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Keywords:	Patient Participation, Research Design, Reproductive medicine < GYNAECOLOGY, Methods, GYNAECOLOGY

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Abstract:

Introduction:

Interventional clinical trials in recurrent miscarriage use varying expected effect sizes to inform their sample size calculations. Often these are not informed by what stakeholders consider a meaningful treatment effect. Adaptive trial designs may integrate stakeholder views on trial success and futility but the criteria to inform this is lacking. This study aims to understand relevant stakeholder views of what is considered a worthwhile treatment effect for miscarriage prevention interventions and what is acceptable stopping criteria in miscarriage clinical trials.

Methods and analysis:

The study is designed as a cross-sectional online anonymous survey. The survey presents different scenarios to respondents relating to varying target differences and probability thresholds and explores success and futility criteria for clinical trials. The survey was developed with personal and public involvement (PPI) through focus groups and a PPI-partner. Eligible participants will be those with a personal history of miscarriage, including partners, and healthcare professionals who manage patients who experience a miscarriage. Convenience, snowball, and purposive sampling techniques will be employed to invite eligible participants to complete the survey. The survey will be accepting responses for an initial two-week pilot to check validity, prior to being open for a further 12 weeks. Descriptive analyses and linear regression analyses will synthesise the survey results.

Ethics and dissemination:

Ethical approval was obtained from the NHS Research Ethics Committee North West – Greater Manchester East (23/NW/0322) on 30/1/24. Informed consent will be obtained prior to survey completions. No personal identifying information will be collected. The results will be published in a relevant scientific journal and communicated through our institutional website.

Estimated start of study: April 2024.

Keywords: Abortion, Habitual; Patient Participation; Pregnancy Complications; Research Design; Sample Size

Strengths and limitations of this study:

- Study findings will impact future clinical trial design, ensuring representation of patient viewpoints and trials designed to identify patient and clinician meaningful treatment differences.
- This study utilises a novel survey instrument for investigating stakeholder views of miscarriage prevention treatment designed in liaison with a PPI partner and PPI input.
- A pilot phase of the survey will examine survey validity before national dissemination.
- The survey is only available in English, which may impact the diversity of viewpoints represented.
- Although some of the questions address how treatment burden may impact stakeholder's expectations of treatment difference, the range of different potential treatment burdens mean this cannot be fully explored.

Introduction:

Miscarriage prevention is an active area of research driven by pronounced clinical need. Miscarriage, defined as the loss of a pregnancy prior to viability, poses not only physical risks but also significant psychological consequences. Regrettably, miscarriage is common, with 10% of the population experiencing at least one miscarriage and 2% experiencing recurrent miscarriage (RM), defined as two or more losses(1).

The most common cause of any early pregnancy loss is a chromosomal abnormality of the developing pregnancy(2). With higher order recurring miscarriages, the underlying causes vary and include immunological, haematological and endometrial pathologies(3). Approximately 50% of recurrent miscarriages remain unexplained and the search for causes and treatment continues(4). Due to this diversity in underlying pathologies, no single treatment to prevent miscarriage can be 100% effective. As new treatment options are developed, robust clinical trials are needed to investigate effectiveness prior to routine introduction.

Interventional clinical trials should be adequately powered to be able detect a difference between treatments if one exists. These sample size calculations combine different statistical parameters including the target difference or effect size of the treatment(5). The target difference may reflect the minimum clinically important difference or be defined by parameters set by the researchers(6). The minimum clinically important difference represents the smallest change in treatment outcomes considered clinically meaningful. The target difference is commonly informed by previous evidence, pilot studies or expert opinion and it should be considered an important difference by at least one stakeholder group(7). In practice, the target difference may be chosen for convenience with unclear supporting rationale(7).

While larger trials are required to detect smaller differences, requiring more funding and resources, it is important that the choice of target difference has a clear rationale. The target differences used in previous miscarriage prevention interventional trials vary greatly; with heterogeneity even amongst large multicentre randomised controlled trials who have aimed to detect treatment differences between 5-20%(8-12).

It is estimated that RM patients have a 50-60% chance of live birth in a future pregnancy without any intervention(9, 11, 13). This figure may increase or decrease depending on previous reproductive

history, age and other factors(14). At present, it is unknown whether stakeholders' expectations of treatment would vary at differing probabilities of live birth without intervention.

Consensus on stakeholder views of a meaningful target difference is needed to inform clinical trial design and the interpretation of results. Adaptive trial designs, such as those using a Bayesian framework, may also use stakeholder views on meaningful difference to influence decisions about when to stop a trial early, if the trial meets the criteria for success or futility(15). This is important because interim analyses may find the treatment difference is very large, making it unethical to continue or that the treatment difference is not enough and that the research is futile. Currently there are no recommended criteria or relevant clinical literature to inform on the statistical thresholds for stopping or continuing recurrent miscarriage trials. Without directly involving the views of stakeholders, researchers cannot presume what should be considered a meaningful intervention.

This is a protocol for an online survey of stakeholders, including people who have experienced miscarriage, their partners and relevant health care professionals. The survey would aim to understand stakeholder views on a meaningful target difference and stopping criteria for miscarriage prevention trials. This research would inform future trial design, interpretation of findings and make novel contribution to adaptive trial methodology in this field.

Methods:

Design:

An online cross-sectional survey of stakeholders will be conducted, hosted via the Qualtrics platform. The survey will be anonymous with no personally identifiable information requested. This study is sponsored by the University of Warwick.

Participants:

Eligible participants include any person or their partners who have experienced miscarriage or healthcare professionals whose job role includes the care of miscarriage patients. The latter includes but is not limited to doctors working within Obstetrics & Gynaecology and nurse specialists in gynaecology, early pregnancy, and fertility. There will be no restrictions on gender, ethnicity, or social background. While the study does not aim to recruit participants under the age of 18, the survey will be available in the public domain and some respondents that fulfil the inclusion criteria

may be below this age. Participant information and the survey will not be available in languages other than English.

Consent:

All participants will be asked to confirm their consent at the start of the online survey (Supplementary material S1). The participants will only gain access to the survey questions if they indicate their consent. As the data collection process is anonymous, it will not be possible to withdraw data from the study. This will be clearly stated on the consent form.

Setting:

The online survey will be hosted by Qualtrics, a cloud-based survey platform. Qualtrics provides a secure and user-friendly interface, allowing ease of access and survey completion by participants. Qualtrics adheres to GDPR regulations and the collection of IP addresses and physical location access will be turned off to allow complete anonymity of respondents.

Recruitment:

Participant recruitment to the survey will be performed through four avenues.

(1) Tommy's net (IRAS ID 213470) is a data platform that holds data from patients who have attended Tommy's national recurrent miscarriage clinics, it holds retrospective and prospective data on patient demographics and pregnancy outcomes. It facilitates research into the causes and treatment options for miscarriage patients. On recruitment to Tommy's net, patients are asked to consent to being contacted about future relevant research studies. Patients who attended the recurrent miscarriage clinic at University Hospitals Coventry and Warwickshire (UHCW), enrolled into Tommy's net and consented to be contacted about relevant future research studies will be emailed an invitation to complete this survey. The email invitation will include a link to the participant information sheet. The email will request patients share the invitation with their partners. An estimated 1800 participants are currently registered with Tommy's net via the UHCW recurrent miscarriage clinic, with most expected to be eligible for recruitment. Although this represents a single centre, referrals to the clinic are received nationally, and the cohort is diverse, as previously described(16).

(2) Recruitment posters will be displayed locally at UHCW in relevant departments, including the recurrent miscarriage clinic, the early pregnancy unit, and the fertility unit. These will be present for the duration of the study.

(3) Miscarriage charities will be approached to request dissemination of the survey via their internal platforms, this may include publication on their website, inclusion in any routine newsletters and via social media channels. The Tommy's charity and The Lily Mae Foundation have already agreed to publicise the survey, with a reach of over eighty thousand social media followers.

(4) Healthcare professionals who work with miscarriage patients will be identified and contacted directly by email. National networks of relevant clinicians will be approached to request dissemination of the survey.

Data collection: Survey questions

The survey contains 20 questions and has been developed for online completion. The questions were developed by researchers with experience in clinical trials in recurrent miscarriage and were presented to a focus group of patients, partners and clinicians held in December 2019. The survey was also reviewed by a PPI partner.

The survey is composed of the following sections:

(Section 1) Respondent demographics with identification of respondents who are patients and partners and the number of previous miscarriages they have had or whether they are a healthcare professional and their clinical role.

(Section 2) Introductory scenarios about whether they consider different treatment differences to prevent miscarriage to be worthwhile.

(Section 3) Further scenarios examining the impact of whether additional testing prior to treatment impacts when a treatment difference is considered worthwhile.

(Section 4) Scenarios examining respondent views on clinical trial stopping criteria at differing treatment difference thresholds.

(Section 5) A free text answer on whether the respondent has any other thoughts on what affects whether a treatment to prevent miscarriage is worthwhile.

Visual representations of questions asking for numeric answers on treatment difference have been incorporated to improve question comprehension and survey engagement(17, 18).

The survey will be piloted for two weeks to check the face validity of the questions(19). The pilot will open locally to participants recruited from UHCW. 250 participants registered with Tommy's net will

be emailed inviting them to complete the survey. If the response rate to this invitation is less than 10% or the responses indicate issues with question comprehension, the study will be stopped, and the survey questions redesigned with appropriate ethical approval amendments.

Management and reporting of adverse reactions:

There are no risks or side effects to participants completing this survey. The survey avoids any probing questions about personal miscarriage history, but it is recognised that thinking about miscarriage may be distressing. Participants will be signposted to several charities that provide information on miscarriage and can provide additional support in the form of a miscarriage helpline and access to support groups and counselling.

Patient and public involvement:

There has been PPI involvement in the development of the survey questions and the patient facing material. The scenarios described in the survey were presented to a focus group. The survey questions and consent process were reviewed by Amy Jackson, co-founder, and operations manager of the Lily-Mae Foundation. The Lily-Mae Foundation is a charity supporting those affected by miscarriage, stillbirth and neonatal death.

Data analysis:

Sample size determination:

A minimum sample size of 250 respondents is proposed. This represents a modest response rate from the sampling frame of Tommy's net alone and the aim is to achieve many more responses than this. However, at minimum, this should provide sufficient diversity of viewpoints to guide conclusions. This is a novel approach in miscarriage research, so there is no literature available to guide a sample size calculation. The survey will close after being open for a two-week pilot and then 12-week window, regardless of number of respondents.

Data analysis plan:

The survey will collect quantitative data using numeric responses or multiple-choice questions and there will be one free text answer exploring any other views the respondents wish to share. Quantitative analysis will be conducted using descriptive statistics to summarise the demographic characteristics and survey responses. Subgroup analyses will be conducted for patients, partners and healthcare professionals. Linear regression analysis is planned to assess the relationship between

number of previous miscarriages and responses. Qualitative analysis of the free text question will be conducted using thematic analysis through managing software NVivo.

Ethical, legal and regulatory aspects:

The study will be conducted in full conformance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. It will comply with all applicable UK legislation and standard operating procedures from the trial sponsor. Ethical approval for this study has been granted through the NHS Research Ethics Committee (REC) North West - Greater Manchester East (REC reference: (23/NW/0322), REC approval date: 30th January 2024.

Data storage and patient confidentiality:

All study information will be held securely in accordance with the Data Protection Act 2018. The data will not collect any personal identifying information. There is one free text response question, and we recognise the possibility of respondents entering identifiable information here. Only the immediate study team will have access to the raw data and will ensure any potentially identifiable information included in the free text section is removed or changed. On completion of the survey, data will be extracted from the Qualtrics platform to a PGP-encrypted folder on secure institutional servers. It will be held for ten years prior to deletion. All data will be deleted permanently deleted from the Qualtrics platform.

Dissemination and impact:

The findings of this research will be disseminated to academics and clinicians working within this field. The study report will be shared on our institutional website as well as by any miscarriage charities that helped disseminate the invitation to the study. The findings will be submitted for publication in a high quality, peer reviewed journal. Abstracts will be prepared for national and international conferences to further disseminate the work.

It is hoped that the findings will inform the design and conduct of future miscarriage trials. It is anticipated that the findings will expand the knowledge base of patient and healthcare professionals' expectations of miscarriage prevention treatment.

Acknowledgements: *We acknowledge Dr Sophie Rees, a qualitative researcher, who was involved in the early development of this project. We also acknowledge Amy Jackson, co-founder and operations manager of The Lily-Mae Foundation, who reviewed the survey questions and consent.*

Author contributions: *JO and SQ conceived the study, it was further developed by NB. NB wrote the first draft of this publication. All authors edited, read, and approved the final version of the manuscript.*

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Competing interest statement*: The study authors have no competing interests to declare.*

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Supplementary material: S1 – Consent for IMPRESS Survey

Study Title: Improving **M**iscarriage **P**revention **R**esearch – a survey exploring the **E**xpectations of **S**ervice users and **S**takeholders (**IMPRESS**)

Study investigators: Dr Joshua Odendaal, Dr Naomi Black and colleagues at the University of Warwick

Thank you for your interest in completing this short survey. This survey contains 20 questions and will take 15 minutes to complete.

This survey aims to find out what people think about the potential effectiveness of treatments for miscarriage prevention. This survey is intended for women with a history of miscarriage, their partners and healthcare professionals that are involved in treating miscarriage.

Your participation is voluntary. You can withdraw at any time whilst completing the questionnaire, and for any reason, simply by closing your browser. All responses will be anonymous, and we do not ask for any personal identifiable information. This means that once your responses have been submitted it will not be possible to withdraw your data as your individual responses cannot be identified.

This survey does not ask probing questions about previous miscarriage experiences; however, we recognise that reflecting on the subject of miscarriage may cause some participants to feel upset. Please remember that you are free to withdraw during completion of the survey. You may find it useful to find out more information about miscarriage and the support available for you at this time. Useful information sources include Tommy's, The Miscarriage Assocation and The Lily Mae foundation. You can find out more by clicking on the icons below.

MISCARRIAGE ASSOCIATION
The knowledge to help

Tommy's
Together, for every baby

The Lily Mae Foundation

Throughout the survey, we use the word 'woman' for ease of reading, but we recognise that it is possible for someone who does not identify as a woman to experience miscarriage.

This study has been granted ethical approval by NHS Health Research Authority (HRA), IRAS reference: 314809

No funding was received for completion of this project. This work will contribute to a doctoral thesis.

Data will be securely stored on the University of Warwick servers in password protected files. Access to the data will be restricted to the study investigators alone. Summaries may be presented at conferences and included in scientific publications. Data will be reviewed on completion of the research, in line with the University of Warwick data retention policy. More information about the University of Warwick Research data and privacy notice are available here: https://warwick.ac.uk/services/idc/dataprotection/privacynotes/researchprivacynotice.

If you require any further information, please contact the study team: impress@warwick.ac.uk

If you wish to make a complaint about this study, please address your complaint the Research & Impact Services at researchgovernance@warwick.ac.uk, if the complaint related to how we have handled your personal data please address your compliant to the Data Protection Officer at DPO@warwick.ac.uk.

Further details about the study and the complaint process can be accessed here: (Link to full PIS)

Consent

1. I confirm that I have read and understand the information for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time whilst completing the questionnaire without giving any reason.
3. I understand that any data I enter cannot be removed from the study once submitted.
4. I understand that data collected during the study, may be looked at by individuals from the University of Warwick where it is relevant to my taking part in this study. I give permission for these individuals to have access to my data.
5. I consent for this data to be used for research purposes to investigate views on the effectiveness of miscarriage treatment in clinical research trials.
6. I confirm that it is my first time completing the survey.

I have read the above and: I consent to take part in this study I do not wish to participate

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All participants will be asked to confirm their consent at the start of the online survey (Supplementary material S1). The participants will only gain access to the survey questions if they indicate their consent. As the data collection process is anonymous, it will not be possible to withdraw data from the study. This will be clearly stated on the consent form.

Setting:

The online survey will be hosted by Qualtrics, a cloud-based survey platform. Qualtrics provides a secure and user-friendly interface, allowing ease of access and survey completion by participants. Qualtrics adheres to GDPR regulations and the collection of IP addresses and physical location access will be turned off to allow complete anonymity of respondents.

Recruitment:

Participant recruitment to the survey will be performed through four avenues.

(1) Tommy's net (IRAS ID 213470) is a data platform that holds data from patients who have attended Tommy's national recurrent miscarriage clinics, it holds retrospective and prospective data on patient demographics and pregnancy outcomes. It facilitates research into the causes and treatment options for miscarriage patients. On recruitment to Tommy's net, patients are asked to consent to being contacted about future relevant research studies. Patients who attended the recurrent miscarriage clinic at University Hospitals Coventry and Warwickshire (UHCW), enrolled into Tommy's net and consented to be contacted about relevant future research studies will be emailed an invitation to complete this survey. The email invitation will include a link to the participant information sheet. The email will request patients share the invitation with their partners. An estimated 1800 participants are currently registered with Tommy's net via the UHCW recurrent miscarriage clinic, with most expected to be eligible for recruitment. Although this represents a single centre, referrals to the clinic are received nationally, and the cohort is diverse, as previously described(16).

(2) Recruitment posters will be displayed locally at UHCW in relevant departments, including the recurrent miscarriage clinic, the early pregnancy unit, and the fertility unit. These will be present for the duration of the study.

(3) Miscarriage charities will be approached to request dissemination of the survey via their internal platforms, this may include publication on their website, inclusion in any routine newsletters and via social media channels. The Tommy's charity and The Lily Mae Foundation have already agreed to publicise the survey, with a reach of over eighty thousand social media followers.

(4) Healthcare professionals who work with miscarriage patients will be identified and contacted directly by email. National networks of relevant clinicians will be approached to request dissemination of the survey.

Data collection: Survey questions

The survey contains 20 questions and has been developed for online completion. The questions were developed by researchers with experience in clinical trials in recurrent miscarriage and were presented to a focus group of patients, partners and clinicians held in December 2019. The survey was also reviewed by a PPI partner, Amy Jackson from The Lily Mae Foundation. The full survey is available is provided in the Supplementary material (S1).

The survey is composed of the following sections:

(Section 1) Respondent demographics with identification of respondents who are patients and partners and the number of previous miscarriages they have had or whether they are a healthcare professional and their clinical role.

(Section 2) Introductory scenarios about whether they consider different treatment differences to prevent miscarriage to be worthwhile.

(Section 3) Further scenarios examining the impact of whether additional testing prior to treatment impacts when a treatment difference is considered worthwhile.

(Section 4) Scenarios examining respondent views on clinical trial stopping criteria at differing treatment difference thresholds.

(Section 5) A free text answer on whether the respondent has any other thoughts on what affects whether a treatment to prevent miscarriage is worthwhile.

Visual representations of questions asking for numeric answers on treatment difference have been incorporated to improve question comprehension and survey engagement(17, 18).

The survey will be piloted for two weeks to check the face validity of the questions(19). The pilot will open locally to participants recruited from UHCW. 250 participants registered with Tommy's net will be emailed inviting them to complete the survey. If the response rate to this invitation is less than 10% or the responses indicate issues with question comprehension, the study will be stopped, and the survey questions redesigned with appropriate ethical approval amendments.

Outcomes:

This study aims to understand stakeholder views on a meaningful target difference and stopping criteria for miscarriage prevention trials. The primary outcome will be meaningful target difference if there is a 50% chance of having a successful pregnancy without the new treatment. Secondary outcomes will look at whether varying the likelihood of successful pregnancy without treatment affects what the respondent considers a meaningful target difference, the effect of investigation invasiveness on consideration of meaningful target difference and thresholds for stopping criteria in clinical trials.

Study timelines:

The survey is planned to commence on 29nd April 2024. It will be open for a two-week local pilot, followed by national dissemination for 12 weeks. The anticipated close date of the survey is 5th August 2024. It is expected that data analysis and the manuscript will be complete by 1st December 2024.

Management and reporting of adverse reactions:

There are no risks or side effects to participants completing this survey. The survey avoids any probing questions about personal miscarriage history, but it is recognised that thinking about miscarriage may be distressing. Participants will be signposted to several charities that provide information on miscarriage and can provide additional support in the form of a miscarriage helpline and access to support groups and counselling.

Patient and public involvement:

There has been PPI involvement in the development of the survey questions and the patient facing material. The scenarios described in the survey were presented to an established focus group within our miscarriage research unit called 'Public Involvement in Pregnancy Research (PIPR). The focus group had fourteen participants: eight patients, one partner, three midwives and two doctors. The survey questions and consent process were reviewed by Amy Jackson, our PPI partner. Amy Jackson

is the co-founder, and operations manager of the Lily-Mae Foundation. The Lily-Mae Foundation is a charity supporting those affected by miscarriage, stillbirth and neonatal death.

Data analysis:

Sample size determination:

A minimum sample size of 250 respondents is proposed. This represents a modest response rate from the sampling frame of Tommy's net alone and the aim is to achieve many more responses than this. However, at minimum, this should provide sufficient diversity of viewpoints to guide conclusions. This is a novel approach in miscarriage research, so there is no literature available to guide a sample size calculation. The survey will close after being open for a two-week pilot and then 12-week window, regardless of number of respondents.

Data analysis plan:

The survey will collect quantitative data using numeric responses or multiple-choice questions and there will be one free text answer exploring any other views the respondents wish to share. Quantitative analysis will be conducted using descriptive statistics to summarise the demographic characteristics and survey responses. Means and standard deviations will be calculated for continuous variables, while frequencies and percentages will be produced for categorical variables. Subgroup analyses will be conducted for patients, partners and healthcare professionals using the Kruskal-Wallis statistic to investigate for significant differences in the primary and secondary outcomes results between groups. Linear regression analysis is planned to assess the relationship between demographics including whether a patient, partner or HCP, number of previous miscarriages, HCP role and the primary and secondary outcomes. Where there is greater than 10% missing data for a question, we will perform multiple imputation using the fully conditional specification approach. Qualitative analysis of the free text question will be conducted using thematic analysis through managing software NVivo.

Data storage and patient confidentiality:

All study information will be held securely in accordance with the Data Protection Act 2018. The data will not collect any personal identifying information. There is one free text response question, and we recognise the possibility of respondents entering identifiable information here. Only the immediate study team will have access to the raw data and will ensure any potentially identifiable information included in the free text section is removed or changed. On completion of

the survey, data will be extracted from the Qualtrics platform to a PGP-encrypted folder on secure institutional servers. It will be held for ten years prior to deletion. All data will be deleted permanently deleted from the Qualtrics platform.

Ethics and dissemination:

The study will be conducted in full conformance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. It will comply with all applicable UK legislation and standard operating procedures from the trial sponsor. Ethical approval for this study has been granted through the NHS Research Ethics Committee (REC) North West - Greater Manchester East (REC reference: (23/NW/0322), REC approval date: 30th January 2024 and HRA approval date: 5th March 2024.

The findings of this research will be disseminated to academics and clinicians working within this field. The study report will be shared on our institutional website as well as by any miscarriage charities that helped disseminate the invitation to the study. The findings will be submitted for publication in a high quality, peer reviewed journal. Abstracts will be prepared for national and international conferences to further disseminate the work.

It is hoped that the findings will inform the design and conduct of future miscarriage trials. It is anticipated that the findings will expand the knowledge base of patient and healthcare professionals' expectations of miscarriage prevention treatment.

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Author contributions: *JO and SQ conceived the study, it was further developed by NB. NB wrote the first draft of this publication. All authors edited, read, and approved the final version of the manuscript. Joshua Odendaal is the guarantor for this work.*

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Competing interest statement*: The study authors have no competing interests to declare.*

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S1 – Supplementary material

Improving **M**iscarriage **P**revention **R**esearch – a survey exploring the **E**xpectations of **S**ervice users and **S**takeholders (**IMPRESS**) – Consent and survey questions

Version: **V3.0**
Date: **23 Nov 2023**

LIST of CONTENTS:

Participant information sheet/opening page of survey

Study Title: Improving **M**iscarriage **P**revention **R**esearch – a survey exploring the **E**xpectations of **S**ervice users and **S**takeholders (**IMPRESS**)

Study investigators: Dr Joshua Odendaal, Dr Naomi Black and colleagues at the University of Warwick

Thank you for your interest in completing this short survey. This survey contains 20 questions and will take 15 minutes to complete.

This survey aims to find out what people think about the potential effectiveness of treatments for miscarriage prevention. This survey is intended for women with a history of miscarriage, their partners and healthcare professionals that are involved in treating miscarriage.

Your participation is voluntary. You can withdraw at any time whilst completing the questionnaire, and for any reason, simply by closing your browser. All responses will be anonymous, and we do not ask for any personal identifiable information. This means that once your responses have been submitted it will not be possible to withdraw your data as your individual responses cannot be identified.

This survey does not ask probing questions about previous miscarriage experiences; however, we recognise that reflecting on the subject of miscarriage may cause some participants to feel upset. Please remember that you are free to withdraw during completion of the survey. You may find it useful to find out more information about miscarriage and the support available for you at this time. Useful information sources include Tommy's, The Miscarriage Association and The Lily Mae foundation. You can find out more by clicking on the icons below.

[Insert logos of above charities with hyperlink]

Throughout the survey, we use the word 'woman' for ease of reading, but we recognise that it is possible for someone who does not identify as a woman to experience miscarriage.

This study has been granted ethical approval by NHS Health Research Authority (HRA), IRAS reference: 314809

No funding was received for completion of this project. This work will contribute to a doctoral thesis.

Data will be securely stored on the University of Warwick servers in password protected files. Access to the data will be restricted to the study investigators alone. Summaries may be presented at conferences and included in scientific publications. Data will be reviewed on completion of the research, in line with the University of Warwick data retention policy. More information about the University of Warwick Research data and privacy notice are available here: https://warwick.ac.uk/services/idc/dataprotection/privacynotes/researchprivacynotice.

If you require any further information, please contact the study team: impress@warwick.ac.uk

If you wish to make a complaint about this study, please address your complaint the Research & Impact Services at researchgovernance@warwick.ac.uk, if the complaint related to how we have handled your personal data please address your compliant to the Data Protection Officer at DPO@warwick.ac.uk.

Further details about the study and the complaint process can be accessed here: (Link to full PIS)

Consent

1. I confirm that I have read and understand the information for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time whilst completing the questionnaire without giving any reason.
3. I understand that any data I enter cannot be removed from the study once submitted.
4. I understand that data collected during the study, may be looked at by individuals from the University of Warwick where it is relevant to my taking part in this study. I give permission for these individuals to have access to my data.
5. I consent for this data to be used for research purposes to investigate views on the effectiveness of miscarriage treatment in clinical research trials.
6. I confirm that it is my first time completing the survey.

I have read the above and:
I consent to take part in this study
I do not wish to participate

SURVEY QUESTIONS

SECTION ONE (DEMOGRAPHICS)

Question 1

Are you a:

Woman with a history of miscarriage (Next question: 2a)

Partner of someone with a history of miscarriage (Next question: 2a)

Health care professional treating patients with a history of miscarriage (Next question: 2b)

Question 2a

(If answer to Question 1: Woman with a history of miscarriage or partner of someone with a history of miscarriage)

How many miscarriages have you or your partner suffered?

1
2
3
4
5
6 or more
Prefer not to say

Question 2b

(If answer to Question 1: Health care professional who treats patients who have a history of miscarriage)

As a health care professional treating patients with a history of miscarriage, what is your job role?

Consultant in Obstetrics & Gynaecology

Doctor working in Obstetrics & Gynaecology (Non consultant grade e.g., specialty trainee, trust grade)

Nurse specialist

Nurse

Midwife

Other (Please specify)

SECTION TWO (INTRODUCTION TO SCENARIOS)

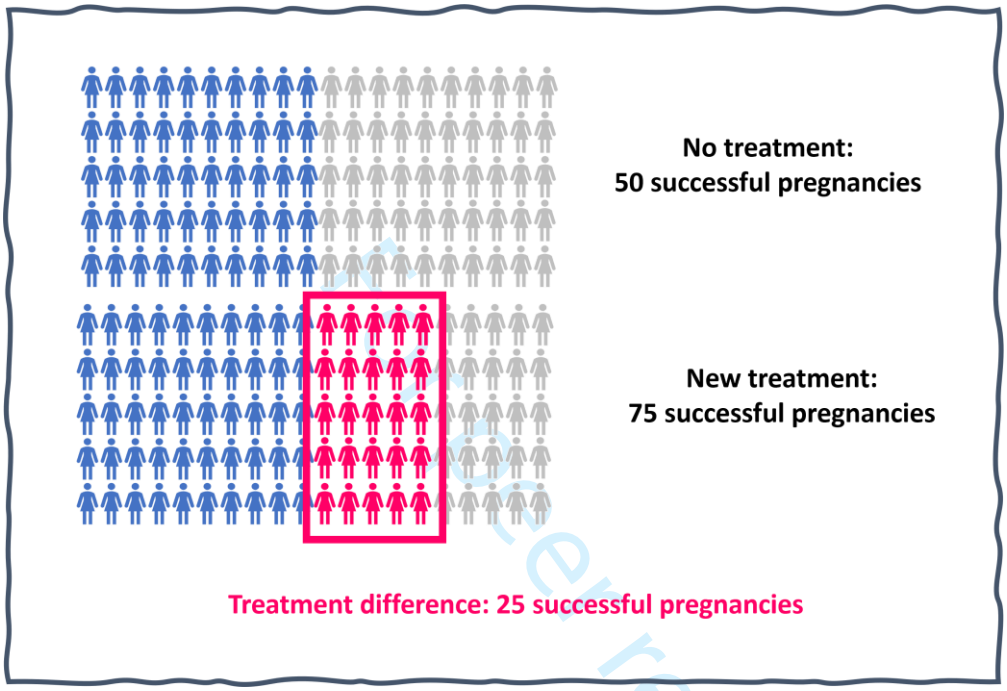
We want to understand what you think would be a worthwhile treatment to prevent miscarriage.

Imagine a new treatment has been developed that prevents miscarriage. Ideally, all treatments are completely effective but this is rarely the case.

Question 3

Imagine 100 women with a history of miscarriage are trying to have a baby. Without treatment 50 women will have a successful pregnancy and with a new treatment 75 women will have a successful pregnancy. This is a difference of 25 successful pregnancies.

Do you think the new treatment is worthwhile?

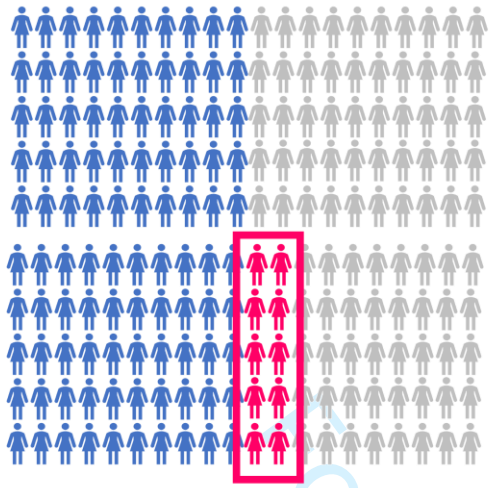


- □ Yes
- □ No
- □ Unsure

Question 4

Now imagine that without treatment 50 women will have a successful pregnancy and with a new treatment 60 women will have a successful pregnancy. This is a difference of 10 successful pregnancies.

Do you think the new treatment is worthwhile?



No treatment:
50 successful pregnancies

New treatment:
60 successful pregnancies

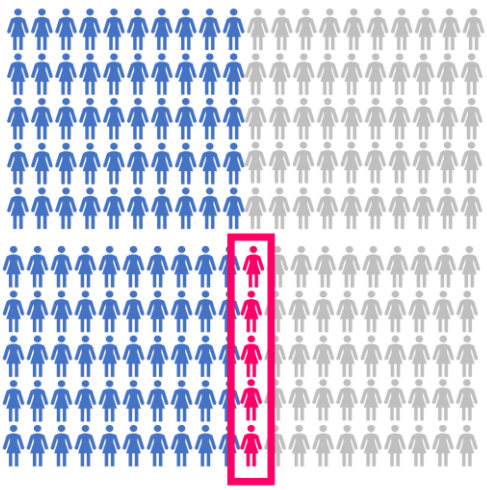
Treatment difference: 10 successful pregnancies

- □ Yes
- □ No
- □ Unsure

Question 5

Now imagine that without treatment 50 women will have a successful pregnancy and with a new treatment 55 women will have a successful pregnancy. This is a difference of 5 successful pregnancies.

Do you think the new treatment is worthwhile?



No treatment:
50 successful pregnancies

New treatment:
55 successful pregnancies

Treatment difference: 5 successful pregnancies

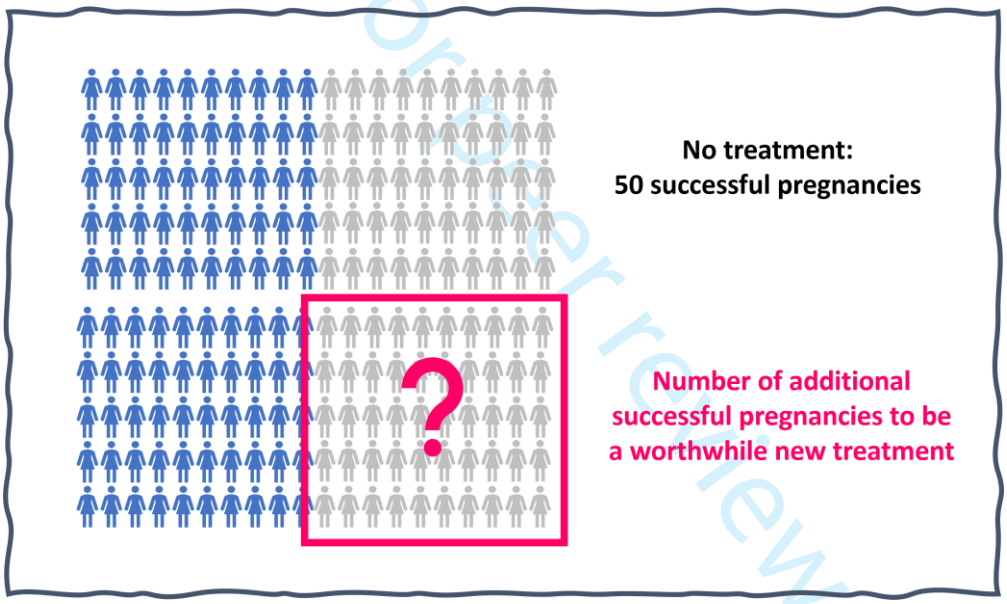
- □ Yes
- □ No
- □ Unsure

Question 6

After a miscarriage, the chance of a successful next pregnancy varies. We want to understand how this affects your threshold for considering a new treatment worthwhile.

100 women with a history of miscarriage are trying to have a baby, 50 women will have a successful pregnancy without treatment. What is the smallest number of additional successful pregnancies needed to make the treatment worthwhile?

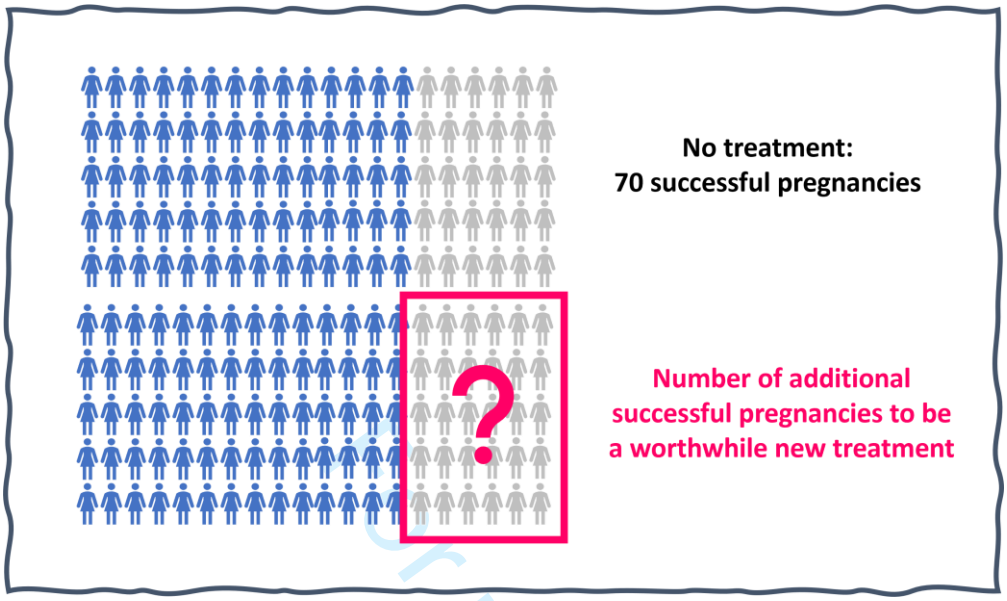
Please give a number between 0-50.



Question 7

What about if 70 of these women will have a successful pregnancy without treatment, what is the smallest number of additional successful pregnancies needed to make a new treatment worthwhile?

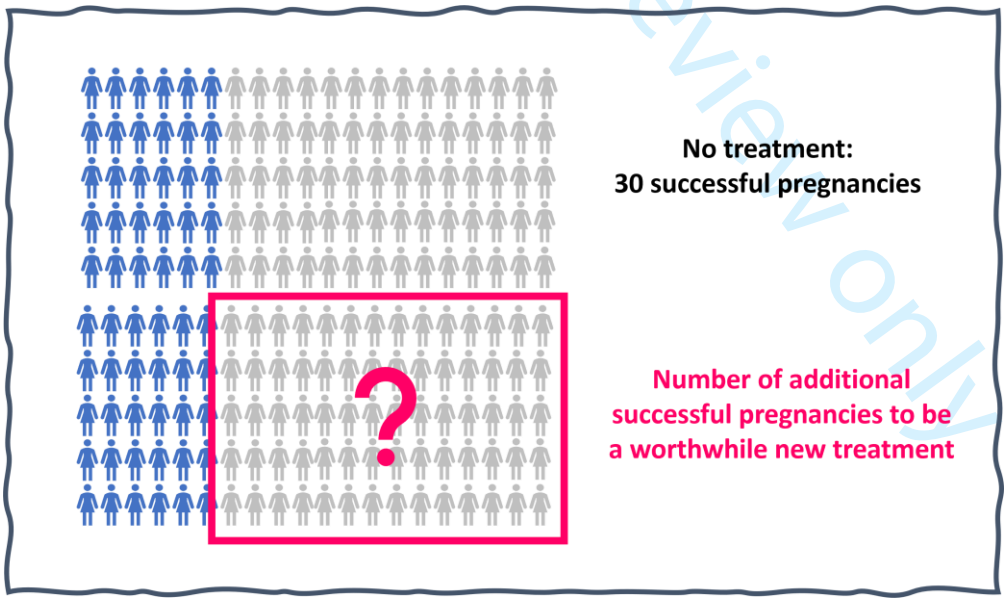
Please give a number between 0-30.



Question 8

What about if 30 of these women will have a successful pregnancy without treatment, what is the smallest number of additional successful pregnancies needed to make the new treatment worthwhile?

Please give a number between 0-70.



SECTION THREE

Additional tests may be needed before a woman undergoes a new treatment. We want to know if this affects your threshold for considering a treatment worthwhile.

Question 9

If the woman needs a blood test before treatment, does this change your threshold for what you would consider a worthwhile treatment?

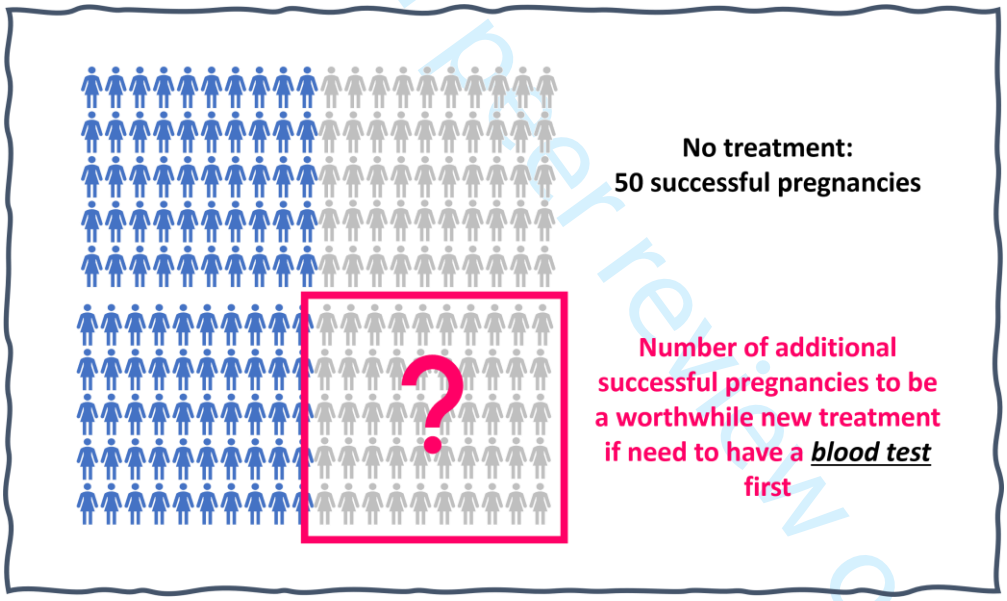
A blood test normally lasts a couple of minutes.

- □ Yes
- □ No
- □ Unsure

Question 10

Assume that out of 100 women trying for a baby with a history of miscarriage, 50 women will have a successful pregnancy without treatment. If the women need a blood test before having the treatment, what is the smallest number of additional successful pregnancies needed to make the new treatment worthwhile?

Please give a number between 0-50.



Question 11

If the woman needs to first undergo a procedure to take a sample from the womb lining (biopsy) before having the treatment, does this change your threshold for considering a treatment worthwhile?

A biopsy of the womb lining normally lasts a couple of minutes and many women find it painful.

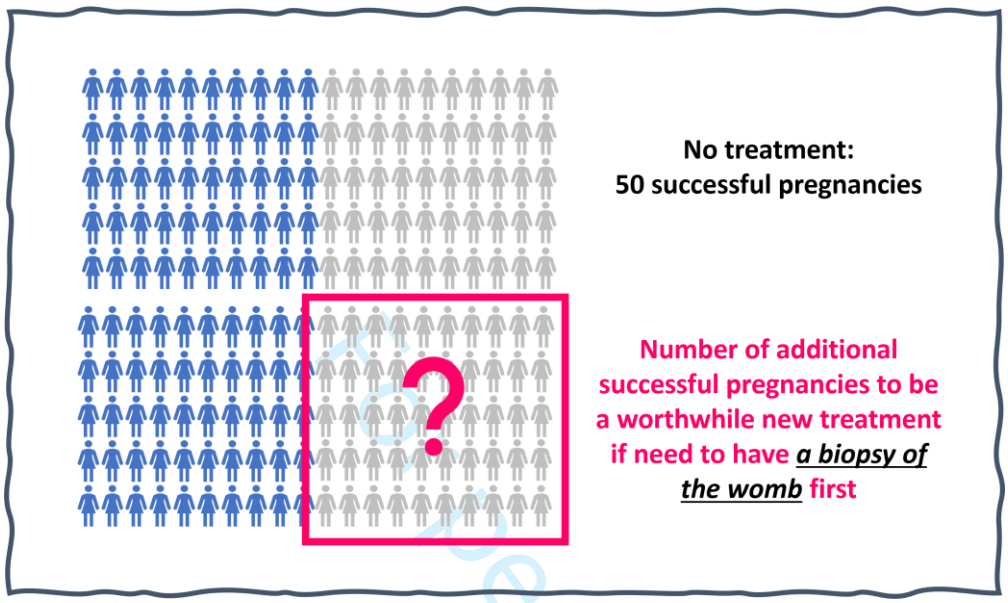
- □ Yes
- □ No
- □ Unsure

Question 12

Assume that out of 100 women trying for a baby with a history of miscarriage, 50 women will have a successful pregnancy without treatment. If the women need a **biopsy of the womb lining before having the treatment**, what is the smallest number of additional successful pregnancies needed to make the new treatment

worthwhile?

Please give a number between 0-50.



Question 13a

Does the number you have given change if there is a risk from the treatment?

- □ Yes
- □ No
- □ Unsure

Question 13b
(If answer to Question 13a: Yes)

Would the number go up or down if there was a risk from the treatment?

- □ It goes up
- □ It goes down
- □ Unsure

Question 14

Would you be willing to see fewer successful pregnancies if there was a lower chance of side effects?

- □ Yes
- □ No
- □ Unsure

SECTION FOUR

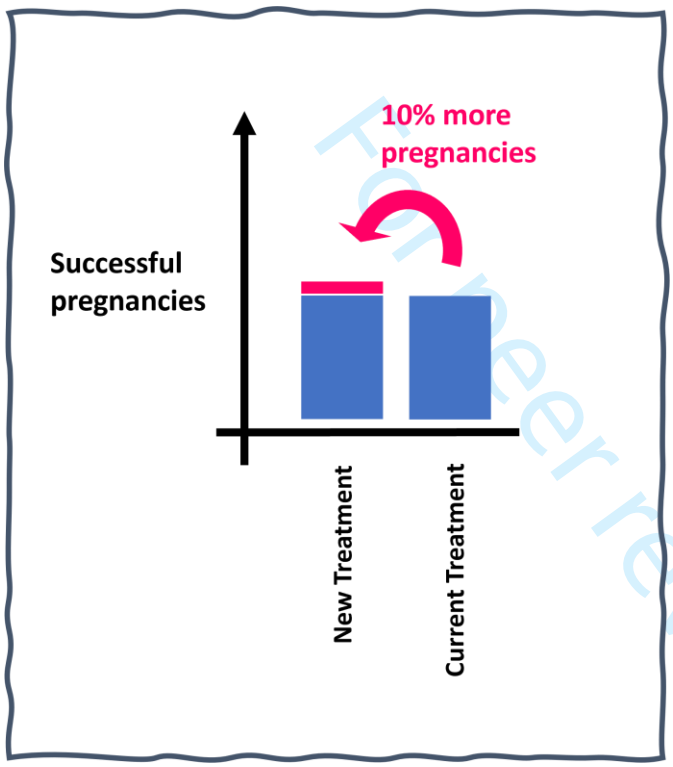
In research trials, scientists test new treatments to see if they are better than the current ones. Sometimes, these trials are stopped early because the new treatment is very clearly better than the old one, is ineffective or harmful.

Question 15a

A trial to test a new treatment to prevent miscarriage needs to recruit 3,000 women to be sure that a new treatment is better than current treatment.

The initial results, after 450 women, show there are 10% more pregnancies in the new treatment group than in the current treatment group.

Do you think it is worthwhile continuing the trial?



- ☐ Yes
- ☐ No
- ☐ Unsure

Question 15b
(If answer to question 15a: No)

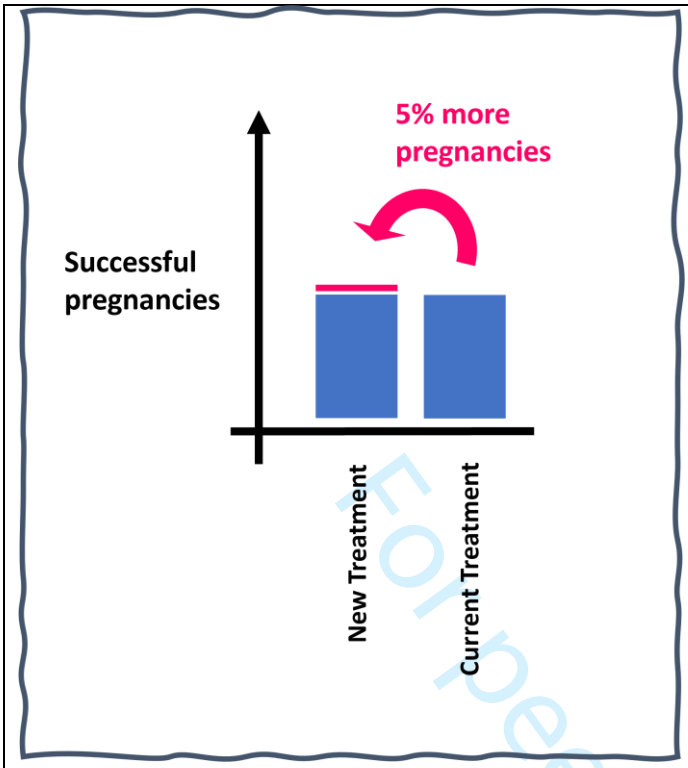
Do you think the trial should stop because:

- ☐ The new treatment is clearly better than the current one
- ☐ The new treatment is ineffective compared to the current one
- ☐ Other (Please specify)

Question 16a

What if there were 5% more pregnancies in the new treatment group.

Do you think it is worthwhile continuing the trial?



- □ Yes
- □ No
- □ Unsure

Question 16b
(If answer to question 16a: No)

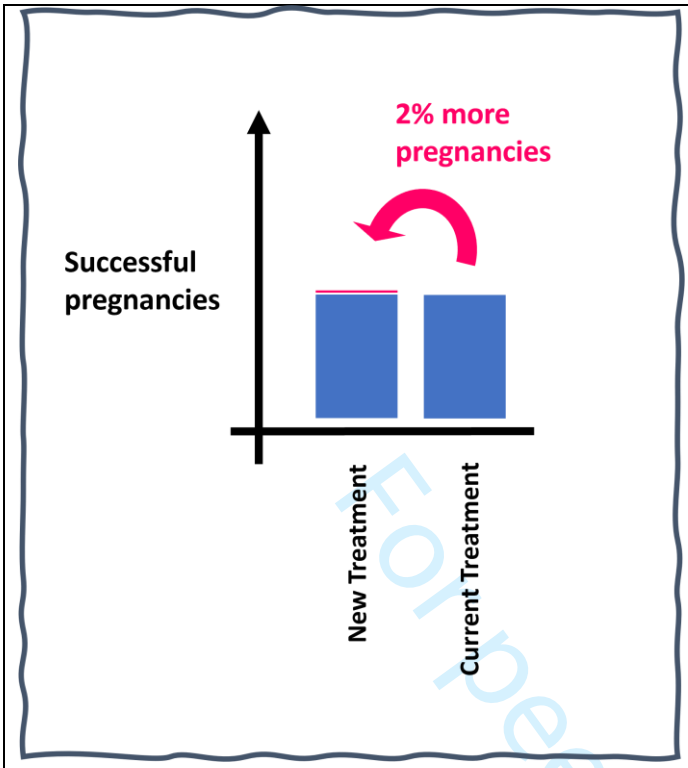
Do you think the trial should stop because:

- □ The new treatment is clearly better than the current one
- □ The new treatment is ineffective compared to the current one
- □ Other (Please specify)

Question 17a

What if there were 2% more pregnancies in the new treatment group.

Do you think it is worthwhile continuing the trial?



- □ Yes
- □ No
- □ Unsure

Question 17b
(If answer to question 17a: No)

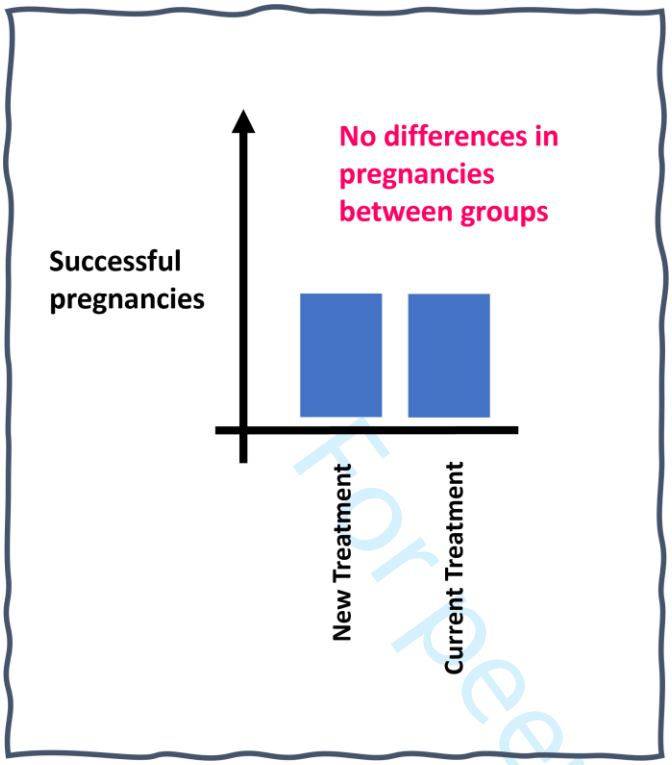
Do you think the trial should stop because:

- □ The new treatment is clearly better than the current one
- □ The new treatment is ineffective compared to the current one
- □ Other (Please specify)

Question 18a

What if there was no difference in the number of pregnancies in the new treatment and current treatment group.

Do you think it is worthwhile continuing the trial?



- ☐ Yes
- ☐ No
- ☐ Unsure

Question 18b
(If answer to question 18a: No)

Do you think the trial should stop because:

- ☐ The new treatment is clearly better than the current one
- ☐ The new treatment is ineffective compared to the current one
- ☐ Other (Please specify)

Question 19

If deciding whether to continue or stop a trial based on the initial results , which is more important to you?

- ☐ Being sure that there is any difference between groups
- ☐ Seeing a large difference between groups
- ☐ Unsure

Question 20

Do you have any other thoughts on what affects whether a treatment to prevent miscarriage is worthwhile?

(Free text answer)

CLOSING PAGE

Thank you for taking the time to complete this survey.

If you have any questions for the research team, please email **IMPRESS@warwick.ac.uk**

When this study has finished, the results will be available on the Warwick University Website.

If you would like some more information about miscarriage or to learn about support available to you please click on the support charity logos below.

MISCARRIAGE ASSOCIATION
The knowledge to help

The Lily Mae Foundation