/.

If you have any queries about the issue of this letter please, in the first instance, see the further information provided in the question and answer document on the HRA website.

Your IRAS project ID is 111142. Please quote this on all correspondence.

Yours sincerely

Elizabeth Bottomley
Application Administrator

Email: hra.approval@nhs.net

Copy to: *Keith Brennan, King's College London*
Mrs Karen Ignatian, Guy's & St Thomas' NHS Foundation Trust

IRAS project ID	111142

NHS
Health Research Authority

London - South East Research Ethics Committee

Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

18 October 2017

Jenny Carter
NIHR Clinical Academic Training Fellow/Research Midwife
Department of Women and Children's Health
King's College London
10th Floor, North Wing
St. Thomas' Hospital
Westminster Bridge Road
London
SE1 7EH

Dear Ms Carter

Study title:	**Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management.**
REC reference:	**14/LO/1988**
Amendment number:	**Substantial Amendment 4**
Amendment date:	**07 July 2017**
IRAS project ID:	**111142**

This amendment consisted of a change to eligibility and extension to end date beyond 31st October. It is proposed that from 1st November 2017 only women having both fetal fibronectin and cervical length measurements as part of their assessment for TPTL would be eligible to participate. They would like to extend the recruitment for a further three years (with a revised end date of 31st October 2020) to ensure the accuracy of the risk prediction algorithm is improved as much as is feasible in a realistic time frame.

The above amendment was reviewed by the Sub-Committee held by correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The members of the Sub-Committee raised no ethical concerns regarding this amendment and were content to issue a Favourable opinion.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment 4	07 July 2017
Participant consent form [clean]	2	01 November 2017
Participant consent form [tracked]	2	01 November 2017
Participant information sheet (PIS) [clean]	5a	01 November 2017
Participant information sheet (PIS) [tracked]	5a	01 November 2017
Research protocol or project proposal [clean]	5	01 November 2017
Research protocol or project proposal [tracked]	5	01 November 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/LO/1988:	**Please quote this number on all correspondence**

Yours sincerely

pp
Professor David Caplin
Chair

E-mail: nrescommittee.london-southeast@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mrs Karen Ignatian, Guy's & St Thomas' NHS Foundation Trust*
Dr Rachel Tribe, King's College London
Keith Brennan, King's College London

London - South East Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 15 October 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Professor David Caplin	Physicist	Yes	Chair
Mr Guy Gardener	Retired Assistant Chief Constable	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Julie Acourt	REC Assistant

17.2. PETRA - Participant Information Sheets (parts 1, 2 and 3)

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact: Principle Investigator Jenny Carter (jenny.carter@kcl.ac.uk or 020 7188 3641).

If you have a complaint, you should talk to your research doctor who will do their best to answer your questions. If you remain unhappy, you may be able to make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 020 7188 7188, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH .

This study is co-sponsored by King's College London and Guy's and St Thomas' NHS Foundation Trust. The sponsors will at all times maintain adequate insurance in relation to the study independently. Kings College London, through its own professional indemnity (Clinical Trials) and no fault compensation and the Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

What will happen to the results of the study?

This study is part of a PhD programme funded by the National Institute of Health Research. The results will be shared with clinical staff, published in health care journals and presented at midwifery and medical conferences. You will not be identified in any report/publication.

Who is paying for this research?

The National Institute for Health Research has funded this study as part of a Clinical Academic Training Fellowship.

The researchers working on this project are paid from this award or through local NHS Trust R&D department funding.

Who has reviewed this study?

The full title of this study is "Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management." It has been reviewed and approved by this NHS Trust's Research & Development Department and an NHS Research Ethics Committee (R&D Ref: RJ115/N074; REC Ref: 14/LO/1988; IRAS no. 111142).

What do I do if I have further questions or want to take part?

For further information please contact:

Jenny Carter
NIHR Clinical Academic Training
Fellow/Research Midwife
jenny.carter@kcl.ac.uk
tel: 020 7188 3641

or

Annette Briley
Consultant Midwife/
Clinical Trial Manager
tel: 020 7188 3643

Women's Health Academic Centre
10th Floor, North Wing
St Thomas' Hospital
London SE1 7EH

Thank you

for taking time to read this leaflet

Guy's and St Thomas' NHS
NHS Foundation Trust

PETRA

Threatened preterm labour: risk and care management

Part 1:

A tool for assessing risk

Participant Information Sheet

Can you help?

PIS version 4a: 09/10/2015

Background

Most babies are born at the right time, after 37 weeks of pregnancy. If pregnant women go into labour too soon, there are treatments that can reduce the chance of problems, such as admission to hospital and medicines to slow labour down and help the baby's lungs, if it is born early. It is important, then, that women who think they might be in labour tell their midwife or doctor if they think this is happening.

Many women experience symptoms of "threatened preterm labour" (TPTL) for example, tightenings and/or abdominal pain, but most of these women are not in labour, and the symptoms will settle down on their own. Sometimes it is hard to know whether symptoms are the start of early preterm labour, so many are admitted to hospital and given medicines they may not need.

Some factors, such as whether a woman has had a baby early before, and some test results, like fetal fibronectin and cervical length, are useful when considering how likely it is that labour is starting. Because a number of factors are involved it is quite complicated, so in this study we want to develop a risk assessment tool that will combine these factors and give a risk score (percentage risk of preterm birth) that will help doctors and midwives decide whether treatment is necessary or not.

Why have I been chosen?

You have been asked to take part because you are under 35 weeks' pregnant and have been experiencing symptoms that might mean you are in labour.

What do I have to do if I take part?

You will be assessed in exactly the same way whether or not you participate in this study. You may have a high vaginal swab to assess levels of a natural protein called fetal fibronectin. This is not normally found in high levels in vaginal fluid until just before labour starts. Some women have the length of their cervix measured by ultrasound scan. You may be offered either, or both, of these tests. These tests do not harm the baby.

If you take part in this study the only difference will be that you agree to information about you and your pregnancy (including results of any tests you have had for symptoms of preterm labour during this pregnancy) being collected and used to see if a risk assessment tool can accurately predict whether or not you give birth early.

After signing a consent form, you will be asked about your medical history and about this and any previous pregnancies. We also want to know how women feel about their experience of threatened preterm labour, any treatments they were offered and decisions they made. If you are happy to consider talking to us about your experience, please indicate this on the consent form and we will contact you to discuss it further. If you would like to go ahead we will arrange a convenient place and time. The interview will take about an hour.

Will my taking part be kept confidential?

If you agree to participate in the study you will be given a study identification number and the information collected about you will be kept on a study database using that number and not your name. It will not be possible to identify you from the information we collect. The database we use is secure and only accessible to people directly involved in the study.

Do I have to take part?

Whether you decide to take part or not is entirely up to you. Your decision will not affect the care you receive in any way. If you agree to take part, you are free to withdraw at a later stage, without giving a reason, although you may be asked if you mind us collecting details about your delivery from your medical notes. Again it is entirely up to you if you agree to this. In the unlikely event that you lose capacity to consent after initially taking part in the study, the data will still be used unless you indicate you do not agree to this on the consent form.

What are the benefits of taking part?

You may not benefit personally from taking part, but you may help us develop a risk assessment tool that helps women in the future.

What are the disadvantages of taking part?

Taking part in the study will involve taking some of your time in answering our questions, but all the procedures and tests that are done to assess whether you are in preterm labour are carried out as part of your normal care.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact: Principle Investigator Jenny Carter (jenny.carter@kcl.ac.uk or 020 7188 3641).

If you have a complaint, you should talk to your research doctor who will do their best to answer your questions. If you remain unhappy, you may be able to make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 020 7188 7188, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH .

This study is co-sponsored by King's College London and Guy's and St Thomas' NHS Foundation Trust. The sponsors will at all times maintain adequate insurance in relation to the study independently. Kings College London, through its own professional indemnity (Clinical Trials) and no fault compensation and the Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

What will happen to the results of the study?

This study is part of a PhD programme funded by the National Institute of Health Research. The results will be shared with clinical staff, published in health care journals and presented at midwifery and medical conferences. You will not be identified in any report/publication.

Who is paying for this research?

The National Institute for Health Research has funded this study as part of a Clinical Academic Training Fellowship.

The researchers working on this project are paid from this award or through local NHS Trust R&D department funding.

Who has reviewed this study?

The full title of this study is "Threatened preterm labour: a prospective cohort study of a clinical risk assessment tool and a qualitative exploration of women's experiences of risk assessment and management." It has been reviewed and approved by this NHS Trust's Research & Development Department and an NHS Research Ethics Committee (R&D Ref: RJ115/N074; REC Ref: 14/LO/1988; IRAS no. 111142).

What do I do if I have further questions or want to take part?

For further information please contact:

Jenny Carter
NIHR Clinical Academic Training
Fellow/Research Midwife
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tel: 020 7188 3641

or

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Consultant Midwife/
Clinical Trial Manager
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Women's Health Academic Centre
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London SE1 7EH

Thank you
for taking time to read this leaflet

Guy's and St Thomas' NHS
NHS Foundation Trust

PETRA

Threatened preterm labour: risk and care management

Part 2:

Women's experience and views

Participant Information Sheet

Can you help?

PIS version 2b: 09/12/2014

Background

Most babies are born at the right time, after 37 weeks of pregnancy. If pregnant women go into labour too soon, there are

treatments that can reduce the chance of problems, such as admission to hospital and medicines to slow labour down and help the baby's lungs, if it is born early. It is important, then, that women who think they might be in labour tell their midwife or doctor if they think this is happening.

Many women experience symptoms of "threatened preterm labour" (TPTL) for example, tightenings and/or abdominal pain, but most of these women are not in labour, and the symptoms will settle down on their own. Sometimes it is hard to know whether symptoms are the start of early preterm labour, so many are admitted to hospital and given medicines they may not need.

Decisions as to whether an intervention is offered, and/or accepted are made between the clinicians and the women experiencing the condition. In this part of the study we want to understand what it is like for women who have symptoms of threatened preterm labour and how they feel about the care they were offered. This information should help us to ensure that care given in the future takes account of what women want and need when they are making decisions.

Why have I been chosen?

You have been asked to take part because you have been experiencing symptoms that might mean you are in labour, and have agreed to participate in the first part of the PETRA study.

What do I have to do if I take part?

After signing a consent form, we will organise the interview either in hospital, or at your home, at a convenient time for you.

The interviewer will ask you about your experience of threatened preterm labour and any treatments you may have had. You will be encouraged to say everything you want to in your own words.

The interview will last about an hour and will be recorded on a digital audio recording device. This recording will later be typed up and used, along with other interviews with women who have had similar experiences, to explore themes and issues around the subject.

Will my taking part be kept confidential?

It will not be possible to identify you from the information we collect. Your name and any information that makes it possible to identify you will be removed or changed to maintain anonymity.

Do I have to take part?

Whether you decide to take part or not is entirely up to you. Your decision will not affect the care you receive in any way. If you agree to take part, you are free to withdraw at any time before or during the interview, without giving a reason, You may also withdraw permission for us to use the data within two weeks of the interview, in which case the material will be deleted.

What are the benefits of taking part?

You may not benefit personally from taking part, but you will help us understand what threatened preterm labour and it's management is like from the perspective of someone who has experienced it. This may lead improvements in care that helps women in the future.

What are the disadvantages of taking part?

If you have been unhappy about your experience or the care you received it is possible that you might find talking about it upsetting. If this happens you are free to stop the interview at any time, and, if you would like them to, the interviewer can arrange for any further support you may require, e.g. debriefing or counselling.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact: Principle Investigator Jenny Carter (jenny.carter@kcl.ac.uk or 020 7188 3634).

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What do I do if I have further questions or want to take part?

For further information please contact:

Jenny Carter
NIHR Clinical Academic Training
Fellow/Research Midwife
jenny.carter@kcl.ac.uk
tel: 020 7188 3641

or

Dr Rachel Tribe
Chief Investigator
tel: 020 7188 3639

Women's Health Academic Centre
10th Floor, North Wing
St Thomas' Hospital
London SE1 7EH

Thank you

for taking time to read this leaflet

Guy's and St Thomas' NHS
NHS Foundation Trust

PETRA

Threatened preterm labour: risk and care management

Part 3:

QUIPP app users experience and views

Participant Information Sheet

Can you help?

PETRA Part 3 PIS version 1: 11/07/2016

Background

Despite our best efforts in research and clinical practice, preterm birth remains a major cause of morbidity and infant death. It affects around 7% of pregnancies in the UK every year and its consequences include substantial emotional and financial costs to the families involved, as well as social and health care providers.

Interventions, such as steroid drugs to improve the preterm baby's lung function and hospitalisation, to ensure birth takes place in a hospital with an appropriate level of neonatal care, can ameliorate the consequences if well-timed (e.g. steroids given within 7 days of the baby's birth).

However, because the consequences of not intervening appropriately could be devastating, doctors are currently prone to over-treating women deemed at risk of preterm birth, and many women are admitted to hospital and given interventions they do not require. Negative side effects of these, potentially unnecessary treatments, include lower birth weights, poor maternal blood sugar control and blocked antenatal beds and neonatal cots.

The QUIPP App

In order to address this problem, we have developed the QUIPP app. This mobile application combines the women's background risk with the two most promising predictors of preterm birth (cervical length and quantitative fetal fibronectin, a point-of-care vaginal swab test).

The app can be used in the antenatal care of pregnant women already known to be at risk (e.g. with a history of previous preterm birth or cervical surgery), and those with no known risk, but with symptoms of threatened preterm labour. When risk factors and test results are entered, the tool instantly provides an individualised % risk of preterm delivery at clinically important time points, e.g. within 7 days, 14 days, before 34 weeks' gestation etc.

We would now like to explore users' experience of the QUIPP app and whether changes can be made that will enhance its utility, for example, alternative or visual methods of illustrating individual risk.

Why have I been chosen?

You have been asked to take part because you have experience in using the QUIPP app in practice.

What do I have to do if I take part?

After signing a consent form, we will organise the interview either in person or by telephone, at a place and convenient time for you.

The interviewer will ask you about your experience of using the QUIPP app. You will be encouraged to say everything you want to in your own words.

The interview will last about half an hour and will be recorded on a digital audio recording device. This recording will later be typed up and used, along with other interviews with QUIPP users to explore themes and issues around the subject.

Will my taking part be kept confidential?

It will not be possible to identify you from the information we collect. Your name and any information that makes it possible to identify you will be removed or changed to maintain anonymity.

Do I have to take part?

Whether you decide to take part or not is entirely up to you. If you agree to take part, you are free to withdraw at any time before or during the interview, without giving a reason, You may also withdraw permission for us to use the data within two weeks of the interview, in which case the material will be deleted.

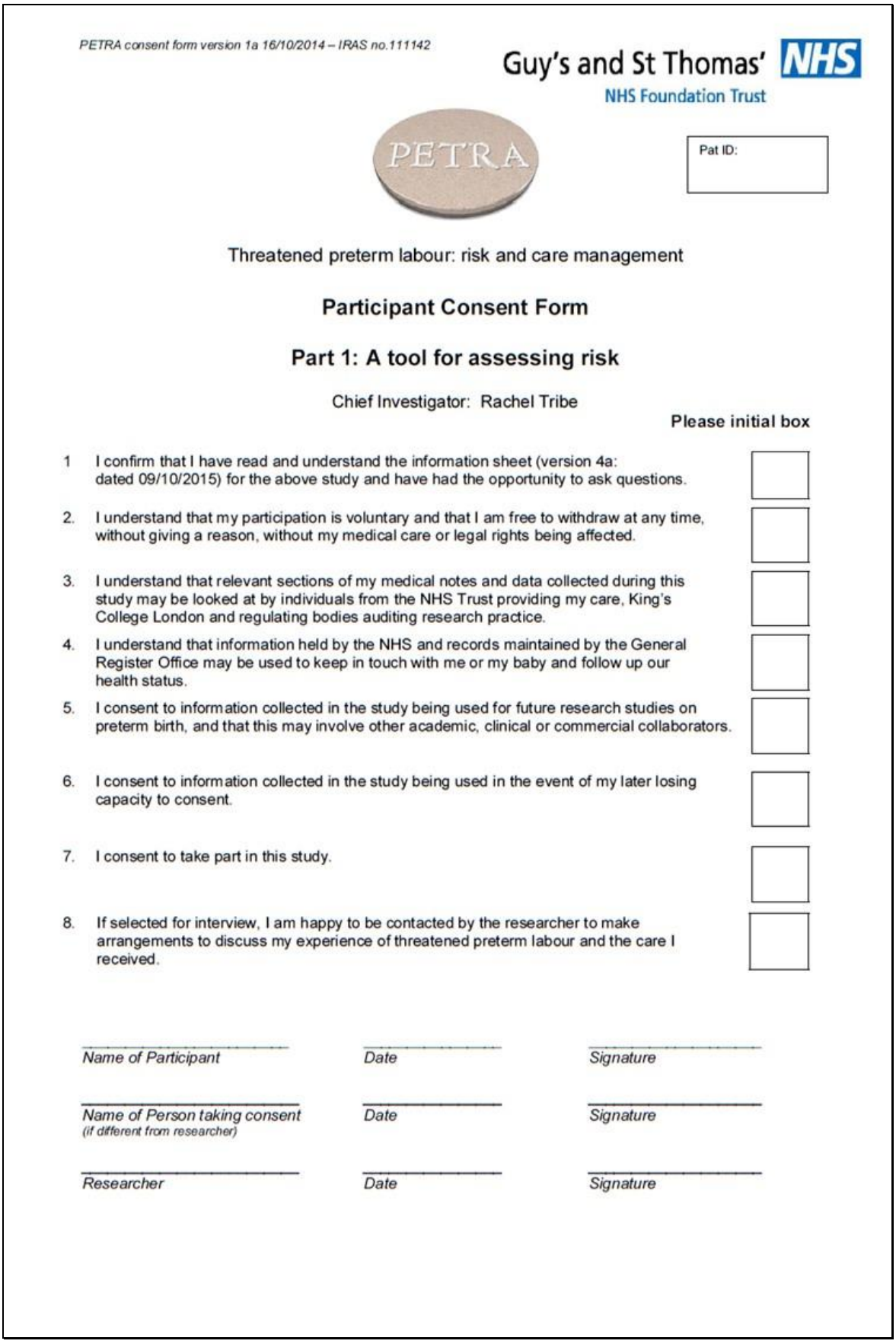
What are the benefits of taking part?

You may not benefit personally from taking part, but you will help us understand the issues around use of the risk assessment tool in practice. This may lead improvements in the future.

What are the disadvantages of taking part?

Apart from your time needed for the interview, there are no anticipated disadvantages of taking part.

17.3. PETRA – Consent forms (parts 1, 2 and 3)



PETRA consent form version 1a 16/10/2014 – IRAS no.111142

Guy's and St Thomas' NHS
NHS Foundation Trust

PETRA

Pat ID:

Threatened preterm labour: risk and care management

Participant Consent Form

Part 1: A tool for assessing risk

Chief Investigator: Rachel Tribe

Please initial box

1. I confirm that I have read and understand the information sheet (version 4a: dated 09/10/2015) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during this study may be looked at by individuals from the NHS Trust providing my care, King's College London and regulating bodies auditing research practice. ☐
4. I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me or my baby and follow up our health status. ☐
5. I consent to information collected in the study being used for future research studies on preterm birth, and that this may involve other academic, clinical or commercial collaborators. ☐
6. I consent to information collected in the study being used in the event of my later losing capacity to consent. ☐
7. I consent to take part in this study. ☐
8. If selected for interview, I am happy to be contacted by the researcher to make arrangements to discuss my experience of threatened preterm labour and the care I received. ☐

Name of Participant	*Date*	*Signature*
Name of Person taking consent (if different from researcher)	*Date*	*Signature*
Researcher	*Date*	*Signature*

PETRA consent form version 1b 16/10/2014 - IRAS no.111142

Guy's and St Thomas' NHS
NHS Foundation Trust

Pat ID:

Threatened preterm labour: risk and care management.

Participant Consent Form

Part 2: Women's Experience and Views

Chief Investigator: Rachel Tribe

Please initial box

1	I confirm that I have read and understand the information sheet (version 2b: dated 09/12/2014) for the above study and have had the opportunity to ask questions.	☐
3.	I understand that my participation is voluntary and that I am free to withdraw at any time before or during the interview, without giving a reason, without my medical care or legal rights being affected.	☐
4	I understand I can withdraw permission to use the data within two weeks of the interview, in which case the material will be deleted.	☐
5	I understand that anonymity will be ensured in the write-up of the study by disguising my identity.	☐
6	I understand that disguised extracts from my interview may be quoted in the write-up of the study and any subsequent publications and I agree to quotations from my interview being used in this way.	☐
9	I consent to take part in this study.	☐

_____	_____	_____
Name of Participant	*Date*	*Signature*
_____	_____	_____
Name of Person taking consent (if different from researcher)	*Date*	*Signature*
_____	_____	_____
Researcher	*Date*	*Signature*

PETRA Part 3 consent form version 1 11/07/2016 - IRAS no. 111142

Guy's and St Thomas' NHS
NHS Foundation Trust

Pat ID:

Threatened preterm labour: risk and care management.

Participant Consent Form

Part 3: QUIPP app users' Experience and Views

Chief Investigator: Rachel Tribe

Please initial box

1	I confirm that I have read and understand the information sheet (version 1: dated 11/07/2016) for the above study and have had the opportunity to ask questions.	☐
3.	I understand that my participation is voluntary and that I am free to withdraw at any time before or during the interview, without giving a reason, without my medical care or legal rights being affected.	☐
4	I understand I can withdraw permission to use the data within two weeks of the interview, in which case the material will be deleted.	☐
5	I understand that anonymity will be ensured in the write-up of the study by disguising my identity.	☐
6	I understand that disguised extracts from my interview may be quoted in the write-up of the study and any subsequent publications and I agree to quotations from my interview being used in this way.	☐
9	I consent to take part in this study.	☐

_____	_____	_____
Name of Participant	*Date*	*Signature*
_____	_____	_____
Name of Person taking consent (*if different from researcher*)	*Date*	*Signature*
_____	_____	_____
Researcher	*Date*	*Signature*

17.4. PETRA - Interview schedules (parts 2 and 3)

PETRA Part 2: Women's experience and views – interview schedule

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I. **Opening**

A. (**Establish Rapport**) [shake hands] My name is Jenny Carter, I am a midwife and I am undertaking this study for my PhD thesis. Thank you for agreeing to take part.
B. (**Purpose**) I would like to ask you some questions about your experience of being in threatened preterm labour, what happened and how you felt about the way you were assessed by the midwives and doctors looking after you. I would also like to know whether you were happy with the decisions that you made about the care you were offered, and what factors affected those decisions.
C. (**Motivation**) I hope to use this information to help women in the future who experience threatened preterm labour.
D. (**Time Line**) The interview should take about one hour. Are you happy to respond to some questions at this time?

(**Transition:** I have some details about your pregnancy so far (from when you took part in the first part of this study), but let me begin by asking a few more questions about this and any other pregnancies.

II **Body**

A. (Topic) Background information
1. This is your first/second… pregnancy...?
2. Is this the first time you have had symptoms of threatened preterm labour?
3. What were the symptoms like?
3. Have the symptoms settled now?

(**Transition to the next topic:** Now I am going to ask you some questions about when you first thought you might be having symptoms of labour)

B. (Topic) Perception of risk
1. Did you think you were at particular risk of having your baby early? If so, why?
2. When did you first think the symptoms you were having might be labour?
3. Did you talk to anyone about it before you called your midwife/the hospital?
4. How long was it before you called/came into hospital?

(**Transition to the next topic:** this final section is about what happened and how you feel about the care you were offered and the decisions you made about it.)

C. (Topic) Decision making
1. When you saw the midwife/doctor, how did they explain what was going to happen?
2. Do you feel you had enough information about the tests they offered?
3. Do you feel they gave you enough information about the results of those tests?
4. What about the treatments/interventions? (confirm interventions as recorded part 1) Are you happy with your decision about whether to accept them, or not?
5. What were the factors/things/people that affected your decisions?
6. Looking at the different illustration cards showing ways of communicating the same risk (e.g. following examples - %; 5:100, visual images) what makes most sense to you? Can you say more about why?

III Closing

A. (Summarize) So, things have settled down/you are still having symptoms/you have had the baby etc. If you would like to talk more about your experience, or feel upset by what happened, or by talking to me about it today, please let me know and I can arrange for (the appropriate person e.g. manager, consultant, bereavement counselor) to meet/talk to you.

B (Maintain Rapport) Thank you very much for talking to me, I appreciate the time you took for this interview. Is there anything else you think would be helpful for me to know?

C. (Action to be taken) I should have all the information I need. Would it be alright to call you at home if I have any more questions? (check telephone no.). Thanks again. I wish you all the best for the rest of your pregnancy/with the baby.

PETRA Part 3: QUIPP Users experience and views – interview schedule

---

I. Opening

A. (**Establish Rapport**) … My name is Jenny Carter, I am a midwife and I am undertaking this study as part of my PhD. Thank you for agreeing to take part.
B. (**Purpose**) I would like to ask you about your experience of using the QUIPP app (threatened preterm labour risk assessment tool). *Give reassurance re. anonymous nature of study etc.*
C. (**Motivation**) This will help us to understand what users think about the app and how we can make it better in the future.
D. (**Time Line**) The interview should take about half an hour. Are you happy to respond to some questions at this time?

(**Transition:** To start with I would like to ask some specific questions about you and your use of the app, and then I would like you to explain in a bit more detail about how you feel about using this app, as well as other decision tools and information technology in healthcare in general.

II Body

A. (Topic) Background information
1. What is your grade?
2. Are you a member of the UK Preterm Clinical Network?
3. How long have you been responsible for making management decisions in the care of women presenting with threatened preterm labour?

(**Transition to the next topic:** I am now going to ask you some questions about your use of the app.)

B. (Topic) About use of the QUIPP app
1. How long have you been using the QUIPP app?
2. How often, would you say, you use it in practice (e.g. every time/not every time you assess a women with TPTL/once a week/once a month)?
3. Have you recommended the QUIPP app to colleagues? (If so, why? If not, why not?)
4. What do you like about the app/what do you see as its values?
5. What about its limitations?
6. In what ways could it be better/how could we improve it?
7. Do you see any potential barriers to the implementation of this app or similar electronic risk assessment tools.

(**Transition to the next topic:** this final section is about your use of other electronic risk assessment or decision tools and the use of information technology in healthcare in general.

C. (Topic) Wider use of electronic risk assessment or decision tools and information technology in healthcare
1. The QUIPP App represents the risk of preterm birth as a % risk, please consider the illustration cards showing different ways of illustrating risk. What makes most sense to you and can you say more about why?
2. Do you use any other electronic risk assessment or decision tools in your practice? (if so, can you tell me a bit more about them and what you like/dislike about them).
3. What do you feel about the use of information technology in healthcare in general?

III **Closing**
Thank you very much for talking to me, I appreciate the time you took for this interview. Is there anything else you think would be helpful for me to know?

17.5. QUIPP v.2 formulae.

Symptomatic women (based on log-normal survival model).

NOTE: the app is designed for women having symptoms suggestive of abnormal or premature uterine activity, and being tested between 23+0 and 34+6 weeks. It was not designed for triplets or higher multiples.

Method 4: Symptomatic women with both CL and fFN measured (methods 1, 2 and 3 relate to asymptomatic models):

Symptoms suggestive of abnormal or premature uterine activity: [D1]
Previous cervical surgery: [D2]
Previous PPROM: [D3]
Previous preterm birth ≤36+6: [D4]
Number of fetuses: [D5]
Gestation of test: [D7]*7+[D8]
Weeks: [D7]
Days: [D8]
Shortest cervical length (mm): [D9]
fFN result (ng/ml): [D10]
Mu: [D11] = 0.00896*CL-0.0007748*fFN-0.1351627 (if twin pregnancy, previous cervical surgery, PPROM or preterm birth) + 5.53231915.
Sigma: [D12] = exp(-1.74601) = .1744687
S(test): [D13] = 1-(NORMSDIST($\log_e$(gestation of test-Mu)/Sigma)
S(30): [D14] = 1-(NORMSDIST($\log_e$(30*7-Mu)/Sigma); likewise, S(34): D[15], S(37): [D16]
S(1week): D[17] = 1-(NORMSDIST($\log_e$(gestation of test+1*7-Mu)/Sigma); likewise, S(2 weeks): D18], S(4 weeks): [D19]
Probability of delivering before 30 weeks: [D20] =MAX((S(test)-S(30))/S(test), 0)
Other probabilities are calculated similarly
[Results are as calculated in anal2_symp_ffn_cl_equiptt_app_ph.txt]

Method 5: Symptomatic women with only CL measured:

Symptoms suggestive of abnormal or premature uterine activity: [D1]
Previous cervical surgery: [D2]
Previous PPROM: [D3]
Previous preterm birth ≤36+6: [D4]
Number of fetuses: [D5]
Gestation of test: [D7]*7+[D8]
Weeks: [D7]
Days: [D8]
Shortest cervical length (mm): [D9]

Mu: [D10] = 2.397495*$\log_e$(CL+1)/10 -.1751846 (if twin pregnancy, previous cervical surgery, PPROM or preterm birth) + 4.9803773
Sigma: [D11] = exp (-1.575416) = .2069215
All other results are calculated as method 4
[Results are as calculated in anal2_symp_cl_equiptt_app_ph.txt]

Method 6: Symptomatic women with only fFN measured:

Symptoms suggestive of abnormal or premature uterine activity: [D1]
Previous cervical surgery: [D2]
Previous PPROM: [D3]
Previous preterm birth ≤36+6: [D4]
Number of fetuses: [D5]
Gestation of test: [D7]*7+[D8]
Weeks: [D7]
Days: [D8]
fFN result (ng/ml): [D9]
Mu: [D10] = -0.0013155*fFN -0.1911503 (if twin pregnancy, previous cervical surgery, PPROM or preterm birth) + 5.936622
Sigma: [D11] = exp (-1.509526) = .22101474
All other results are calculated as method 4
[Results are as calculated in anal1_symp_ffn_equiptt_app_ph.txt]

Abbreviations:

fFN Fetal Fibronectin (ng/mL)
CL Cervical length (mm)
$\log_e$ Log base e; natural log. In Excel written LN().
NORMSDIST() Cumulative probability function of the Standard Normal distribution; in algebra written as Φ(). NORMSDIST(0) = 0.5, NORMSDIST(1.96) = 0.975.
Exp() Natural exponent; inverse of natural log. Exp(x) = e^x. Exp(log(x)) = log(exp(x)) = x for x > 0
^ Power. a^b = a^b. 10^2 = 10^2 = 100.
MAX(,) Maximum. MAX(a,b) = larger of a or b. It is used only to ensure that a zero probability is presented for risk of delivery at dates that have already passed.
√ Square root. In Excel: SQRT().

17.6. Comparison of statistics from Kuhrt *et al*. (2016a) and PETRA study.

Table 54. Summary of predictive statistics for delivery at < 30, < 34 and < 37 weeks' gestation and delivery within 2 weeks from fFN test in validation sets from PETRA and Kuhrt *et al*., (2016).

	sPTB at less than						sPTB within			
Outcome	30 wk	*95% CI*	34 wk	*95% CI*	37 wk	*95% CI*	1 wk	*95% CI*	2 wk	*95% CI*
Sensitivity %										
Kuhrt et al.	50.0%	*(18.7-81.3%)*	78.6%	*(49.2-95.3%)*	72.0%	*(50.6-87.9%)*	*Not reported*		50.0%	*(18.7-81.3%)*
PETRA	90.0%	*(55.5-99.7%)*	84.6%	*(65.1-95.6%)*	80.9%	*(69.5-89.4%)*	53.8%	*(25.1-80.8%)*	83.3%	*(58.6-96.4%)*
Specificity %										
Kuhrt et al.	96.2%	*(92.2-98.4%)*	87.6%	*(81.9-92.1%)*	77.2%	*(70.1-83.4%)*	*Not reported*		94.0%	*(89.4-96.9%)*
PETRA	90.8%	*(86.7-94.0%)*	70.9%	*(66.6-74.8%)*	56.9%	*(52.5-61.2%)*	92.0%	*(89.5-94.1%)*	84.2%	*(80.9-87.2%)*
Likelihood ratio - positive										
Kuhrt et al.	13.0	*(5.0-33.8)*	6.4	*(3.9-10.3)*	3.2	*(2.2-4.6)*	*Not reported*		8.3	*(3.5-19.2)*
PETRA	9.8	*(6.4-15.2)*	2.90	*(2.3-3.6)*	1.9	*(1.6-2.2)*	6.7	*(3.8-12.0)*	5.3	*(4.0-7.0)*
Likelihood ratio - negative										
Kuhrt et al.	0.5	*(0.3-1.0)*	0.2	*(0.1-0.7)*	0.4	*(0.2-0.8)*	*Not reported*		0.5	*(0.3-1.0)*
PETRA	0.1	*(0.02-0.7)*	0.2	*(0.1-0.5)*	0.3	*(0.2-0.6)*	0.5	*(0.3-0.9)*	0.2	*(0.1-0.6)*
Positive Predictive Value (%)										
Kuhrt et al.	41.7%	*(15.2-72.3%)*	33.3%	*(18.0-51.8%)*	32.1%	*(20.3-46.0%)*	*Not reported*		31.3%	*(11.0-58.7%)*
PETRA	27.3%	*(13.3-45.5)*	13.3%	*(8.5-19.4%)*	20.1%	*(15.5-25.3%)*	13.5%	*(5.6-25.8%)*	14.6%	*(8.4-22.9%)*
Negative Predictive Value (%)										
Kuhrt et al.	97.2%	*(93.0-100%)*	98.1%	*(94.6-99.6%)*	94.9%	*(89.7-97.9%)*	*Not reported*		97.2%	*(93.5-99.1%)*
PETRA	99.6%	*(97.7-100%)*	98.9%	*(97.1-99.7%)*	95.7%	*(92.8-97.7%)*	98.9%	*(97.5-99.6%)*	99.4%	*(98.2-99.9%)*
Area under the ROC										
Kuhrt et al.	0.88	*(0.74-1.0)*	0.83	*(0.67-0.98)*	0.77	*(0.65-0.90)*	*Not reported*		0.77	*(0.55-0.99)*
PETRA	0.96	*(0.94-0.99*	0.85	*(0.78-0.92)*	0.77	*(0.71-0.83)*	0.91	*(0.87-0.96)*	0.92	*(0.88-0.96)*

Table 55. Prevalence rates of sPTB at <30, <34 and <37 weeks' gestation and within 1 and 2 weeks of delivery in Kuhrt and PETRA cohorts.

	sPTB at less than						sPTB within			
Outcome	30 wk	*n*	34 wk	*n*	37 wk	*n*	1 wk	*n*	2 wk	*n*
Prevalence % (rate of sPTB)										
Kuhrt et al. (n=192)	5.2%	*10*	7.3%	*14*	13.0%	*25*	*Not reported*		5.2%	*10*
PETRA (n=576)	1.7%	*10*	4.5%	*26*	11.8%	*68*	2.3%	*13*	3.1%	*18*