IMPROVE study

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Study Title: Implementation of a tool for predicting early pregnancy outcome in women with initial pregnancy of uncertain viability: a psychological impact study

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

This protocol describes the study and provides information about procedures for entry. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

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1. SYNOPSIS

Study Title	Implementation of a tool for predicting early pregnancy outcome in women with pregnancy of uncertain viability: a psychological impact study	
Short Title/Acronym	IMPROVE	
Study Design	Single centre, non-blind randomised intervention study	
Study Participants	Women diagnosed with an intrauterine pregnancy of uncertain viability (IPUVI) will be recruited to one of two groups: Group I – women randomised to receive prediction tool Group II – women randomised to not receive the prediction tool	
Planned Sample Size	250 participants	
Planned Study Period	2 years	
	Objectives	**Endpoints**
	Primary	To assess whether providing an individualised risk prediction of early pregnancy viability, in women diagnosed with intrauterine pregnancy of uncertain viability, has a beneficial psychological impact during the time to final diagnosis
	Secondary	To assess patient experience of the prediction tool To assess healthcare professionals experience of offering and providing more accurate information regarding pregnancy outcome to patients

2. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CWFT	Chelsea and Westminster Hospital Foundation Trust
EPAU	Early Pregnancy Assessment Unit
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale

HCP	Healthcare Professional
ICF	Informed Consent Form
IPUVI	Intrauterine Pregnancy of Uncertain Viability
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure

3. BACKGROUND AND RATIONALE

Early pregnancy can be a particularly distressing time for women and their partners, especially those who experience complications such as bleeding or pain. 10-28% of women seen in the early pregnancy assessment unit (EPAU) setting are diagnosed with a pregnancy of uncertain viability (IPUVI)[1-5]. Such women have a pregnancy correctly sited within the uterus but the viability of the pregnancy cannot be determined at the initial scan. This finding may represent a normally developing (but early) pregnancy. However, approximately 50% of these pregnancies will eventually miscarry[1,4,5]. The current recommendation from The National Institute for Health and Care Excellence (NICE) is to offer a confirmatory scan after 14 days[6].

This 14-day interval between scans is a difficult time for patients. Studies have previously identified the negative impact on psychological health where early pregnancy complications arise[2,3]. We know that miscarriage is positively associated with grief, anxiety, stress, depression[7] and even post-traumatic stress disorder (PTSD)[8]. Studies have also shown that this is not necessarily an immediate reaction as women with early pregnancy loss have met criteria for conditions such as probable PTSD and major depressive disorder at 3 and 6 months' respectively after the event[7,8]. More recently, Richardson et al (2016) found that the diagnostic uncertainty in early pregnancy, as experienced with an IPUVI diagnosis, is associated with significant ($p < 0.001$) heightened levels of anxiety compared with those who receive an early certain diagnosis of either a positive (ongoing pregnancy) or negative (miscarriage) outcome[3]. We want to find out whether this psychological response to an uncertain diagnosis can be modified by offering more detailed prognostic information to women.

NICE Clinical Guideline CG154(2012) does not recommend specific tools or scoring systems to predict the viability of intrauterine pregnancy[6]. However, NICE Evidence Update 71(2014) suggests the availability of more information (prior to repeat ultrasound) on which to base estimates of viability in early pregnancy, could be useful and may benefit patients' psychological health[9]. Published models and scoring systems for predicting outcome do exist with excellent performance results for the test populations[5,10]. One

randomised controlled trial (RCT) looked at psychological outcomes when women were randomised to receive a prediction of their pregnancy outcome through means of a validated blood test. The results showed that anxiety levels were significantly reduced (p=0.04) in those who received the prediction of pregnancy outcome. The authors concluded that even if further information is not definitive, women benefit psychologically from tests that give them an indication of what a subsequent ultrasound might show[2].

We have previously developed, validated and published a mathematical tool to predict pregnancy viability after diagnosis of IPUVI (549 participants)[5]. The tool (which takes account of maternal age, vaginal bleeding score and ultrasound measurements) is established as an accurate *research* tool having been externally validated in a different test population[10]. Having established its performance, we now wish to provide women with this individualised prediction of their pregnancy outcome. If psychologically beneficial (and not harmful) this tool may help up to a third of the EPAU population.

There is an increasing need for a shift towards patient-centred care in the early pregnancy setting[12]. It has been suggested that health professionals underestimate the psychological impact of early pregnancy complications for women and couples[13].

An audit within the EPAU at Chelsea and Westminster was conducted assessing the variation in information given to women by the medical professional who diagnoses IPUVI at the initial ultrasound. This demonstrated wide inter-professional differences. The most commonly reported explanation of the ultrasound findings to the woman was “it is too early to tell.” 2/3 of the healthcare professionals (HCP) stated that they offered different intervals to the subsequent ultrasound (i.e. 7 days, 10 days or 14 days) to different women, all with the same IPUVI diagnosis. When asked about likely percentage outcome of a viable pregnancy by the end of the first trimester in all IPUVI diagnoses, responses were varied between 50 to 70%, others were “unsure”. 80% of HCP’s felt they would find it beneficial to be able to offer a predicted outcome of the pregnancy being viable at the follow-up ultrasound. This ambiguity in advice that these women receive when given an uncertain diagnosis may have an impact upon psychological well-being.

4. STUDY HYPOTHESIS

We hypothesise that providing women diagnosed with IPUVI with a percentage likelihood of ongoing viability of their pregnancy, will result in improved psychological well-being (reduced anxiety and depression) at the time of the follow-up ultrasound.

5. AIMS AND OBJECTIVES

Objectives	Outcome Measures/Endpoints

Primary Objective	1. To assess whether providing an individualised risk prediction of early pregnancy viability, in women diagnosed with intrauterine pregnancy of uncertain viability, has a beneficial psychological impact during the time to final diagnosis
Secondary Objectives	2. To assess patient experience of the prediction tool 3. To assess healthcare professionals experience of offering and providing more accurate information regarding pregnancy outcome to patients

5.1. Aims

The aims of this study are:

1. To assess and compare if there is any significant difference in symptoms of anxiety and depression during the uncertain period, as measured by the Hospital and Anxiety Depression Score in two groups of women all diagnosed with IPUVI. The two groups will be; 1) women randomised to receive the prediction tool and 2) women randomised to not receive the prediction tool.

2. To assess and compare whether the symptoms of anxiety and depression in the two groups of women change over three defined time points: immediately after the initial ultrasound/ diagnosis, at 72 hours post ultrasound and immediately prior to the follow-up ultrasound at 14 days.

3. To assess the patient experience during the study period by applying a self-reported experience questionnaire on the acceptability and perceived usefulness of the prediction tool, in those women who receive it. The questionnaire has been developed by the study investigators using modified versions of the Technology Acceptance Model by Davis et al, 1989.

6. STUDY DESIGN

This will be a single centre, non-blind, randomised intervention controlled trial.

6.1. Participant groups

A total of 250 eligible women with an ultrasound classification of IPUVI at Chelsea and Westminster Hospital will be identified and recruited to the study. Women will participate in one of the following groups:

- **Group I (intervention) – women randomised to receive the prediction tool (125 participants)**
- **Group II (control) – women randomised to not receive the prediction tool (125 participants)**

6.2. Data collection tools

Data will be collected from women at three points during the course of the study (see flow diagram). A single, validated scale will be used for data collection regarding psychological well-being: -

The Hospital Anxiety and Depression Scale (HADS), (Appendix 1, Zigmond and Snaith 1983)

Participants will also be invited to give a free text response to detail any additional information arising from the questions they have been asked in the HADS questionnaire.

Each questionnaire will take approximately 5-10 minutes to complete.

The questionnaires will be sent to participants via email (or post if participants do not have access to email). If they do not initially respond the researcher may send a maximum of two email reminders and contact them by telephone on one occasion with prior consent from the participant. If they do not respond following these reminders they will be withdrawn from the study. The local researcher will monitor the progress of each participant's pregnancy prior to sending out the questionnaires. Women who are known to have undergone termination of pregnancy prior to completion of all three questionnaires will be withdrawn from the study and not contacted with further questionnaires.

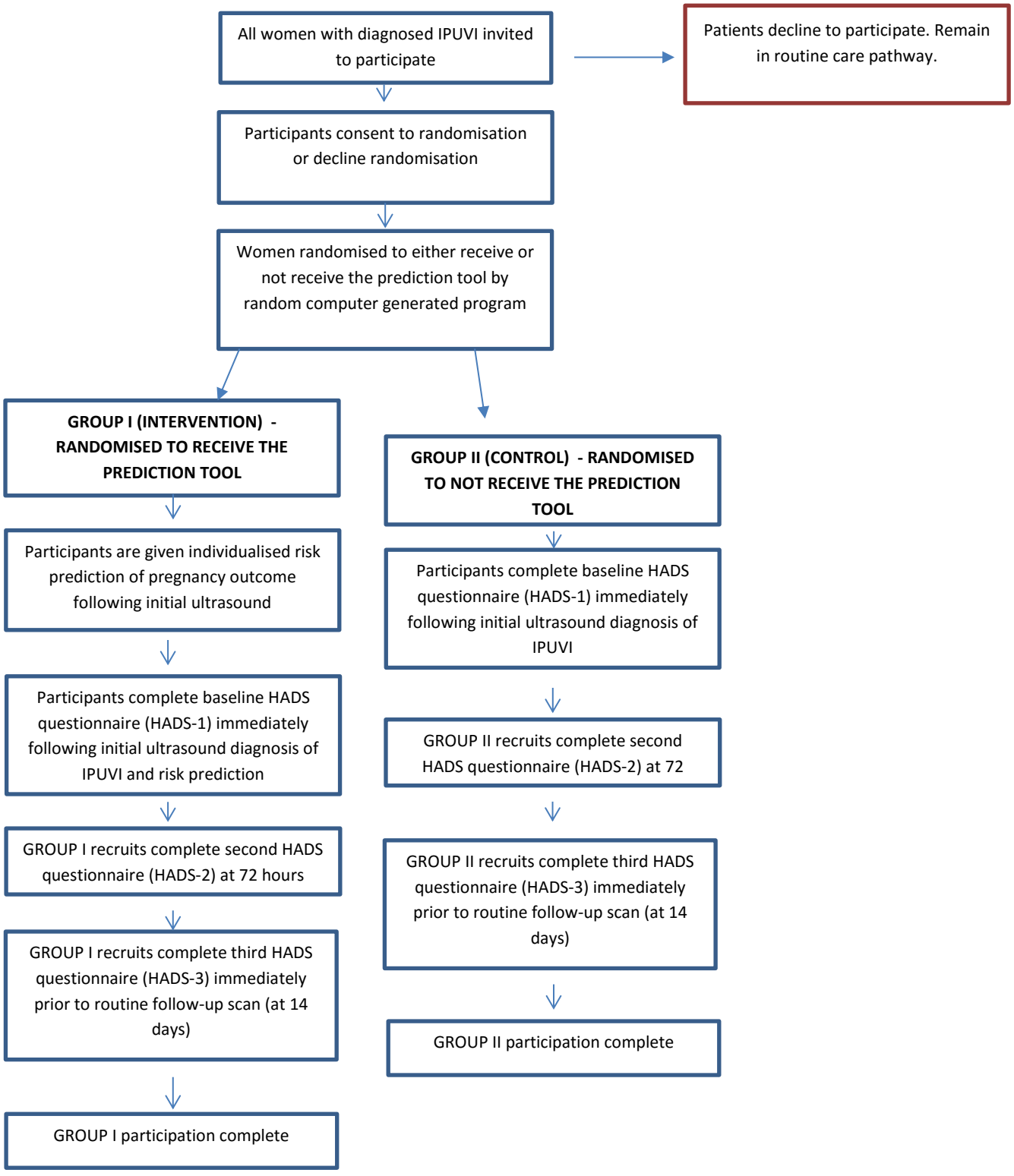
Participants in Group I will also be invited to complete a patient experience questionnaire at the end of the study period to assess their perceived acceptability and usefulness of the tool. This has been developed specifically for this study using modified versions of the Technology Acceptance Model (Davis et al 1989) (Appendix 2)[14].

6.3 Study Centres

Single centre recruitment will take place at Chelsea and Westminster Hospital.

Consecutive women diagnosed with IPUVI will be approached during the recruitment period.

6.4 Participant journey



7. PARTICIPANT IDENTIFICATION

7.1. Study Participants

All women (both elective and emergency admissions) seen in the EPAU at Chelsea and Westminster Hospital with a diagnosis of IPUVI will be approached to consider participation following their initial ultrasound.

7.2. Inclusion Criteria

- Age 18 years+
- Diagnosis of IPUVI on initial ultrasound

7.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Current mental health condition (anxiety, depression, eating disorder). The condition will be considered current if it has required one or more consultations with a medical professional (including a psychologist) over the past 6 months (women with past mental health condition will not be excluded)
- The patient is planning a termination
- Multiple order pregnancies
- Women who in the opinion of the researcher by virtue of language or learning impairment would be unable to give fully informed consent to the study

8. STUDY PROCEDURES

8.1. Recruitment

Potential participants will be identified on a daily basis by those that regularly perform ultrasound scans within the department; sonographers, nurse specialists, research fellows and consultants. Once identified, they shall be approached by the local researcher for a face-to-face consultation who will confirm their eligibility criteria and explain the study. In addition, the detailed patient information sheet (PIS) will be provided before taking informed written consent. Clinicians who perform ultrasound scans out of hours, will be notified of the study and asked to inform eligible women about the study and obtain consent for the local researcher to contact them the next working day.

8.2. Informed Consent

Participants will sign and date the informed consent form (ICF), before any study specific procedures are performed. Written and verbal versions of the PIS and ICF will be presented to the participants detailing the nature of the study and what it will involve for the participant. It will clearly state that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. A copy of the signed ICF will be given to the participant, and a copy of the signed ICF will be placed in the patient's medical notes. The original signed form will be retained at the study site in the Investigator Site File. The participant will be allowed adequate time to consider the written information before giving their consent.

8.3. Potential risks and benefits

Potential benefits

Patient specific

This study will confirm whether this prediction tool is of clinical and psychological benefit to the patient.

Women may find the questionnaires they are asked to complete prompt them to seek help earlier for conditions which may otherwise have gone untreated such as anxiety and depression. In addition, they may find it therapeutic to be able to express their opinions, emotions and feelings during the period of uncertainty.

Resource specific

If the study shows that the prediction tool is acceptable to patients (as well as being accurate in terms of the actual pregnancy outcome) this will allow units to more appropriately triage follow-up plans were resources are limited.

Following the study, we anticipate that the use of the tool could be extended to other clinical sites to aid the management and expectations of women diagnosed with IPUVI. The NICE Evidence Update specifically refers to this prediction tool and it is anticipated that this will be a nationally recommended tool if validated in this study.

Potential risks/ burdens

No physical risks will be incurred by participation in the study.

Recruited women will not be expected to have any additional visits to the hospital during the study, over and above usual care.

We are aware that when conducting a study of mental health symptoms, we could potentially identify a woman with an undiagnosed mental health condition, issues of self-harm or potential harm to others. The CI will check the survey responses regularly and will highlight any of serious concern to CB. The CI will then contact the woman directly to discuss her responses. She will be encouraged to see her GP if deemed necessary. If the woman does not wish to see her GP or there is continued concern from the local researcher the confidentiality clause may need to be broken in the interest of safety of the woman and others. The CI will then contact the woman's GP directly after informing the patient of their intended actions, to report their concerns.

It is possible that the women will not perceive any individual benefit from participating in this study.

8.4. Screening and Eligibility Assessment

Participants will be asked the eligibility questions prior to obtaining informed consent and a checklist will be completed for each participant which will be attached to the consent form in the study folder.

8.5. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the CI/PI may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Withdrawal of consent
- Non-response to the questionnaires despite reminder emails and/or a telephone call with prior consent obtained to contact the patient
- Confirmation of pregnancy termination prior to completing 2nd or 3rd questionnaire

If a participant withdraws from the study, data already collected with consent will be retained and used in the study but no further data will be collected or any other research procedures carried out on or in relation to the participant. The reason for withdrawal (if provided) will be recorded in the case report form (CRF).

8.6. Definition of End of Study

The end of the study will be when the desired number of women are recruited in all groups or at the end of a 12 month recruitment period, whichever is sooner. It is anticipated that the recruitment, follow-up and analysis will take no longer than 24 months.

9. INTERVENTIONS

All recruited women will be asked to provide data at three stages:

1. **At initial diagnosis**

All women will be asked to complete the HADS questionnaire (HADS 1).

Women recruited to Group I will be provided with an individualised prediction of their pregnancy outcome (following informed written consent to be randomised) before completing the first HADS questionnaire.

2. **72 hours following diagnosis**

All women will be sent the HADS questionnaire (HADS 2).

3. At follow-up (14 days)

All women will be asked to complete the HADS questionnaire (HADS 3) prior to their follow-up scan.

All women in Group I will be asked to complete a patient experience questionnaire at the end of the study period.

10. STATISTICS AND ANALYSIS

10.1. The Number of Participants

To calculate the sample sizes, power calculations were performed on the HADS scale. Puhan et al (2008) report the minimal important difference in HADS scores is 1.5 units for a significance level of 0.05 and a statistical power of 80% when considering an intervention. Based upon this assumption and a common standard deviation of 4 points, 125 women are needed for each group (total 250 women). A drop-out rate of 10% is anticipated.

10.2. Description of Statistical Methods

A statistician will be consulted to assist in analysis of the data collected from the study.

The following statistical analyses will be performed:

- Descriptive statistics will be used to compare the two groups in terms of baseline demographic characteristics
- Continuous variables normally distributed will be described reporting mean and standard deviation, otherwise median and interquartile range will be used. Categorical variables will be reported with frequency tables.
- To compare HADS scores between groups I and II, the t-test will be performed for continuous variables normally distributed, otherwise the Mann-Whitney U test will be used. The Chi-squared test will be used for categorical variables.

A statistically significant difference will be considered as a p-value <0.05. The data will be checked for abnormalities, spurious and missing data. These will be coded separately and treated accordingly. Analyses will be carried out using Stata statistical software, Release 14 (StataCorp, College Station, TX).

Throughout the study (and afterwards), the research investigators will welcome inspections and monitoring of the conduct of the research to ensure that the quality of the research is upheld. This includes offering direct access to any documents.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations. The study may be monitored, or audited in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

11.2. Data Recording and Record Keeping

Data will be stored on secure computers at Chelsea and Westminster Hospital using password protected access to databases.

The data that is inserted into the prediction tool will be stored securely within a Microsoft excel database. Access will be granted using a single user log-in and password known only to the CI and PI. The database will be securely stored on a hospital computer within the unit in a locked area.

Hard copy data (ICFs and registration forms) will be stored within the unit site files which will be kept in secure areas.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice.

12.3. Approvals

All relevant documentation will be submitted to the NHS Research Ethics Committee (REC), and host institution R&D departments. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4. Reporting

An End of Study notification and final report will be submitted to the NHS REC and host R&D departments. The study is registered with clinicaltrials.gov and results will be submitted electronically.

12.5. Participant Confidentiality

The acquired data will be stored on a computer that is password protected. Data will be held in the NHS database of the host institution. Data will be kept for three years.

All paperwork will be stored in a locked clinical office within the Department of Early Pregnancy and Acute Gynaecology of the host institution.

A unique patient/volunteer identification number will be used to prevent identification of subjects involved in the study.

13. FINANCE AND INSURANCE

13.1. Funding

No external funding is required. The CI is employed as a clinical research fellow at Chelsea and Westminster Hospital.

13.2. Insurance

Chelsea and Westminster Hospital NHS Foundation Trust has appropriate indemnity arrangements in place.

14. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

15. REFERENCES

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16. APPENDIX

Appendix 1: Hospital Anxiety and Depression Score, Zigmond and Snaith 1983

Hospital Anxiety and Depression Score (HADS)

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an "X" on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time (occ.)	1
	Not at all	0
D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite as much	1
	Only a little	2
	Hardly at all	3
A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0
D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3
A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not often	1
	Only occasionally	0
D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0
A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	**I get a sort of frightened feeling like "butterflies" in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite often	2
	Very often	3
D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care	0
A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	**I can enjoy a good book or radio/TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

Appendix 2: Patient Experience Questionnaire, modified from Davis et al 1989

IMPROVE study

PATIENT EXPERIENCE OF USING THE PREDICTION TOOL

Thank you for taking the time to complete this short questionnaire regarding your experience of receiving the predicted outcome of your pregnancy, as part of the IMPROVE trial.

We feel it is important to measure your experience to determine if the tool is both acceptable and useful to you during this difficult time.

Satisfaction with medical care

1) I am satisfied with the medical care that I have received overall

1 2 3 4 5 6 7 (please circle)

strongly disagree strongly agree

Health Knowledge Scale

2) I have a good understanding of my current diagnosis

1 2 3 4 5 6 7 (please circle)

strongly disagree strongly agree

Information seeking preference

3) I am someone who will always want to find out more information about a diagnosis using resources such as the internet

1 2 3 4 5 6 7 (please circle)

strongly disagree strongly agree

4) I have used “Google” or other internet sites to search for “intrauterine pregnancy of uncertain viability” following my initial scan

1 2 3 4 5 6 7 (please circle)

strongly disagree strongly agree

Please state which internet sites were used…….
……
……

5) I found these sites to be useful

1 2 3 4 5 6 7 (please circle)

strongly disagree strongly agree

Perceived Usefulness

6) The prediction tool has helped me better manage my expectations for my pregnancy

1 2 3 4 5 6 7 (please circle)

strongly disagree strongly agree

7) I believe the prediction tool result is correct

1 2 3 4 5 6 7 (please circle)

strongly disagree strongly agree

8) If offered I would use the prediction tool again in any future pregnancies diagnosed as IPUV

1 2 3 4 5 6 7 (please circle)

strongly disagree strongly agree

17. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	November 2017	Kim Lawson	Minor wording changes made
2	3.0	January 2018	Kim Lawson	Major changes made to study design