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Quantitative assessment of pregnancy outcome following recurrent miscarriage clinic care: a prospective cohort study

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Abstract

Objectives

To measure pregnancy outcome following attendance at a recurrent miscarriage service and identify factors that influence outcome.

Design

Prospective, observational electronic cohort study.

Setting

Participants attending specialist recurrent miscarriage clinic, within a tertiary centre, with a history of two or more pregnancy losses. The clinic serves a diverse population (33% of residents belong in a minority ethnic group and over 33% in low-income households). Participant data were recorded on a bespoke study database, 'Tommy's Net'.

Participants

777 women consented to participate. 639 (82%) women continued within the cohort, and 138 were lost to follow up. Mean age of active participants was 34 years for women and 37 years for partners, with a mean of 3.5 (1-19) previous pregnancy losses. Rates of obesity, BMI>30 (maternal: 23.8%, paternal: 22.4%), smoking (maternal:7.4%, paternal: 19.4%) and alcohol consumption (maternal: 50%, paternal: 79.2%) were high and 55% of participants were not taking folic acid.

Outcome measures

Biannual collection of pregnancy outcomes (ongoing pregnancy, live birth, still birth, pregnancy loss prior to 24 weeks), either through prompted self-reporting, or existing hospital systems.

Results

639 (82%) women were followed up. 404 reported conception and 106 reported no pregnancy, at least 6 months following registration. Of those that conceived, 72.8% (294/404) had a viable pregnancy. Analysis identified a conception of rate of over 80% and viable pregnancy rate of 60% two years after attending the recurrent miscarriage clinic. 30% of couples had potentially modifiable risk factors for miscarriage.

Conclusions

Tommy's Net provides a secure electronic repository on data for couples with recurrent pregnancy loss and associated outcomes. The study identified that subfertility, as well as repeated miscarriage, contributed to failure to achieve live birth. Study findings can enable comparison of clinic management strategies and inform the development of a personalized holistic care package.

Strengths and Limitations of this study (related to the method)

- The 'Tommy's Net' e-repository and associated database contains baseline and prospective pregnancy outcome data from the largest known population of couples with recurrent miscarriage in the UK.
- Time to conception and viable pregnancy can be calculated from this data using time to event analysis.
- Obtaining follow up data is challenging but can be improved by using a variety of data collection methods.
- Follow up data is only requested biannually, therefore this is an inevitable lag in data collection.
- Limited use of the English language can be a barrier for participants completing the initial lengthy questionnaire.

Key points

- 20% of this recurrent miscarriage population do not conceive and two years after first consultation 40% have not had a viable pregnancy. Early identification of this group could help facilitate early referral to fertility services or targeted research.
- Miscarriage is physically and psychologically challenging. Some couples may decide not to try to conceive again because of this. Ensuring appropriate psychological support is essential.
- Preconception care is inadequate. Over one third of couples attend their initial consultation with modifiable risk factors known to impact on miscarriage. Tackling these should be a priority.
- Having a BMI over 30 and being a smoker is more common within this cohort in women that do not conceive. Targeting of these risk factors may improve conception rate.

Introduction

Miscarriage, the loss of a pregnancy prior to viability (24 weeks gestation) is common, with 15% of pregnancies ending in miscarriage[1]. Most miscarriages are sporadic and occur before 12 weeks of gestation[2]. Recurrent miscarriage (RM) is defined as two or three (or more) consecutive miscarriages[3,4]. It is estimated that 3% of women experience two consecutive miscarriages, and approximately 1% suffer three or more consecutive miscarriages[5,6]. In recurrent miscarriage, the incidence of euploidic foetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases[7]. Recurrent miscarriage is a debilitating disorder, associated with considerable psychological morbidity[8].

European and national miscarriage care guidelines recognise the importance of providing good physical care and psychological support[3,4] however there are no standardised outcomes to assess care within clinics. A systematic review by MMJ van den Berg and colleagues (2018)[9], evaluating features of care that couples valued within miscarriage services, found that information giving, including explaining potential causes of pregnancy loss and planning for future pregnancies were identified as areas for improvement.

Accurate information following attendance at a recurrent miscarriage clinic is important for couples' counselling, stratifying care and directing research. Whilst data does exist around outcomes in a recurrent miscarriage setting[2,10,11] it requires prospective update from clinics working under ESHRE guidance[3], including all couples regardless of their outcome and not only those who conceived or who participate within a research trial.

The Tommy's National Centre for Miscarriage Research brings together an interdisciplinary Translational Medicine research grouping jointly at the University of Warwick, University of Birmingham and Imperial College London. The Centre is dedicated to research across all aspects of miscarriage and early pregnancy complications including medical, basic scientific, social and ethical issues. A secure electronic data collection tool and e-repository (with associated database), Tommy's Net, has been developed to facilitate recording of participant data, including follow up[12].

Objectives

Our objective was to quantify the long term cumulative live birth rate after first attendance at a recurrent miscarriage clinic. A cohort of couples was developed, with prospective data collection of the medical and obstetric histories of both partners, investigation results and pregnancy and neonatal outcomes. The tool for collecting data on this cohort is designed to be used in multiple clinics so that success rates between clinics can be benchmarked. This should also allow clinics to support and assess new care pathways, identify areas needing further research, develop outcome prediction modelling and investigate new tests in future clinical trials.

Methods

The e-repository and associated database has been developed over several years by a team with representation from University Hospital Coventry and Warwickshire (UHCW) NHS Trust and University of Warwick, Imperial College and University of Birmingham. The cohort was initiated at UHCW, but designed so other clinics can join.

Sponsorship, Ethics, Data management and Information Governance

Sponsorship (from primary hospital Trust), ethical permissions (IRAS No: 213740, 2225751 REC Ref: 17/WM/0050: 17/WM/208) and adherence to information technology governance standards was obtained. The study database complies with the regulatory requirements for Good Clinical Practice.

Patient and public involvement

An established patient and public involvement (PPI) group from within the Tommy's centre at UHCW was consulted during initial protocol development. Two further PPI sessions with 10 service users, each including 9 women and 1 partner, where consulted to ensure follow up methods where acceptable to participants and to optimise response rates.

Setting

This cohort was established within a specialist recurrent miscarriage clinic in a tertiary referral centre (UHCW) within the UK. Miscarriage care followed European Society of Human Reproduction and Embryology (ESHRE) guidelines[3].

Eligibility

All couples with a history of two or more pregnancy losses (including biochemical loss[1], miscarriage, molar pregnancy, ectopic pregnancy and stillbirth) were eligible.

Recruitment

Couples are referred to the recurrent miscarriage clinic by their General Practitioner. Signposting prior to referral can occur from other hospital departments (e.g., Early Pregnancy Assessment Unit, Acute Gynaecology, Fertility unit) or charities (e.g., Tommy's, The Miscarriage Association). Couples are then sent information about Tommy's Net by post along with a baseline questionnaire. At their first clinic visit a member of the research team explains Tommy's Net and asks them to consent to storage of their data.

Data Collection

Both partners complete initial baseline questionnaires including demographic details, obstetric and medical history. Investigation results, blood pressure and body mass index (BMI) are recorded by clinic staff and entered into Tommy's Net (for questionnaires see supplementary file).

The Tommy's Net e-repository and database system, used for data collection and storage in the study, is based on the CURe framework[13], a modular system for collecting research data in secondary care settings. The framework includes methods for the standardised, flexible capture and storage of

1. Defined as no pregnancy identified on ultrasound scan

data. The system is intended to link to the participating centre's clinical information systems where possible to access relevant data already collected, such as laboratory test results. Tommy's Net includes a database to organise data collected as part of the study and a web application for healthcare professionals to use for data entry, review and use in clinic. Data in Tommy's Net can be exported for analysis. The development of Tommy's Net has seen continuous improvements based on feedback from clinicians, researchers and patients. The design of the system is intended to promote interoperability with existing hospital systems to allow researchers to use information already collected, collect pregnancy outcomes to benchmark clinics and allow researchers to identify high risk groups of patients for future research.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics. Time to event analysis was performed using Kaplan-Meier curves, a non-parametric method for assessing the probability of an event occurring over time. Multi-variant analysis was conducted using age, BMI, cigarette smoking status, alcohol consumption and use of folic acid.

Retention and Pregnancy Outcomes collection

A variety of methods were assessed to collect patient reported pregnancy outcomes after the first clinic visit. Initially women were encouraged to self-report outcomes by telephoning the clinic, or completing an outcome collection form sent by email. Automated invitations to complete this survey are sent via SMS every six months requesting information for follow up. This invitation consists of a single use link allowing the research team to trace the responses back to the patient identifiable baseline information.

Further outcome data is collected through viability scan visits, which can be accessed following initial review in the recurrent miscarriage service, and using existing hospital systems. Researchers used a maternity database, Evolution©, and a local intranet service to improve follow up and to validate participant reported information.

Using a variety of methods to collect outcomes improves follow up rate, however this does require researcher vigilance to avoid duplicate data entry. 17.8% of participants are still lost to follow up, therefore more work is needed in this area to encourage continuous engagement of participants.

Improving baseline data

In the first three months of recruitment, a number of couples (n=83) consented to the study but did not complete the baseline questionnaire. This resulted in their data being marked as 'inactive' within the database (i.e., consented to the cohort study but not returned initial baseline questionnaires). On receipt of the baseline questionnaires, participants are 'activated' and followed up six monthly (n=10/83 to date). Our process has been updated so critical data items are collected by the clinician, from all couples who consent before leaving the initial clinic appointment. Participants are no longer registered within the database until they have completed the initial baseline questionnaire.

Improving pregnancy outcome data collection

Initial pregnancy outcome data collection was poor with only 25% reporting their outcome, mainly due to technical difficulties in filling electronic versions of the forms for the participants. The response rate has gradually improved with development of a text message system. This was followed by other improvements such as a series of changes to the text message wording, by including partners in the messages, and changing the timing of the texts (with the majority sent in the afternoon or evening). Reminder messages are sent after 48 hours and after one week (if no responses from the initial text are received). Changes have been informed by patient and public involvement (PPI) groups, which were used to understand further why participants fail to respond to follow up SMS text message. Some explained that once they had had a baby, they were busy with their baby and forgot to reply. Conversely, repeated reporting of no pregnancy, or miscarriage was felt to be disheartening, or less important. We hope through education and careful wording of the questionnaire the response rate will continue to improve.

These approaches have contributed to an increase in response rate and combined with data from existing hospital systems, the response rate for pregnancy outcomes was 82.2%.

Data linkage with a general practice database was not deemed useful, because few miscarriages are recorded on the local general practice databases. Furthermore, there was a lack of standardisation in pregnancy data in primary care, though automated links with both primary and secondary care electronic health systems are still planned. The maternity services database may provide a fruitful source of pregnancy outcome data in the future.

Results

Analysis of cumulative live birth rate

Between May 2017 and January 2020, 777 women (and 480 partners) who attended the recurrent miscarriage clinic completed a baseline questionnaire and consented for their data to be included in the database. One hundred and thirty-eight (17.8%) participants were lost to follow up (no response to SMS, or information obtained for hospital databases), therefore 639 women are active within Tommy's Net. One hundred and thirty-four of these women are within six months of consenting to the study and have not yet received a scheduled SMS. Five of these women have reported conceiving out with the SMS system with the data captured through early pregnancy scan clinics. Of the active women, their mean age was 34 years (see table I) and mean number of previous pregnancy losses was 3.5 (range 1-19). Demographic characteristics including age, ethnicity, alcohol intake, folic acid use and previous live birth were not statistically different between participants who conceived and those who did not (table I). Statistically more participants who did not conceive smoked and had a BMI over 30.

	Continuing in cohort	No pregnancy	Lost to follow up	P value
Number	639	106	138	
Age	33.7	34.03	33.7	0.092
Ethnicity	White: 84% (436/519) Mixed: 2.1% (11) Asian: 8.9% (46) Black: 3.3% (17) Other: 1.7% (9) Unknown (120)	White 85.5% (65/76) Mixed: 2.6% (2) Asian: 6.6% (5) Black: 3.9% (3) Other: 1.3% (1) Unknown (30)	White 83.5% (101/121) Mixed: 1.6% (2) Asian: 9.8% (12) Black: 2.4% (3) Other: 2.4% (3) Unknown (17)	
Average no. of previous live birth	0.6	0.15	0.23	0.36
Average no. of previous miscarriages	3.5	3.6	3.43	
BMI over 30	23.8% (n=126/530)	30% (n=26/87)	18.2% (n=20/110)	0.001
Smoking Y/N Number	Yes:41 (7.4%)	Yes: 12 (13.5%)	Yes: 18 (14.9%)	0.001 0.000
Alcohol Y/N Units	Yes: 278 (50%) 5.54 (0.5-30)	Yes: 51 (58%) 5.03 (0.5-35)	Yes: 75 (60%) 5.38 (0.5-30)	0.083 0.000
Folic acid	Yes: 292 (45.5%)	Yes: 35 (47.17%)	Yes: 57 (41.9%)	0.000

Table I: Comparison of demographics for all active participants, participants that did not conceive and those that were lost to follow up

Pregnancy results

Four hundred and four of these women reported conceiving. One hundred and six (16.6%) women reported no pregnancy at least six months following registration, 31 (4%) of whom are no longer trying to conceive. Of those that conceived 72.8% (294/404) had a viable pregnancy (215 live births, 1 stillbirth, remainder currently <24 weeks at time of initial analysis). Analysis of data exported from the database in January 2020, revealed a conception of rate of 81% after two years within the cohort and viable pregnancy rate (pregnancy over 24 weeks or live birth at time of export) of 60% two years after attending the recurrent miscarriage clinic (fig 1). Age does impact on time to conception and time to viable pregnancy, with women of 25-34 years being more likely to have a viable pregnancy two years after initial review than other age groups.

The difference between couples who conceive and those who reach viable pregnancy starts at 30% (at 300 days conception rate is 70% and 40% reach over 24 weeks of gestation). This difference/gap gradually decreases and plateaus after 900 days to a difference of 19% (conception rate 82% with 63% reaching over 24 weeks gestation). The couples within this 'gap' represent those within our clinic who conceive but miscarry prior to viability despite current intervention and support. This gap is maintained within the 30-39years age group, but is less pronounced within those who conceive aged 25-29years (fig 2). Female BMI over 30 and female smoking status along with miscarriage history increases the time from initial consultation to conception and viable pregnancy within this patient group (fig 3-5).

A healthy BMI increases the chance of viable pregnancy, particularly when compared to a maternal BMI over 30kg/m2 (fig. 3). Having a BMI over 30 increases the time taken to viable pregnancy by 100-200 days. Within this population BMI does not appear to significantly change the time to conception (fig 3a), particularly within the first 300 days.

Couples who have had 4 or more miscarriages take longer to conceive, compared to couples who have has 3 or less miscarriages (fig. 4). There is a 17% gap within couples who have had 4 or more losses when comparing the rate of conception with viable pregnancy. This gap represents those that continue to miscarry and should be a population where research should be focused.

Smoking status impacts on time to conception. Females that smoke take longer to conceive with significantly more never conceiving.

Discussion

Database

We have developed an electronic method of obtaining outcomes from women following attendance at a recurrent miscarriage clinic. These outcomes can be used to assess recurrent miscarriage care and form a 'benchmark' to compare clinical services and interventions. The electronic cohort provides clinic outcome data in real time (on a dashboard, see supplementary file), and can be used for counselling couples as to both the chance of their next pregnancy succeeding and their cumulative time to live birth. This is novel, as data[2,10,11] identified at literature review could not be generalised to the UK population. Lund and colleagues[10] used a national, Danish registry to collect live birth data from attendees up to 5 years after their visit to a recurrent miscarriage clinic. Registry data were collected retrospectively and lacks information from couples who moved to other countries. Brigham[2] analysed 716 couples over a 10-year period in their Liverpool clinic, with pregnancy outcome data on 325 patients with unexplained recurrent miscarriage. Data were only reported on those who conceived and had their pregnancy and birth care at the same hospital. These datasets are now over 20 years old. Kling and colleagues[11] published more recent data based on a tertiary referral immunological centre within Germany. Seven hundred and nineteen couples were followed up for a median of 33.7 months, producing time to pregnancy and time to delivery over a five-year period. Whilst this is valuable data the study excluded couples who already had children within the partnership (25% within our clinic) and used immunotherapy in a proportion of couples which is not routinely used within the UK. It also asked for patient reported outcomes between nine months to four years after the event which could be prone to recall bias. This database will continue to collect and provide prospective outcomes of all those who attend this

recurrent miscarriage clinic and, as use increases within the other sites it will allow comparison of outcomes with the aim of sharing good practice to improve patient care.

Infertility

The time to conception curve within our RM population is similar to that in the general population[14]. Analysis to date has identified that within our cohort 16.6% (n=106) of couples fail to conceive within the follow up period. These patients are similar in age and ethnicity when compared to all within the active cohort. They do have a trend to a higher BMI, are statistically more likely to smoke.

Reasons why couples do not conceive are complex. Anecdotal evidence from the text message system and PPI groups shows some couples can feel unable to continue trying to conceive because of the potential risk of miscarriage. Recent research[15] has documented an increased risk of post-traumatic stress disorder following pregnancy loss. We hypothesise that the psychological impact of miscarriage may stop couples from trying to conceive again. This is an important area in which to focus research and facilitate additional counselling and support.

Other couples may be unable to conceive despite actively trying. Identifying this subgroup of couples earlier could facilitate prompt referral to fertility services and hopefully increase their chance of conception and ultimately live birth. Within this population rate of conception decreases significantly 1 year after initial consultation (fig 1). 65% of couples conceive within 1 year of initial consultation, with only an additional 15% conceiving in the second year. In view of this decrease in pace of conception we suggest referral to fertility services should be considered within this population after 1 year.

Through-out the UK, access to NHS funded fertility treatment is dependent on maternal weight, smoking status, as well as age and parity. Addressing these factors early in the couple's fertility journey may help to manage expectations prior to referral and reduce any delay in starting treatment. We recognise that weight particularly can be very sensitive issue and difficult to manage. Open and honest discussion, without blame, along with support and advice that joining group programmes for exercise and dietary modification can lead to more pregnancies than weight loss alone[16] should be given. Referral to weight management services including dietetics and bariatric surgeons could be discussed if appropriate.

There may be a role for assessment of ovarian reserve within women with a BMI over 30, or who have previously waited over 12months to conceive. Having strong links, or an integrated multi-disciplinary preconception service may allow a more cohesive approach to these couples and increase their chance of having a viable pregnancy.

Outcome Data

Comparing the 'time to conception' and 'time to viable pregnancy' curves illustrate the importance of assessing cumulative data. There is by definition a lag between conception and reaching 24 weeks pregnant, but following this the difference between the curves represents delay in live birth due to miscarriage. This gap decreases initially and may represent an impact from interventions and support within the recurrent miscarriage service. The importance of support to couples will be studied further during a planned qualitative study using semi-structured interviews of affected

couples. After 900 days the gap between the curves is static and represents those whom despite conceiving have not yet had a child. This is a group which resources and research should be targeted to further understand reasons for miscarriage.

Health Education

It is well documented that miscarriage risk increases with BMI over 30kg/m2 and smoking status[17-20]. Despite this 23.8% of women within the cohort have a BMI over 30kg/m2 and 7.4% smoke tobacco. Modifying these lifestyle factors through pre-conception counselling may reduce the chance of miscarriage and improve pregnancy outcome by reducing the incidence of, for example, gestational diabetes. Future research could be targeted at support in weight loss and smoking cessation.

Limitations and strengths

The Tommy's Net e-repository and associated database contains baseline and prospective pregnancy outcome data from the largest known population of couples with recurrent miscarriage in the UK. It allows calculation of 'time to conception' and 'time to viable pregnancy' using time to event analysis. This large dataset aims to facilitate future studies within a recurrent miscarriage population.

Obtaining follow up data is challenging. Using a variety of methods including self-reporting through the text message link and local hospital systems has improved our follow up rate.

Couples with limited English were unlikely to complete the lengthy questionnaire, which is currently only available in English. This means that this study may be missing high risk groups within our community

The introduction of the maternity services database could provide a valuable resource to enable improved follow up. Couples attend this RM clinic from all over the UK. Currently couples who deliver within our trust have at least two ways in which we can capture their outcome (SMS text message and hospital database with or without scan clinic information). These checks are not available to couples who have travelled some distance to attend and therefore may be under represented within the active participants group.

SMS text message requests for follow up are only sent every six months. This means that for the first six months that participants are within the study we do not expect to collect any outcome data. Some of these participants may go on to become 'inactive' and be removed from analysis.

Conclusion

We have developed a user-friendly electronic database, storing comprehensive data, which can provide accurate time to conception and data on viable pregnancies to facilitate analysis into factors contributing to recurrent miscarriage. 16.6% of women within our clinic did not conceive and early referral to fertility services should be facilitated. Over 20% of women within the cohort have a BMI of over 30 and 7.4% smoke. Preconception counselling should be targeted at weight and smoking status with an aim of reducing miscarriage.

Contributorship statement

SQ had the initial concept. OK, SNLCK and TNA designed and developed Tommy's net database and extracted initial data. RCS analysed the data and interpreted it along with SQ. RCS wrote the initial draft which was revised by SQ and DB, and reviewed by AH, OK, SNLCK, TNA, AB, AD, SDQ and SK. All commented on initial drafts and approved the final version.

Competing interests

Nil

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Data sharing statement

Data Available on Reasonable Request (under ethics restrictions).

Ethics statement

Ethical approval for was obtained from West Midlands- South Birmingham Regional Ethics Committee IRAS No: 213740, 2225751 REC Ref: 17/WM/0050: 17/WM/208

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- Figure 1: Cumulative rate over time, from initial consultation to conception and viable pregnancy (>24 weeks gestation)

- Figure 2: Comparing conception to >24weeks gestation by age

- Figure 3: Time from initial consultation to conception/>24 weeks gestation by female BMI range
- Figure 3a: Time from initial consultation to conception by BMI
- Figure 4: Time from initial consultation to conception/>24weeks gestation by miscarriage history
- Figure 5: Time from initial consultation to conception by female smoking status

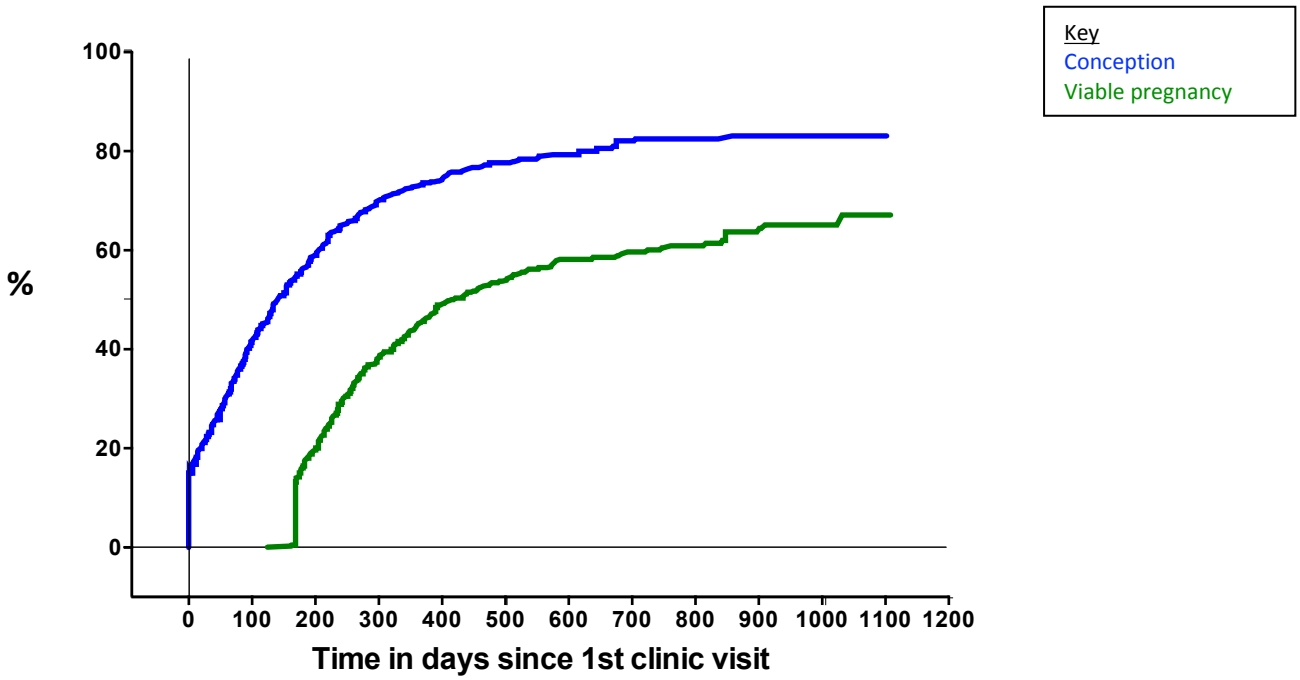


Figure 1: Cumulative rate over time, from initial consultation to conception and viable pregnancy (>24 weeks gestation)

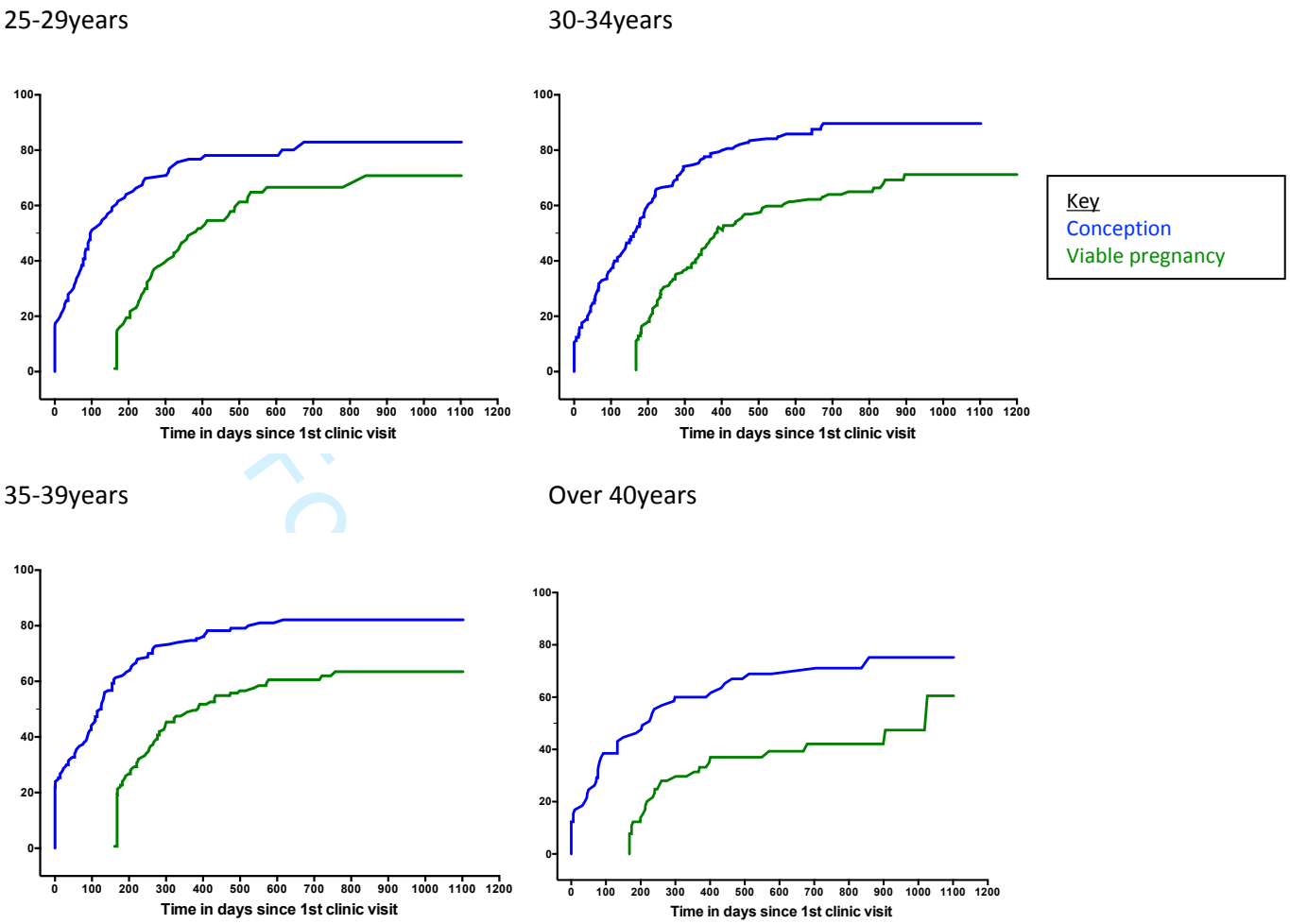


Figure 2: Comparing conception to >24weeks gestation by age

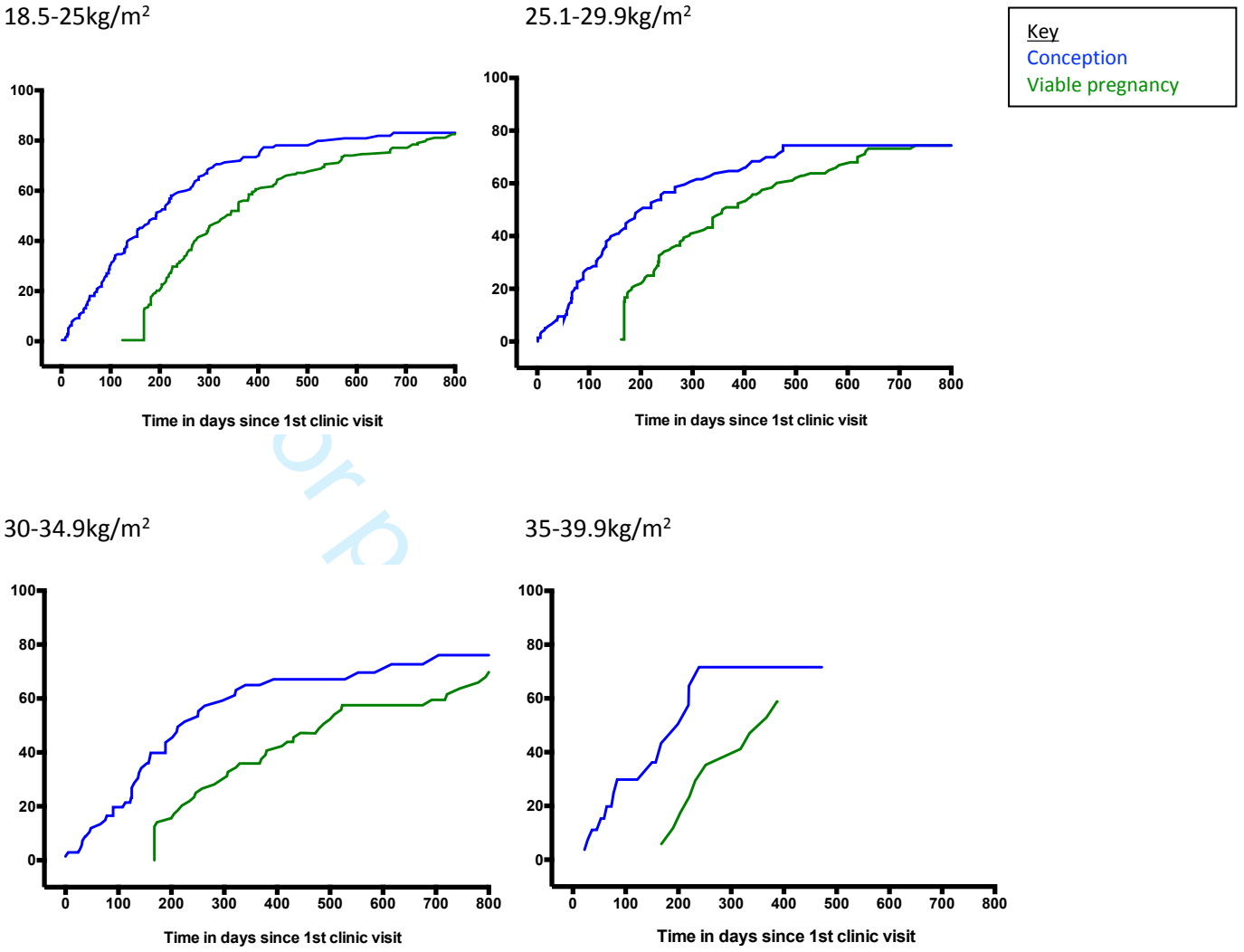


Figure 3: Time from initial consultation to conception/>24 weeks gestation by female BMI range

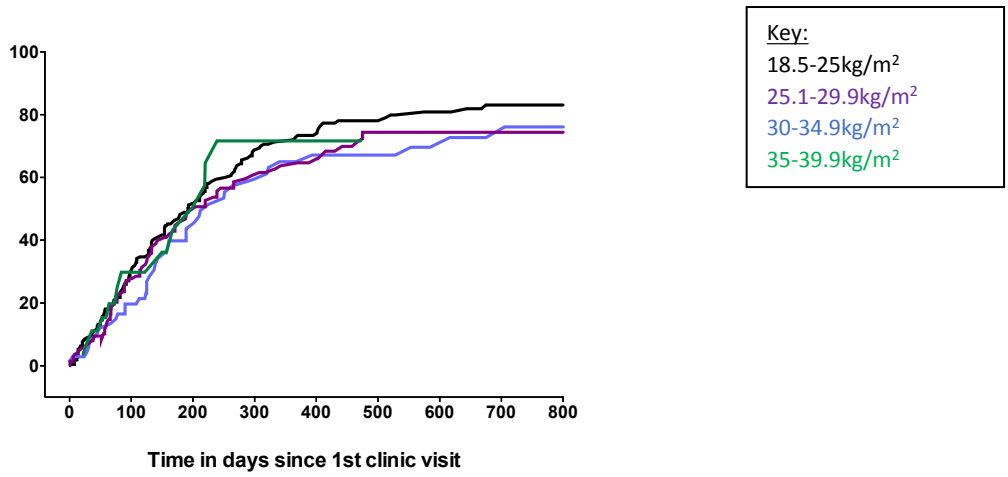


Figure 3a: Time from initial consultation to conception by BMI

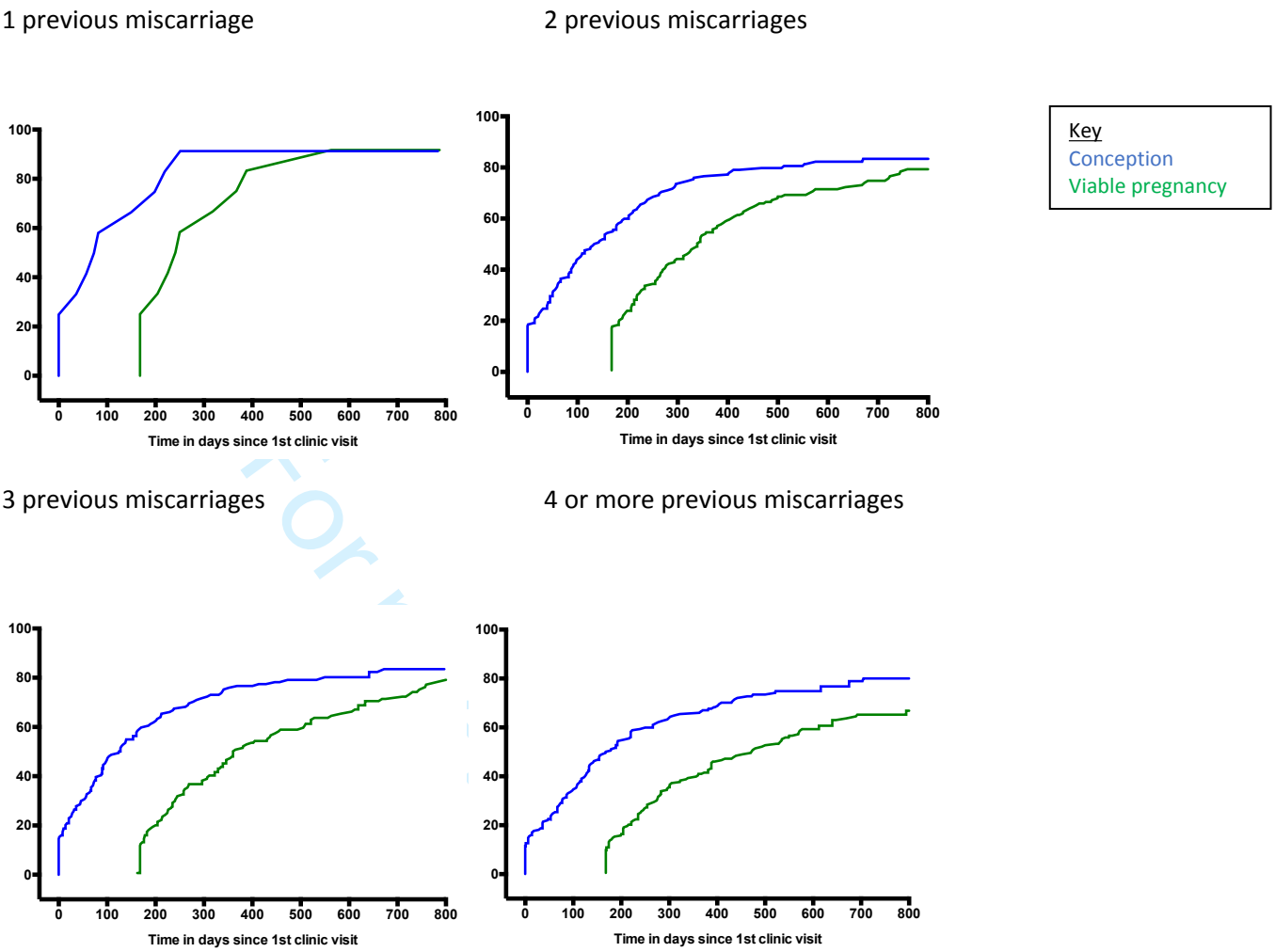


Figure 4: Time from initial consultation to conception/>24weeks gestation by miscarriage history

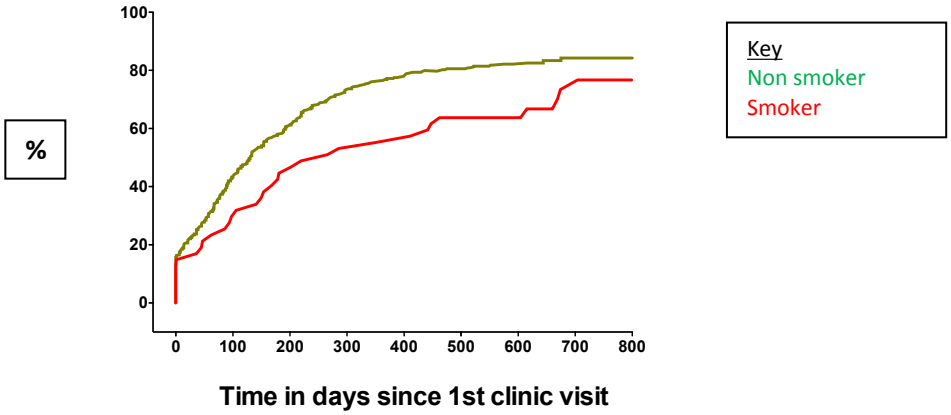


Figure 5: Time from initial consultation to conception by female smoking status

1

Figure 5: Dashboard

Historic Data (Pre Registration)

Trust	No of Couples	No of Women	No of Men	No of Pregnancies
University Hospitals Coventry and Warwickshire	897	897	736	3768

Age at Registration (female only)

	No of Patients	% of Patients
<35	445	50
35-40	318	35
>40	124	14

History of miscarriage/live births

Patients	No of Patient	% of Patients
2 miscarriages	221	25
3 miscarriages	248	28
4 miscarriages	173	19
5 miscarriages	87	10
>5 miscarriages	118	13
1 or more live births	335	37

Ongoing Miscarriage Outcomes (Post Registration)

Trust	Pregnancies Post Registration
University Hospitals Coventry and Warwickshire	634

Miscarriage/Live Birth Rates by conception type (percentages by row)

	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
All conception types	634	32	1	40	2	20	4	0
Natural conception only	538	33	1	40	2	20	4	0

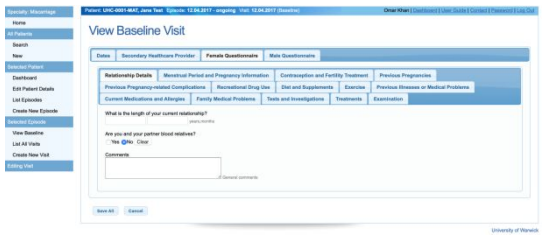
Miscarriage/Live Birth Rates by age of mother at delivery (percentages by row)

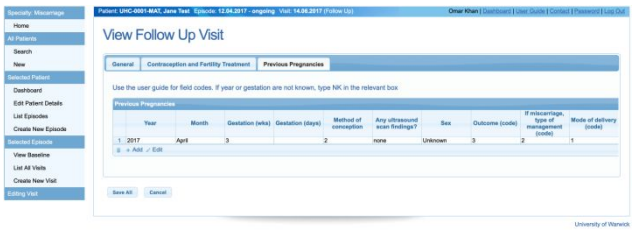
	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
<35	315	32	1	42	3	18	4	0
35-40	247	30	1	41	2	23	3	0
>40	71	39	0	31	1	20	8	0

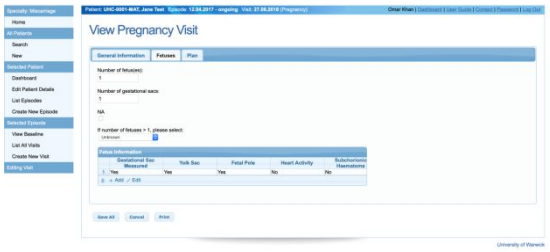
Miscarriage/Live Birth Rates by history of miscarriage (percentages by row)

	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
2	178	24	1	48	1	26	1	0
3	172	29	1	45	2	18	4	0
4	118	36	0	35	3	19	7	1
5	71	41	1	34	0	17	7	0
>5	81	42	4	31	7	12	4	0

2







3

4

Tommy's National Centre for Miscarriage Research

University Hospitals Coventry and Warwickshire NHS Trust

Registration form

Female details

Title	**Date of birth**	
Surname	**Ethnic group (see last page)***	
First and forename(s)	**Religion (see last page)***	
Address	**Marital status (see last page)***	
	Education (see last page)*	
	Occupation	
	NHS number	
	Hospital number	
City/town	**GP name**	
County	**GP address**	
Telephone (Home)		
Telephone (Mobile)	**GP telephone**	
E-mail address (we will use this to correspond with you):		

* - enter the relevant code from the list of tables on the last page of this form

Data Disclosure and Protection: By completing this form, you hereby give your consent for the data to be held within the NHS in accordance with the requirements of the 1998 Data Protection Act (UK).

Female signature:	
Date:	

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Please complete this form with as much information as you are able to. If you are uncertain about any of the questions you will be able to check these with your healthcare provider at your clinic appointment. Please include all medical information in your history even if you think it may be insignificant.

Relationship details

What is the length of your currentrelationship? ☐☐ years ☐☐ months

Are you and your partner blood relatives? Yes ☐ No ☐

Please describe: _

Menstrual period and pregnancy information

What was the first date of your last menstrual period? d d - m m - y y y y

What age did your periods start? ☐☐ years

Are your periods regular? Yes ☐ No ☐

If yes, what is your cycle length (time from the beginning of one period to the beginning of the next)? ☐☐ days

If no, what is your cycle length? **MIN** ☐☐ days

MAX ☐☐ days

How many days do you bleed for? ☐☐ days

Do you get any bleeding in between your periods? ☐ ☐

Do you have any problems with intercourse? ☐ ☐

How frequently do you have intercourse? ☐☐ per/wk

or ☐☐ per/month

Have you ever had a delay (>12 months) in trying to get pregnant? ☐ ☐

Are you currently pregnant? ☐ ☐

Are you currently trying to become pregnant? ☐ ☐

How long have you been trying to conceive? ☐☐ years ☐☐ months

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Contraception and fertility treatment

*Please complete the table below with all forms of contraception you have previously used (e.g. coil (IUCD), Depo-Provera injection, oral contraceptive pill). Use of condoms **DOES NOT** need to be included.*

Type of contraception	How long did you use it (years)?	How long ago did you stop using it (years)?

Have you ever used fertility treatment to try and get pregnant? Yes ☐ No ☐

Please tick all treatments you've had, and enter the number of attempts

Clomid/other ovary stimulation ☐ ☐☐ attempts

IVF/ICSI ☐ ☐☐ attempts

IUI ☐ ☐☐ attempts

Donor sperm treatment ☐ ☐☐ attempts

Donor egg treatment ☐ ☐☐ attempts

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Previous pregnancies

*Use the key opposite to complete the fields marked with *. If year or gestation are not known, state NK in the relevant box*

Year	Gestation (wks)	Time taken to get pregnant (months)	Method of conception*	Any ultrasound scan findings? (e.g. please tell us if the baby's heart-beat was seen)	Sex (M or F, if known)	Outcome** (enter code)	If miscarriage, type of management*** (enter code)	Mode of delivery**** (enter code)	With current partner (Yes or No)	Additional clinician's notes

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*** Method of conception**

1	Natural
2	IVF/ICSI
3	IUI
4	Donor sperm treatment
5	Donor egg treatment
6	Ovarian stimulation

****Outcome**

1	Live birth
2	Stillbirth
3	Pregnancy loss without ultrasound confirmation of pregnancy
4	Miscarriage after ultrasound confirmation of pregnancy
5	Late miscarriage (>12 weeks to <24 weeks)
6	Ectopic pregnancy
7	Molar pregnancy
8	Resolved pregnancy of unknown location
9	Termination

*****Type of management**

1	Expectant (waited for nature to take its course)
2	Surgical (operation)
3	Medical (took a tablet(s))

****** Mode of delivery**

1	Unassisted vaginal
2	Instrumental vaginal (forceps or suction cup delivery)
3	Elective caesarean section
4	Emergency caesarean section
5	Vaginal breech
6	Not applicable

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Previous pregnancy-related complications

	Yes	No
Do you have a history of polycystic ovaries?	☐	☐
Do you have a history of fibroids?	☐	☐

If yes: Distorting womb cavity ☐
Not distorting womb cavity ☐
I don't know ☐

Do you have a history of endometriosis?	☐	☐
Do you have a history of pelvic inflammatory disease?	☐	☐
Do you have a history of uterine (womb) abnormalities?	☐	☐
Have you ever had a sexually transmitted disease?	☐	☐
If yes, when: m m - y y y y — Was it treated?	☐	☐
Have you ever had any previous gynaecological surgeries?	☐	☐

If yes, tick all applicable:

Laser or loop excision of the cervix (LLETZ)	☐ →	If yes, how many operations? ☐☐ operations	
Removal of fibroids	☐	Removal of scar tissues in the womb	☐
Endometriosis surgery	☐	Womb septum removal	☐
Fallopian tube surgery	☐	Other gynaecological surgeries	☐ If yes, state: _____
Removal of ovarian cyst(s)	☐	Other gynaecological disorders	☐ If yes, state: _____
Surgical management of miscarriage	☐	I don't know	☐

Date of last cervical smear test? m m - y y y y

Result? ☐ Normal ☐ Abnormal

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Recreational drug use

	Yes	No
Do you currently drink alcohol?	☐	☐

If yes: How many units per week? ☐☐ units per week

	Yes	No
Do you currently smoke?	☐	☐

If yes:

How many cigarettes? ☐☐ per day **or** ☐☐ per week

How many vaping sessions? ☐☐ per day **or** ☐☐ per week

One session is classified as 5 or more inhalations

If no:

Have you recently stopped? ☐ Yes ☐ No

If yes, how recently did you stop? ☐ < 1 month ☐ 1-6 months ☐ > 6 months

	Yes	No
Do you take any other recreational drugs?	☐	☐

If yes, please complete table:

Type	Frequency of use (tick one option)
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months

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Diet and supplements

How many days a week do you eat the following foods:

Tick one box per food type

	Number of days per week							
	0	1	2	3	4	5	6	7
Red meat	☐	☐	☐	☐	☐	☐	☐	☐
White meat	☐	☐	☐	☐	☐	☐	☐	☐
Fish	☐	☐	☐	☐	☐	☐	☐	☐
Eggs	☐	☐	☐	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐	☐	☐	☐
Dairy products	☐	☐	☐	☐	☐	☐	☐	☐
Soya products	☐	☐	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐	☐	☐
Nuts (almonds/walnuts)	☐	☐	☐	☐	☐	☐	☐	☐

Do you consume sugar substitutes daily or most days of the week? ☐ Yes ☐ No

How many cups of coffee* do you drink in a typical day? ☐ cups of coffee/day

How many cups of tea* do you drink in a typical day? ☐ cups of tea/day

How many cans (or equivalent) of soft drink do you consume per day (e.g. energy drinks, cola)? ☐ cans/day

Do you currently take any vitamins or supplements? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	How long have you been taking it? (weeks)
1			
2			
3			
4			

* Do not count decaffeinated drinks

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Diet and supplements

If you are not taking vitamins or minerals currently but have taken them in the last four months please complete this table.

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Are you currently taking any protein shakes or protein bars? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Exercise

Do you follow a regular routine of physical exercise? ☐ Yes ☐ No

How many days a week do you exercise?

Tick one option

- 0 ☐
- 1-2 ☐
- 3-4 ☐
- 5-6 ☐
- 7 ☐

If you exercise, how many hours a day do you exercise?

Tick one option

- < 30 min ☐
- 30 min - 1 hr ☐
- > 1 hr - 1.5 hrs ☐
- > 1.5 hrs - 2 hrs ☐
- > 2 hrs - 2.5 hrs ☐
- > 2.5 hrs ☐

On average how many hours do you spend sitting on a chair per day?

Sofa or armchair ☐ hours/day Work chair ☐ hours/day

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Previous illnesses or medical problems

Have you had any serious illnesses or medical problems? Yes ☐ No ☐

If yes, tick all applicable:

Diabetes	☐	Rheumatism or painful joints	☐
Thyroid problems	☐	Skin rashes or other skin disorders	☐
Cancer	☐	Irritable Bowel Syndrome	☐
Heart problems	☐	Coeliac disease	☐
Liver problems	☐	Crohn's disease	☐
Migraines	☐	Autoimmune disease	☐
Epilepsy	☐	Other inflammatory disorder	☐
Depression	☐	Thrombosis (clots in legs or chest)	☐
High blood pressure	☐	Candida (thrush)	☐
Lupus (SLE)	☐	Bacterial vaginosis	☐
Abnormal vaginal discharge	☐		
Other illnesses	☐	Please state: _____	

If you have ticked any of the boxes above, please provide further details below:

Current medications and allergies

Please provide details on any allergies you have and medication you are currently taking below:

Tommy's National Centre for Miscarriage Research

Family medical problems

Has your mother, father, siblings or maternal aunt(s) had any medical complications? Yes ☐ No ☐

If yes, tick all applicable:

- Miscarriage ☐
- Recurrent (3 or more) miscarriages ☐
  - If yes: Number of 1st trimester losses (<12 weeks) ☐☐
  - Number of 2nd trimester losses (>12 weeks) ☐☐
  - ☐ I don't know
- Obstetric complications (such as pre-eclampsia and growth restriction) ☐
- Genetic or developmental problems ☐
- Heart problems under the age of 50 ☐
- Stroke under the age of 50 ☐
- Still birth ☐
- Pre-term birth ☐
- Infertility ☐
- High blood pressure ☐
- Diabetes ☐
- Blood clots (thrombosis) ☐
- Depression ☐
- Other ☐

Please state: _____

If you have ticked any of the boxes above, please provide further details below:

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Tests and investigations

Please give details of any tests or investigations you've had as a part of your miscarriage treatment.

Test/investigations	Date of test	Result	Which hospital or clinic did you have the test at?
FSH			
LH			
Oestradiol			
Haemoglobin			
Platelets			
Rubella immunity			
Thrombophilia screening			
Thyroid antibodies			
Thyroid function test			
Sexually transmitted disease			
Ultrasound			

If you've had any other tests, please state below:

Test/investigation	Date of test	Result	Which hospital or clinic did you have the test at?

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Treatments

Please give details of any treatments you've previously received or are currently receiving as a part of your miscarriage management. Please also include any medications that you've bought yourself.

Treatment (please include medicines and operations)	Dose	Date from*	Date to	Tick if ongoing	Additional clinician's notes
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	

* If an operation, please give the date of operation

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Examination

This section should be completed in conjunction with a member of the research team who attends to you in the clinic

Weight: ☐☐☐ kg Height: ☐☐☐ cm BMI: ☐☐.☐

Blood pressure: ☐☐☐ / ☐☐☐ mmHg
Systolic Diastolic

Examination findings (if appropriate)

For Tommy's research office use only if patient is consented and registered to take part in Tommy's research

Date of consent: d d - m m m - y y y y

Patient ID: ☐☐☐☐ - M A T

Recruiting site: -

Date entered onto database: __/___/____ Entered Date checked: __/___/____ Checked by:

Tommy's National Centre for Miscarriage Research

Ethnicity codes

WHITE		Category includes
A	White British	English, Scottish, Welsh, Cornish
B	White Irish	
C	Any other white background	Former USSR, Baltic States, Former Yugoslavia, Other European, White South African, American, Australian, New Zealander, Mixed White
CF	Greek	
CG	Greek Cypriot	
CH	Turkish	
CI	Mediterranean	Italian, Portuguese and Spanish
CJ	Turkish Cypriot	
CN	Jewish	
CY	Other White European	
MIXED		
D	White & Black Caribbean	
E	White & Black African	
F	White & Asian	
G	Any other mixed background	
ASIAN OR ASIAN BRITISH		
H	Indian	British Indian, Punjabi
J	Pakistani	British Pakistani, Kashmiri
K	Bangladeshi	British Bangladeshi
L	Any other Asian background	British Asian, East African Asian, Sri Lankan, Tamil, Sinhalese, Caribbean Asian, Nepalese, Mixed Asian
BLACK OR BLACK BRITISH		
M	Black Caribbean	Caribbean, West Indian Islands (and also Guyana) apart from Puerto Rican, Dominican and Cuban, which are
N	Black African	Nigerian, Kenyan, Black South African, Other Black African Countries
P	Other Black background	Black American, Mixed Black
PA	Somali	
PE	Black British	
OTHER ETHNIC GROUPS		
R	Chinese	inc. Hong Kong
S	Any other ethnicity	Japanese, Filipino, Malaysian, Aborigine, Afghani, Burmese, Fijian, Inuit, Maori, Native American Indian, Thai, Tongan, Samoan, Iranian, Israeli, Kurdish, Latin American (inc. Cuban, Puerto Rican, Dominican, Hispanic), Moroccan, Multi Ethnic Islands (inc. Seychellois, Maldivian, St. Helena), Other Middle Eastern (inc. Iraqi, Lebanese, Yemeni), Other North African, South American (inc. Central America).
SA	Africa—colour not defined	
SC	Arab	
SD	Vietnamese	
Z	Not stated	

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Religion codes

A	Christian (all denominations)
B	Buddhist
C	Hindu
D	Jewish
E	Muslim
F	Sikh
G	Agnostic
H	Atheist
I	I'd rather not say
J	Other (please specify)

Marital status codes

A	Single
B	Married
C	Separated
D	Divorced
E	Widowed

Education codes

A	No formal qualifications
B	1-4 GCSEs (A*-C) or equivalent
C	5+ GCSEs (A*-C) or equivalent
D	Apprenticeship
E	2+ A-levels or equivalent
F	Degree or above
G	Other (please specify)

Tommy's National Centre for Miscarriage Research

University Hospitals Coventry and Warwickshire NHS Trust

Registration form

Male details

Title	**Date of birth**	
Surname	**Ethnic group (see last page)***	
First and forename(s)	**Religion (see last page)***	
Address	**Marital status (see last page)***	
	Education (see last page)*	
	Occupation	
	NHS number	
	Hospital number	
City/town	**GP name**	
County	**GP address**	
Telephone (Home)		
Telephone (Mobile)	**GP telephone**	
E-mail address (we will use this to correspond with you):		

* - enter the relevant code from the list of tables on the last page of this form

Data Disclosure and Protection: By completing this form, you hereby give your consent for the data to be held within the NHS in accordance with the requirements of the 1998 Data Protection Act (UK).

Male signature:	
Date:	

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Miscarriage Research

Please complete this form with as much information as you are able to. If you are uncertain about any of the questions you will be able to check these with your healthcare provider at your clinic appointment. Please include all medical information in your history even if you think it may be unimportant.

Previous illnesses or medical problems

	Yes	No
Have you had any serious illnesses or medical problems?	☐	☐

If yes, tick all applicable:

Diabetes	☐	Rheumatism or painful joints	☐
Thyroid problems	☐	Skin rashes or other skin disorders	☐
Cancer	☐	Irritable Bowel Syndrome	☐
Heart problems	☐	Coeliac disease	☐
Liver problems	☐	Crohn's disease	☐
Migraines	☐	Autoimmune disease	☐
Epilepsy	☐	Other inflammatory disorder	☐
Depression	☐	Thrombosis (clot in the leg or chest)	☐
High blood pressure	☐	Candida	☐
Lupus (SLE)	☐	Bacterial urethritis	☐
		Abnormal urethral discharge	☐

Other illnesses ☐ Please state: _____

If you have ticked any of the boxes above, please provide further details below:

Current medications and allergies

Please provide details on any allergies you have and medication you are currently taking below:

Tommy's National Centre for Miscarriage Research

Andrological history

Have you had a testicular examination before? Yes ☐ No ☐

What was found? _____

Have you had any of the following diagnosed?

Please tick all applicable options

Absence of a testicle (cryptorchidism)	☐	Mumps	☐
Testicular pain	☐	Tuberculosis (TB)	☐
Twisted testicles (torsion)	☐	Impotence/erectile dysfunction	☐
Testicular cancer	☐	Ejaculatory dysfunction	☐
Varicose veins in your scrotum	☐	Infertility	☐
		STI's	☐

If you have ticked any of the boxes above, please provide further details below:

Have you had any of the following surgeries?

Please tick all applicable options

Groin surgery	☐
Varicocelectomy	☐
Orchidectomy	☐
Orchidopexy	☐
Surgery for hernia	☐

Tommy's National Centre for Miscarriage Research

Family medical problems

Has your mother, father, siblings or maternal aunt(s) had any medical complications? Yes ☐ No ☐

If yes, tick all applicable:

- Miscarriage ☐
- Recurrent (3 or more) miscarriages ☐ → *If yes:* Number of 1st trimester losses (<12 weeks) ☐☐ Number of 2nd trimester losses (>12 weeks) ☐☐ ☐ I don't know
- Obstetric complications (such as pre-eclampsia and growth restriction) ☐
- Genetic or developmental problems ☐
- Heart problems under the age of 50 ☐
- Stroke under the age of 50 ☐

- Still birth ☐
- Pre-term birth ☐
- Infertility ☐
- High blood pressure ☐
- Diabetes ☐
- Blood clots (thrombosis) ☐
- Depression ☐
- Other ☐

Please state: _____

If you have ticked any of the boxes above, please provide further details below:

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Previous paternal history

	Yes	No
Have you had children in another relationship?	☐	☐
If yes, number of children:	☐☐	
Have you ever had a delay (>12 months) trying to father a child?	☐	☐

What age did you enter puberty? ☐☐ years

What is your current average ejaculatory frequency per week? ☐☐☐ times/week

What is your usual ejaculatory frequency per month (4 weeks)? ☐☐☐ times/month

Occupational exposure

	Yes	No
Have you been exposed to any harmful substances during your current or previous jobs? (see below for examples of such substances)	☐	☐

Exposure Type/Substance: (Years of exposure)

Dust	☐☐	Asbestos	☐☐
Fumes	☐☐	Noxious Gases	☐☐
Harmful vapours	☐☐	Chemicals	☐☐

Other (please specify): _____

Please provide further details:

_____

_____

_____

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Type of underwear

What type of underwear do you wear?

Tick one option

Boxer shorts ☐
Boxer briefs/trunks ☐
Briefs ☐
Thongs/Bikinis/G-strings ☐
Long underwear ☐
Jockstraps ☐
None ☐

What type of fabric is the underwear most commonly made from?

Tick one option

Cotton ☐
Synthetic ☐
Lycra ☐
Other (please specify) ☐ _____

Do they hold your testicles to the body, or are they loose?

Tick one option

Tight ☐
Loose ☐
Unsure ☐

Is the tightness of your underwear similar to before the last time your partner fell pregnant?

Tick one option

Yes ☐ No ☐ Don't know ☐

Technology habits

Do you ever sit with a laptop computer on your lap? Yes ☐ No ☐

↓

How many hours per day? ☐☐ hours ☐☐ minutes

Do you keep your mobile phone (that's switched on) in your trouser pocket?

Front pocket? Yes ☐ No ☐

↓

How many hours a day? ☐☐ hours/day

Back pocket? Yes ☐ No ☐

↓

How many hours a day? ☐☐ hours/day

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Diet and supplements

How many days a week do you eat the following foods:

Tick one box per food type

	Number of days per week							
	0	1	2	3	4	5	6	7
Red meat	☐	☐	☐	☐	☐	☐	☐	☐
White meat	☐	☐	☐	☐	☐	☐	☐	☐
Fish	☐	☐	☐	☐	☐	☐	☐	☐
Eggs	☐	☐	☐	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐	☐	☐	☐
Dairy products	☐	☐	☐	☐	☐	☐	☐	☐
Soya products	☐	☐	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐	☐	☐
Nuts (almonds/walnuts)	☐	☐	☐	☐	☐	☐	☐	☐

Do you consume sugar substitutes daily or most days of the week? ☐ Yes ☐ No

How many cups of coffee* do you drink in a typical day? ☐ cups of coffee/day

How many cups of tea* do you drink in a typical day? ☐ cups of tea/day

How many cans (or equivalent) of soft drink do you consume per day (e.g. energy drinks, cola)? ☐ cans/day

Do you currently take any vitamins or supplements? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	How long have you been taking it? (weeks)
1			
2			
3			
4			

* Do not count decaffeinated drinks

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Diet and supplements

If you are not taking vitamins or minerals currently but have taken them in the last four months please complete this table.

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Are you currently taking any protein shakes or protein bars? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Exercise

Do you follow a regular routine of physical exercise? ☐ Yes ☐ No

How many days a week do you exercise?

Tick one option

0 ☐
1-2 ☐
3-4 ☐
5-6 ☐
7 ☐

If you exercise, how many hours a day do you exercise?

Tick one option

< 30 min ☐
30 min - 1 hr ☐
1 hr - 1.5 hrs ☐
1.5 hrs - 2 hrs ☐
2 hrs - 2.5 hrs ☐
> 2.5 hrs ☐

On average how many hours do you spend sitting on a chair per day?

Sofa or armchair ☐ hours/day Work chair ☐ hours/day

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Recreational drug use

Question	Yes	No
Do you currently drink alcohol?	☐	☐

If yes → How many units per week? ☐☐ units per week

Question	Yes	No
Do you currently smoke?	☐	☐

If yes:

How many cigarettes? ☐☐ per day **or** ☐☐ per week

How many vaping sessions? ☐☐ per day **or** ☐☐ per week

One session is classified as 5 or more inhalations

If no:

Have you recently stopped? ☐ Yes ☐ No

If yes, how recently did you stop? ☐ < 1 month ☐ 1-6 months ☐ > 6 months

Question	Yes	No
Do you take any other recreational drugs?	☐	☐

If yes, please complete table:

Type	Frequency of use (tick one option)
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months

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Tests and investigations

Please give details of any tests or investigations you've had as a part of your treatment.

Test/investigations	Date of test	Result	Which hospital or clinic did you have the test at?
Semen analysis			
Sexually transmitted infection screening			

If other tests, please state below:

Test/investigation	Date of test	Result	Which hospital or clinic did you have the test at?

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Treatments

Please give details of any treatments you've previously received or are currently receiving as a part of your miscarriage management. Please also include any medications that you've bought yourself.

Treatment (please include medicines and operations)	Dose	Date from*	Date to	Tick if ongoing	Additional clinician's notes
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	

* If an operation, please give the date of operation

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Examination

This section should be completed in conjunction with the a member of the research team who attends to you in the clinic

Weight: ☐☐☐ kg Height: ☐☐☐ cm BMI: ☐☐.☐

Blood pressure: ☐☐☐ / ☐☐☐ mmHg
Systolic Diastolic

Examination findings (if appropriate)

For Tommy's research office use only if patient is consented and registered to take part in Tommy's research

Date of consent: d d - m m m - y y y y

Patient ID: ☐☐☐☐ - P A T

Recruiting site: -

Date entered onto database: __/___/____ Entered by: Date checked: __/___/____ Checked by:

Ethnicity codes

WHITE		Category includes
A	White British	English, Scottish, Welsh, Cornish
B	White Irish	
C	Any other white background	Former USSR, Baltic States, Former Yugoslavia, Other European, White South African, American, Australian, New Zealander, Mixed White
CF	Greek	
CG	Greek Cypriot	
CH	Turkish	
CI	Mediterranean	Italian, Portuguese and Spanish
CJ	Turkish Cypriot	
CN	Jewish	
CY	Other White European	
MIXED		
D	White & Black Caribbean	
E	White & Black African	
F	White & Asian	
G	Any other mixed background	
ASIAN OR ASIAN BRITISH		
H	Indian	British Indian, Punjabi
J	Pakistani	British Pakistani, Kashmiri
K	Bangladeshi	British Bangladeshi
L	Any other Asian background	British Asian, East African Asian, Sri Lankan, Tamil, Sinhalese, Caribbean Asian, Nepalese, Mixed Asian
BLACK OR BLACK BRITISH		
M	Black Caribbean	Caribbean, West Indian Islands (and also Guyana) apart from Puerto Rican, Dominican and Cuban, which are Latin America
N	Black African	Nigerian, Kenyan, Black South African, Other Black African Countries
P	Other Black background	Black American, Mixed Black
PA	Somali	
PE	Black British	
OTHER ETHNIC GROUPS		
R	Chinese	inc. Hong Kong
S	Any other ethnicity	Japanese, Filipino, Malaysian, Aborigine, Afghani, Burmese, Fijian, Inuit, Maori, Native American Indian, Thai, Tongan, Samoan, Iranian, Israeli, Kurdish, Latin American (inc. Cuban, Puerto Rican, Dominican, Hispanic), Moroccan, Multi Ethnic Islands (inc. Seychellois, Maldivian, St. Helena), Other Middle Eastern (inc. Iraqi, Lebanese, Yemeni), Other North African, South American (inc. Central America).
SA	Africa—colour not defined	
SC	Arab	
SD	Vietnamese	
Z	Not stated	

Religion codes

A	Christian (all denominations)
B	Buddhist
C	Hindu
D	Jewish
E	Muslim
F	Sikh
G	Agnostic
H	Atheist
I	I'd rather not say
J	Other (please specify)

Marital status codes

A	Single
B	Married
C	Separated
D	Divorced
E	Widowed

Education codes

A	No formal qualifications
B	1-4 GCSEs (A*-C) or equivalent
C	5+ GCSEs (A*-C) or equivalent
D	Apprenticeship
E	2+ A-levels or equivalent
F	Degree or above
G	Other (please specify)

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods	5

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	n/a
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	
6			
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6
Statistical methods	#12c	Explain how missing data were addressed	n/a
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	
7			
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	7

		included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	
14			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
7			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
7			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
7			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
n/a			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			

Key results	#18	Summarise key results with reference to study objectives	3
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	3
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	8
Generalisability	#21	Discuss the generalisability (external validity) of the study results	8
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

This checklist was completed on 19. April 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Version 5.0, 21-Jan-2020

University Hospitals Coventry and Warwickshire NHS Trust

STUDY PROTOCOL

Tommy's Net

A cohort study of pregnancy outcome in couples who miscarry

Sponsor: University Hospitals Coventry and Warwickshire NHS trust
Sponsor reference: SQ186916

Funder: Tommy's Charity

REC reference: 17/WM/0050 for data collection
Reference for database: 17/NW/0208

IRAS No: 213740 for data collection
IRAS No: 225751 for database
ISRCTN: 17732518

Parts with no fill relate to both projects
Part in light grey refers to data collection 17/WM/0050
Parts in light yellow refer to database application

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Research Governance Framework, the ICH Good Clinical Practice guidelines and the Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..... …...../...../.....

Name: (please print):

.....

Position:

.....

KEY TRIAL CONTACTS

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Funder	Tommy's Charity Nicholas House, 3 Laurence Pountney Hill, London, EC4R 0BB Email: mailbox@tommys.org.
Trial Co-ordinator / Co-ordination centre	Institute of Digital Healthcare University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL

INDEX

1. Aims and Objectives

We seek to achieve the following objectives:

- To undertake a large cohort study of pregnancy outcome following miscarriage.
- To facilitate the development and validation of tests and prediction models that could determine pregnancy outcome.
- To stratify couples with history of miscarriages into distinct phenotypes, allowing targeted management.
- To enable population-based epidemiological studies on miscarriage.
- To facilitate randomised controlled trials in terms of identifying eligible recruits and managing the trials.
- To enable participating hospitals to work together in a way that brings added benefits to all parties and the populations whom they serve.
- To facilitate the clinical/research interface.

We aim to do this by creating an online electronic patient record system, which will be designed and constructed by our specialist team within the University of Warwick, Institute of Digital Healthcare, for use by early pregnancy services.

2. Introduction

Miscarriage, defined as the loss of pregnancy before the fetus reaches viability, is the most common complication of pregnancy. As many as 15-25% of pregnancies end in miscarriage, and 25-50% of women experience at least one sporadic miscarriage in their reproductive life.(1) The number of miscarriages in the UK is estimated to be approximately 200,000 per year.(2) Most miscarriages are sporadic and occur before 12 weeks of gestation.(3) They frequently involve numeric chromosome errors in the conceptus.(4)

Recurrent miscarriage is generally viewed as a condition distinct from sporadic miscarriages. It is estimated that 5% of women experience two consecutive miscarriages, and approximately 1% suffer three or more consecutive miscarriages. (5,6) In recurrent miscarriage, the incidence of euploidic fetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases.(7) Recurrent miscarriage is a debilitating disorder, associated with considerable psychological morbidity, for which there is no effective medical intervention. Fortunately, the cumulative live birth rate for most recurrent miscarriage patients is high; more than around 65% of women with recurrent losses go on to have a successful subsequent pregnancy.(8–14)

The risk factors associated with miscarriage include maternal age, previous pregnancy history, body mass index (BMI), maternal medical conditions, thrombophilia's, parental structural chromosome abnormities, uterine anomalies and lifestyle factors such as smoking.

There are no robustly developed and widely validated prediction models in current clinical use. Couples are currently not provided with accurate estimates of their future risk of miscarriage, or obstetric and perinatal outcomes.

Effective management of miscarriage requires the rigorous study of risk factors and test outcomes, as well as the development of new tests to allow stratification of patients according to the likelihood of future reproductive failure. The development and assessment of prognostic tests require effective and long-term follow-up work with accurate recording and analysis of future pregnancy outcomes. To facilitate such recording, we will establish an online data and record management system that will allow patients to continuously update their reproductive history.

Currently couples suffering miscarriage are stratified according to the number of previous losses. Many clinics in the UK will only investigate women after 3 losses.(11) Our aim is to change this counting of losses as an indicator of disease to an approach that takes multiple risk factors into account, producing distinct miscarriage phenotypes that allow targeted tests and interventions to improve outcomes.

For example, sporadic miscarriages frequently result from aneuploidy, whereas recurrent miscarriage, defined by consecutive miscarriages, is generally viewed as a distinct disorder in which the incidence of euploidic fetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases. Currently affected couples are routinely screened for various anatomical, endocrine, immunological, thrombophilic and genetic risk factors,(11) but the ability of these tests to stratify women in terms of pregnancy outcome and appropriate treatment has not been vigorously tested.

The Tommy's National Centre for Miscarriage Research is a Research Centre which brings together an interdisciplinary Translational Medicine research grouping jointly at the University of Warwick, University of Birmingham and Imperial College London. The Centre is dedicated to research across all aspects of miscarriage and early pregnancy complications including medical, basic scientific, social and ethical issues. In facilitating this research portfolio, one aspect includes the centralised secure storage of all data relating to the research from every participating site, which is to be known as Tommy's Net.

3. **Methods & Design**

3.1 Overview

In this project we plan to use digital technology to store information about the patient's and their partner's demographic details history, investigation results and pregnancy outcome. Thus we will create a large cohort study of women presenting with miscarriage. The crucial feature of the cohort will be the ascertainment of pregnancy outcome. Analysis of this cohort will allow us to assess the utility of existing investigations and new test in predicting pregnancy outcome.

3.2 Centres

This project will initially involve three centres with specialist clinics:

- University Hospitals Coventry and Warwickshire NHS trust (UHCW)
- Birmingham Women's Hospital Foundation Trust (BWH)

- Imperial College Healthcare NHS Trust (Imperial)

Any additional centres will be notified to the responsible REC as a substantial amendment.

3.3 Population

Women attending specialist services at the participating trusts will be invited to participate:

- UHCW; it will include couples attending, early pregnancy, implantation, recurrent miscarriage and preterm prevention clinics.
- BWH; will include individuals attending early pregnancy assessment unit and recurrent miscarriage clinic.
- Imperial; will include individuals attending early pregnancy assessment unit and recurrent miscarriage clinic.

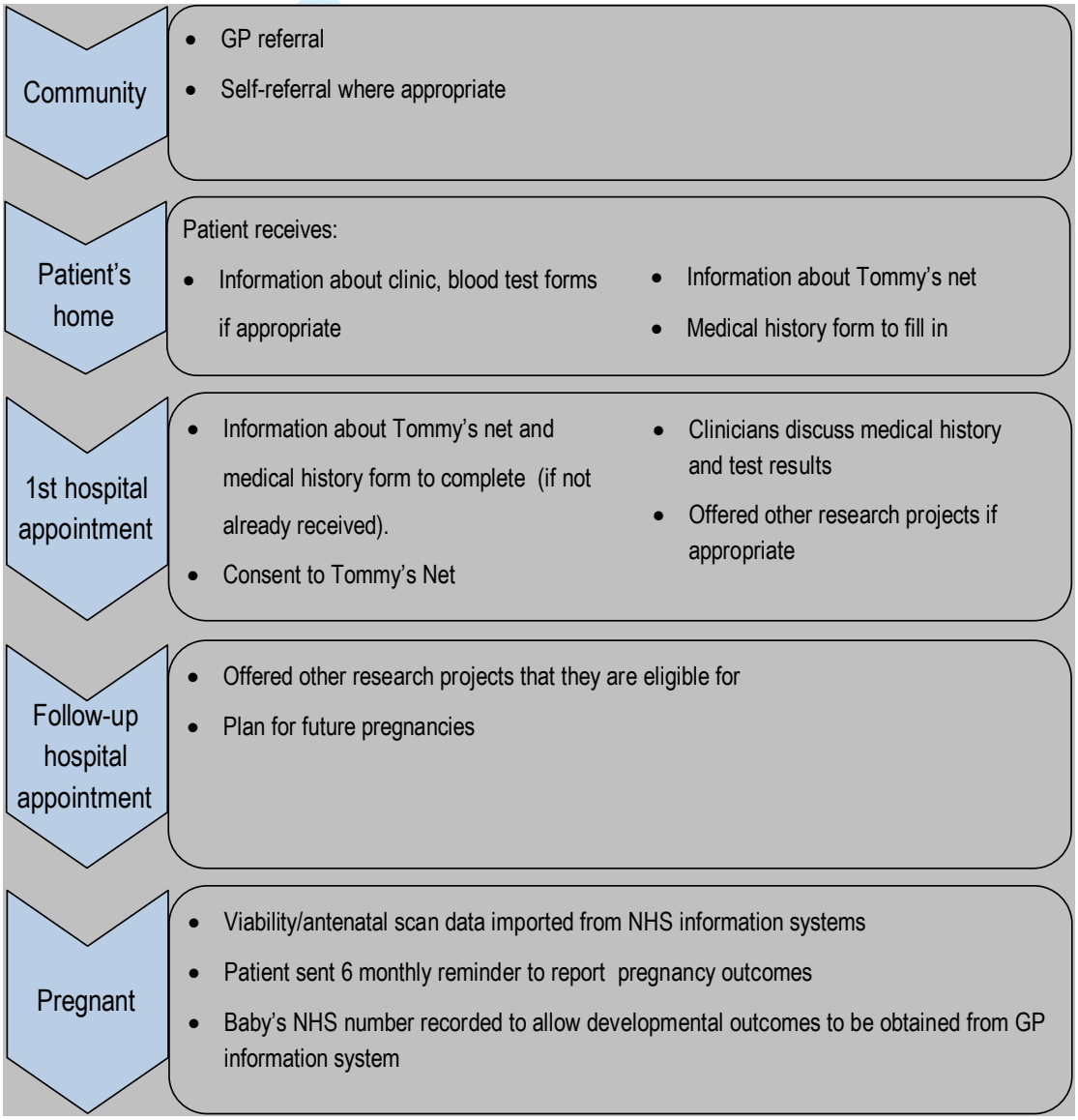

Figure 1. Tommy's Net flow diagram for recurrent miscarriage clinic patients

Pregnant:

- Update of demographics including weight, smoking status, alcohol intake and folic acid use.

May also receive 6-12 information/support text messages annually

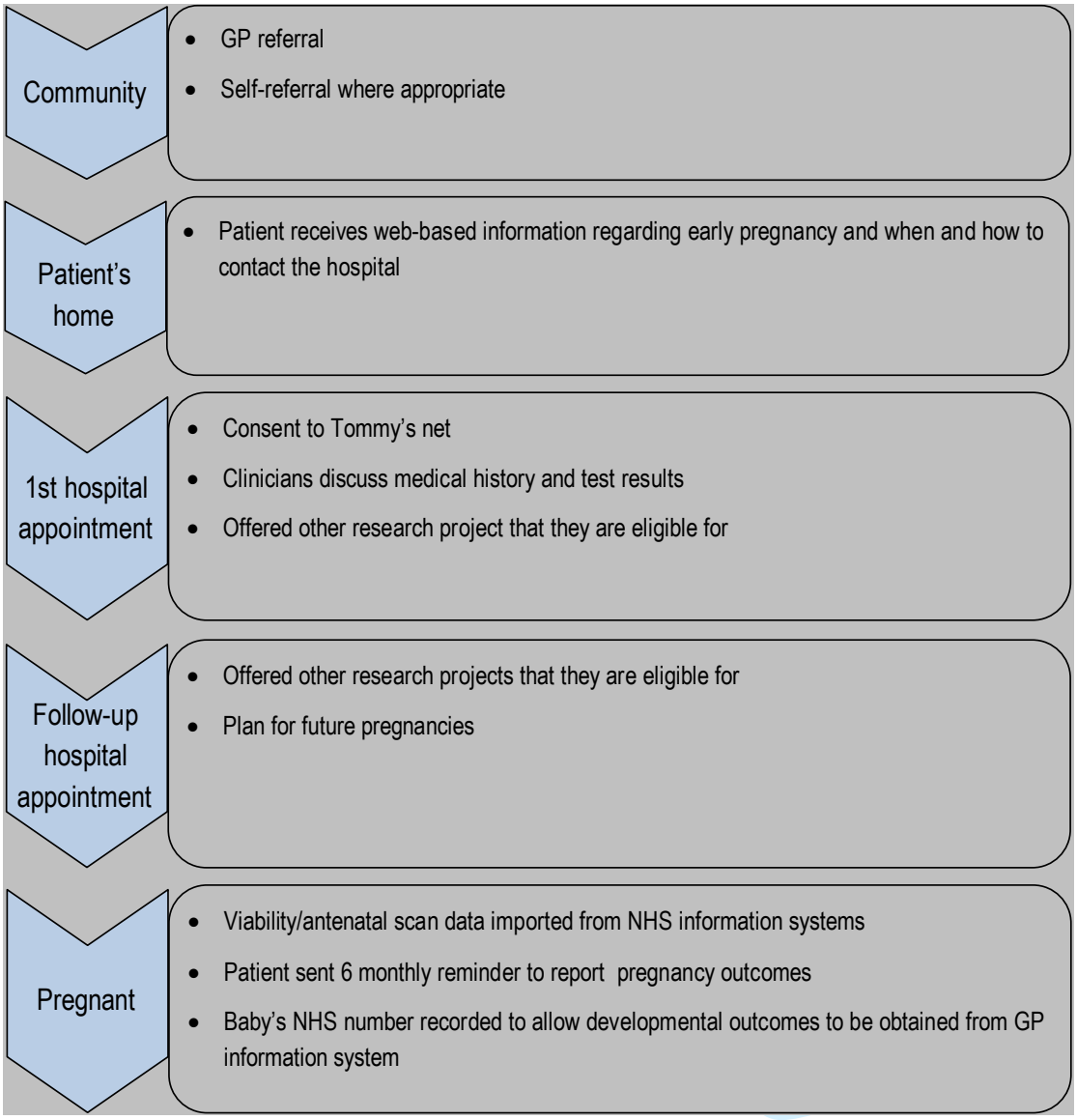

Figure 2. Tommy's Net flow diagram for emergency patients

3.4 Duration

This project is funded for 5 years initially but we would hope this to be renewed.

3.5 Inclusion criteria

- Couples with a history of one or more pregnancy losses;
  - Miscarriage
  - Molar pregnancy
  - Ectopic pregnancy

- Stillbirth
- Bleeding in early pregnancy

3.6 Exclusion criteria

Decline to consent to having their information stored.

3.7 Methods

Couples will be referred by their GP or self-refer. They will then be sent information about Tommy's Net by post and directed to websites (PIS) as well as other trials, the standard NHS information about the clinic and a history sheet. Patients can attend in person or have a telephone consultation:

When they arrive at the clinic a member of the research team will explain Tommy's Net and ask them to consent to the study. If they consent they will be asked to fill the Tommy's Net registration form on paper, after which, their data will be entered on an online system, this will include demographics information, reproductive history, delivery details and related test results. They will then see the clinician who will discuss their history and advise on further investigations and eligibility for other studies and trials.

Prior to telephone consultation the patient will be contacted by telephone and directed to Tommy';s net online consent form. If consented they will be directed to an online registration form and asked to complete this prior to review in the telephone consultation. ~~When they arrive at the clinic a member of the research team will explain Tommy's Net and ask them to consent to the study. If they consent they will be asked to fill the Tommy's Net registration form, after which, their data will be entered on an online system, this will include demographics information, reproductive history, delivery details and related test results. They will then see the clinician who will discuss their history and advise on further investigations and eligibility for other studies and trials.~~

All existing relevant investigation results will be imported into the trial database system (Tommy's Net) from existing hospital systems (for example CRRS/Lorenzo). Where investigations relate only to the trial, the data from these will be entered directly into the trial system. Tommy's Net will assist in the production of the clinic letter to the GP and patient as a record of this visit. Thus as well as being a research tool the Tommy's net will facilitate the clinical service. Other related trials will have separate ethical approvals.

Follow up appointments will be offered by telephone or in person to discuss investigation results and plan future pregnancies. Tommy's Net will produce a letter to the GP and patient as a record of this visit which will fit into existing NHS systems this will be in place of the current letter to the GP following an appointment.

In future pregnancies, patients will be offered viability scans in the first trimester and information about these scans, as well as the anonymized scans themselves, will be stored on Tommy's Net. These will be imported from the current Viewpoint, digital, ultrasound results storage system. Participants' details will be updated during these visits (including BMI, smoking status, alcohol intake and folic acid use).

Patients and their partners will be asked to complete an optional anxiety questionnaire (Generalised Anxiety Disorder Questionnaire, GAD-7) prior to the initial ultrasound in each pregnancy and following each subsequent ultrasound. Scores will be recorded on Tommy's net. Any patient scoring over 10 will be offered additional support from the staff at the Biomedical research unit and referred to their GP if required.

Information about antenatal care including, serum screening, booking scans, anomaly scans and growth scans will be recorded (imported from Viewpoint where they exist or entered directly into the research system if inappropriate for the clinical record).

Pregnancy outcome details will be requested from the patient either by filling in a paper copy, which can then be entered into the system via an authorized researcher or by direct patient entry into an online, link anonymised, patient accessible system, hosted at the University of Warwick, every 6 months. The data collected by this system will be transferred to the Tommy's Net system hosted at the hospital, and deleted from the University system, after review by the research midwives. Women will be sent reminders to update us regarding their reproductive outcomes 6 monthly (these can be automated if the patient consents to having their email address or mobile phone number registered on the system to be used for reminders). They may also receive information/support text messages 6-12 times annually.

The baby's NHS number will be requested through appropriate consent so that follow up of the baby's development could be facilitated. Information regarding developmental follow up will be requested from GP records. During the project, direct connections to GP sockets will be developed to facilitate sharing of information, and avoid duplicate data entry, in the presence of approved data sharing agreements.

3.8 Recruitment and consent

The underlying principle of the Centre is that patients should give informed generic consent to use their data in the medical research relating to the Tommy's National Centre for Miscarriage Research. Consent will be obtained within the clinical setting, or over the telephone via an online consent form, by a trained member of the team in accordance with Good Clinical Practice.

For male participants, they will either be consented face to face in a clinical setting if they attend with their partner, or over the telephone via an online consent form. If not, the documents will be posted out to them and they will be asked to complete the questionnaires and consent form at home and return it with their partners at the next clinic appointment or post it straight back to the study office. They will be offered the opportunity to speak to a member of the research team on the phone if they are uncertain about any aspect of the questionnaire or consent form.

In some cases participants fill in the registration form with their clinical details which are stored in the clinical notes but have not signed the consent forms. In these cases participants will have the PIS and consent forms posted to them and they will receive a telephone call from by a research nurse or midwife to ensure they understand the study and to ask them to sign the consent form online or ~~and~~ post it back.

Standard Operating Procedures will be used that clearly set out the processes of obtaining consent, data collection and storage, and define the roles and responsibilities of the parties involved. All documentation associated with obtaining informed consent, e.g. patient information sheets and consent forms, will be approved by the Host institution, REC and HRA. The responsible team member will confirm eligibility, encourage open discussion and answer any questions that patient(s) may have. The consent discussion will be noted in the medical record along with the signed consent form which should be retained in support of data collection. A copy of the consent form will be given to the patient.

3.9 cohort multiple Randomised Controlled Trial (cmRCT) design

In addition to providing consent for the Tommy's Net cohort study, participants will also be invited to join a cohort multiple Randomised Controlled Trial (cmRCT), which is embedded in Tommy's Net. cmRCT is a relatively new trial design that simplifies the recruitment and conduct of trials compared with current RCTs (12). In this trial design, participants are asked to agree to participate in the control arm of any future trials that will be conducted by the research team. Once a substantial cohort of participants has been established that have given their consent to participate in the cmRCT, one is able to conduct a trial by identifying and selecting a random sample of participants who will receive the intervention, and another group that will continue to receive standard care. Those patients that are allocated to the intervention will be invited to give their written, informed consent to participate in the intervention arm. However, those allocated to standard care (control arm), can continue to be followed up in the usual way with no additional contact required. Relevant outcomes and other measures are taken on all patients in both arms as part of the regular follow-up process. A large benefit of this trial design is that the same cohort can be used for multiple interventions, so are large number of clinical trials can be conducted within the same core cohort of patients.

The detailed description of each trial will be provided in Appendix 1 of this protocol. A substantial amendment will be submitted to the responsible REC each time a new trial is embedded within this cohort and added to the protocol.

3.10 Withdrawal

A patient is entitled to withdraw consent at any time. They should either inform the clinician responsible for their care, contact the Centre directly, or contact the Research and Development Office within their Trust. Withdrawal of consent, and details of all data involved, will be recorded by the Centre. They will also be able to leave their data but decline to receive reminders to update us with their reproductive

history outcomes. Any data on explicitly withdrawn patients will be removed from the database.

3.11 Documentation and confidentiality

The clinical information system will reside within the University Hospital Coventry and Warwickshire NHS trust (UHCW). At UHCW there is an Information Governance Framework in place that represents itself as the annual Information Governance Tool Kit assessment. This is a key performance measurement for the trust and comprises of the following;

- Robust management and accountability for all aspects of information governance.
- An information governance committee with direct accountability to the quality and Governance committee, that is chaired by the Director of Corporate affairs and has access to appropriately skilled expertise across the entire Information Governance Agenda
- There is a register of all major information assets with assigned responsibility for each asset.
- Information risks are managed, were applicable though owners of information assets and linked to established risk management processes and governance arrangements.
- There is an effective information security even reporting and management processes and governance arrangements
- There is an effective information security event reporting and management procedures in line with Department of Health policies and guidelines
- There are formal contractual arrangements in place with all contractors and support organizations and that these include compliance with information governance requirements.
- Policies and procedures are documented to ensure compliance with common law obligations of confidentiality, Current Data Protection legislation and the NHS Care Record Guarantee . Key areas include but are not limited to:
    - Consent and management and ethical practice
    - Information sharing protocols
    - Fair processing
    - Subject access request and other GDPR requirements
    - Confidentiality code of conduct
    - Business continuity and disaster recovery
    - Physical security
    - Network security
    - Remote/home/teleworking
    - Secure data transfer
    - Access controls and access management
    - Data and media destruction
    - Local data warehousing
    - Cross boundary information sharing
    - Records management

- Data flow mapping
- Record retention
- Archiving
- Data quality including NHS number implementation

The database will be hosted at University Hospitals Coventry and Warwickshire on secure servers, specific members of the Institute of Digital Healthcare, WMG, and University of Warwick will be given access to the server to administer the system. Information from other sites will be transferred through the secure NHS N3 network (n3.nhs.uk). Data stored will remain on the UHCW network and no data will be transferred to the IDH. Any patient identifiable data required for the trial will, similarly, be kept at the Trust sites, linked to the data stored within the system via a unique identifier, all data stored outside the trusts, e.g. for the purposes of statistical analysis, will be appropriately anonymised.

Certain information from participants consented to the Tommy's National Centre for Miscarriage Research study (Trial IDs, mobile numbers and email addresses) will be transferred securely to the University of Warwick hosted online survey system in order to collect follow up information. Only the IDH administrators and hospital research team will have access to the system. Automated invitations will be sent via SMS (or email if a mobile phone number is not available). A welcome message will be sent asking to confirm mobile phone number, followed by 6monthly requests for information. This invitation will consist of a one-time use link allowing the Tommy's team to trace the responses back to the patient identifiable baseline information, stored at UHCW. No identifiable information will be sent out in communications and no participants or members of the public will be able to access stored information (unless through a data subject request). The data collected, through the secure patient portal, will not be identifiable (will not contain the patient details section of the follow-up form) and will be transferred to the hospital and subsequently deleted from the system after review by an authorised research midwife. Patient may also receive up to 6-12 text messages a year for support/information.

The initial SMS will read: Thank you for joining Tommy's net. You will receive 6monthly texts with a link to a short questionnaire. Click here (LINK) to confirm your number. Tommy's
The 6monthly follow up will read: Update your record quickly by completing this questionnaire (LINK). All information will be used to improve our understanding of miscarriage. Tommy's
A reminder message will be sent around 48hours and 96hours.

Examples of the information text messages:

- Emotional well-being is important when trying to conceive and when pregnant. See tommys.org for support (LINK)
- Tommy's net has been looking at weight in couple's who are trying to conceive. For support in optimizing your weight visit tommys.org (LINK)
- It can be difficult to stop smoking. See tommys.org (LINK) for help and advice

- Folic acid is important when preparing for a pregnancy and in the first 12 weeks to help the baby's spine develop. See tommys.org (LINK)

Management of the database will be subject to the NHS IG Tool kit and Standard Operating Procedures in place at the IDH. Specifically, access to the clinician/research portal will be limited to authorised users on NHS computers, access to the data will be allowed according to the user's role:

- Principal Investigators will have access to all patient information at their site, including patient identifiable information stored at their trust. They will also have access to anonymised data originating from other sites. They will be able to create new records and modify records they have entered (all of which will be logged by the system)
- Researchers will only have access to anonymised data but will be able to view information across sites. They will not be able to modify data.
- Data Managers, such as the database administrators at the IDH will not have access to the web portal and will not be able to read the raw data.
- Once a patient portal is developed, this will be accessible through a secure web login by registered patients. Patients logging in to the patient portal will only be able to see their own data and will be able to submit new data for review by the site PI.

Access to existing hospital systems from Tommy's Net will be restricted to those results relevant to the trial and only the treating clinician will be authorized to view and import this data from any hospital or healthcare system. Any data copied to or from the trial system will only be transferred through encrypted channels to ensure data is kept secure at all times.

The research system has been validated through functional and user testing and approved use cases have been documented. An approved process for failure recovery is also in place which ensures that, even in the event of catastrophic failure, the system can be restored within 2 working days and, at most, 1 days' worth of data will be lost.

3.12 MHRA Compliance

The trial database developed complies with MHRA requirements as detailed in the Annex 11 guidelines published under Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and the electronic record requirements for Good Clinical Practice:

- Data integrity is ensured via ongoing data review.
- There is a clear and documented change control process which ensures all changes are approved and have a clear audit trail.
- Any changes to the data within the system is logged automatically, time stamped and recorded along with the user who made the change.

- All information entered into the system can be reviewed by the investigator regardless of who entered the data.
- Originals of any scans or images imported into the system will be kept on their respective clinical systems and appropriate quality controlled procedures will be used to anonymize the images.
- Access to trial data and audit trails can be granted to inspectors and sponsor representatives for auditing and monitoring purposes.
- Data and metadata on the system can be archived in accordance with Clinical Trials Regulations for up to 25 years.
- Written procedures are in place to cover all the above processes.

In addition to the above mentioned procedures, Trust R&D will be granted oversight access to the research system allowing them to detect and report any breaches of GCP.

Customisation of the trial system for Tommy's will be conducted in collaboration with the investigators to ensure the sponsor's established requirements for completeness, accuracy, reliability and performance are met. The design process and user requirements will be documented. Standard Operating Procedures (SOPs) will be drafted and maintained for the use of the system.

3.13 Data access and sharing

The underlying principle of the Tommy's National Centre for Miscarriage Research is that data stored within Tommy's Net is made available to all the research centres that have been granted approval by the responsible ethics committee. This provides a reciprocal arrangement whereby anonymised data can be uploaded to Tommy's Net and then shared between all approved parties within the Centre. The Centre has procedures in place to ensure the security, confidentiality and data protection of the collection. The aim is to ensure that researchers do not have access to personal identifiers through these data.

All stored data that relates to specific research projects within the Tommy's National Centre for Miscarriage Research will have obtained separate ethical and regulatory approval where appropriate. This will have been obtained for the site responsible for each specific research project with approval for the data access and sharing arrangements described above.

3.14 Analysis

The data will be interrogated so that all clinics will have anonymized information on:

- Numbers and demographic of attendees.
- Running live birth rates per clinic and per subgroup.
  For each investigation undertaken by the NHS clinical service the investigation will be assessed for its ability to predict pregnancy outcome. Mathematical models will be created in liaison with appropriate statisticians to

construct outcome prediction using demographic data and investigation results. Aurelio Tobias a statistician with significant expertise in outcome prediction will advise on the outcome prediction models used.

- A semantically enabled query tool will be developed alongside the research database to allow clinicians and researchers to query anonymized information stored in the database for initial hypothesis testing.
- Further ethical approval will be sought for other studies involving tissue collection. Once results from these new test are available they will we assess with the outcome prediction models that have been developed.

4. Study supervision

The investigators who will receive progress reports every 4 months will oversee the study. The Warwick investigators and representative from Birmingham and Imperial and will have twice monthly virtual meetings to report on the progress.

5. Ethics and Sponsorship & indemnity

The study will be conducted in compliance the principles of the ICH GCP guidelines and in accordance with all applicable regulatory guidance, including, but not limited to, the Research Governance Framework. Ethical approval for this study will be sought from the Research Ethics Committee combined with Health Research Authority (HRA) approval. No study activities will commence until favorable ethical opinion and HRA approval has been obtained. Progress reports and a final report at the conclusion of the trial will be submitted to the approving REC within the timelines defined by the committee. Confirmation of capacity and capability will be obtained from the R&D departments obtained prior to commencement of the study at all participating sites.

UHCW NHS Trust has agreed to act as sponsor for this trial and will undertake the responsibilities of sponsor as defined by the UK Policy Framework for Health and Social Care Research and ICH Good Clinical Practice. An authorised representative of the Sponsor has approved the final version of this protocol with respect to the trial design, conduct, data analysis and interpretation and plans for publication and dissemination of results.

“The study will be monitored by the Research and Development Department at UHCW as representatives of the Sponsor, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The

approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study."

As sponsor, UHCW provides indemnity for this trial and, as such, will be responsible for claims for any negligent harm suffered by anyone as a result of participating in this trial. The indemnity is renewed on an annual basis and will continue for the duration of this trial."

6. Publications policy

All publications arising from this data will be agreed by all investigators prior to submission.

7. Intellectual property

The legal arrangements relating to intellectual property (IP) will be adhered as per the signed agreement between Tommy's Charity and the University of Birmingham (lead site for the Tommy's National Centre for Miscarriage Research).

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Appendix 1. cmRCT protocols

BMJ Open

Quantitative assessment of pregnancy outcome following recurrent miscarriage clinic care: a prospective cohort study

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Quantitative assessment of pregnancy outcome following recurrent miscarriage clinic care: a prospective cohort study

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Quantitative assessment of pregnancy outcome following recurrent miscarriage clinic care: a prospective cohort study

Abstract

Objectives

To measure pregnancy outcome following attendance at a recurrent miscarriage service and identify factors that influence outcome.

Design

Prospective, observational electronic cohort study.

Setting

Participants attending specialist recurrent miscarriage clinic, with a history of two or more pregnancy losses. 857 new patients attended over a 30month period and were invited to participate. Participant data were recorded on a bespoke study database, 'Tommy's Net'.

Participants

777 women consented to participate (90.7% of new patients). 639 (82%) women continued within the cohort, and 138 were lost to follow up. Mean age of active participants was 34 years for women and 37 years for partners, with a mean of 3.5 (1-19) previous pregnancy losses. Rates of obesity (maternal: 23.8%, paternal: 22.4%), smoking (maternal:7.4%, paternal: 19.4%) and alcohol consumption (maternal: 50%, paternal: 79.2%) were high and 55% of participants were not taking folic acid.

Outcome measures

Biannual collection of pregnancy outcomes, either through prompted self-reporting, or existing hospital systems.

Results

639 (82%) women were followed up. 404 reported conception and 106 reported no pregnancy, at least six months following registration. Of those that conceived, 72.8% (294/404) had a viable pregnancy. Analysis identified a conception rate of over 80%, with 16.6% not conceiving at least six months after joining the cohort, and viable pregnancy rate of 60% two years after attending the clinic. Maternal smoking and BMI over 30 were significantly higher in those who did not conceive (p=0.001)

Conclusions

Tommy's Net provides a secure electronic repository on data for couples with recurrent pregnancy loss and associated outcomes. The study identified that subfertility, as well as repeated miscarriage, maternal BMI and smoking status, contributed to failure to achieve live birth. Study findings may enable comparison of clinic outcomes and inform the development of a personalized holistic care package.

Strengths and Limitations of this study (related to the method)

- The 'Tommy's Net' e-repository and associated database contains baseline and prospective pregnancy outcome data from the largest known population of couples with recurrent miscarriage in the UK.
- Time to conception and viable pregnancy can be calculated from this data using time to event analysis.
- Obtaining follow up data is challenging but can be improved by using a variety of data collection methods.
- Follow up data is only requested biannually, therefore this is an inevitable lag in data collection.
- Limited use of the English language can be a barrier for participants completing the initial lengthy questionnaire.

Introduction

Miscarriage, the loss of a pregnancy prior to viability (24 weeks gestation) is common, with 15% of pregnancies ending in miscarriage[1,2]. Most miscarriages are sporadic and occur before 12 weeks gestation[3]. Recurrent miscarriage (RM) is defined as two or three (or more) consecutive miscarriages[4,5]. It is estimated that 1.9% of women experience two consecutive miscarriages, and approximately 0.7% suffer three or more consecutive miscarriages [1,6,7]. In recurrent miscarriage, the incidence of euploid fetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases[8]. Recurrent miscarriage is a debilitating disorder, associated with considerable psychological morbidity[9].

European and national miscarriage care guidelines recognise the importance of providing good physical care and psychological support[4,5] however there are no standardised outcomes to assess care within clinics. The recent Lancet series[1] on miscarriage which brought together best evidence and expert opinion, clearly outlines essential investigations for couples, dependent on their history, together with a graded model of care to optimise outcome. This could address deficiencies identified by couples in a systematic review by MMJ van den Berg and colleagues (2018)[10], which evaluated features of care that couples valued within miscarriage services, identified that explaining potential causes of pregnancy loss and planning for future pregnancies were specific areas for improvement.

Accurate information following attendance at a recurrent miscarriage clinic is important for couples' counselling, stratifying care and directing research. Whilst data does exist around outcomes in a recurrent miscarriage setting[3,11,12] it requires prospective update from clinics working under standardised guidance[4], including all couples regardless of their outcome and not only those who conceived or who participate within a research trial.

The Tommy's National Centre for Miscarriage Research brings together an interdisciplinary Translational Medicine research grouping jointly at the University of Warwick, University of Birmingham and Imperial College London. The Centre is dedicated to research across all aspects of miscarriage and early pregnancy complications including medical, basic scientific, social and ethical issues. A secure electronic data collection tool and e-repository (with associated database), Tommy's Net, has been developed to facilitate recording of participant data, including follow up[13].

Objectives

Our objective was to quantify the long term cumulative live birth rate after first attendance at a recurrent miscarriage clinic. A cohort of couples was developed, with prospective data collection of the medical and obstetric histories of both partners, investigation results and pregnancy and neonatal outcomes. The tool for collecting data on this cohort is designed to be used in multiple clinics so that success rates between clinics can be benchmarked. This objective will also allow clinics to support and assess new care pathways, identify areas needing further research, develop outcome prediction modelling and investigate new tests in future clinical trials.

Methods

The e-repository and associated database has been developed over several years by a team with representation from University Hospital Coventry and Warwickshire (UHCW) NHS Trust and University of Warwick, Imperial College and University of Birmingham. The cohort was initiated at UHCW but designed so other clinics can join.

Sponsorship, Ethics, Data management and Information Governance

Sponsorship (from primary hospital Trust), ethical permissions (IRAS No: 213740, 2225751 REC Ref: 17/WM/0050: 17/WM/208) and adherence to information technology governance standards was obtained. The study database complies with the regulatory requirements for Good Clinical Practice.

Patient and public involvement

An established patient and public involvement (PPI) group from within the Tommy's centre at UHCW was consulted during initial protocol development. Two further PPI sessions with 10 service users, each including 9 women and 1 partner, where consulted to ensure follow up methods where acceptable to participants and to optimise response rates.

Setting

This cohort was established within a specialist recurrent miscarriage clinic in a tertiary referral centre (UHCW) within the UK. Miscarriage care followed European Society of Human Reproduction and Embryology (ESHRE) guidelines[4].

Eligibility

All couples with a history of two or more pregnancy losses (including biochemical loss[1]*, miscarriage, molar pregnancy, ectopic pregnancy and stillbirth) were eligible (supplementary file 1).

Recruitment

Couples are referred to the recurrent miscarriage clinic by their General Practitioner (family doctor). Signposting prior to referral can occur from other hospital departments (e.g., Early Pregnancy Assessment Unit, Acute Gynaecology, Fertility unit) or charities (e.g., Tommy's, The Miscarriage Association). Couples are then sent information about Tommy's Net by post along with a baseline questionnaire (supplementary file 2). At their first clinic visit a member of the research team explains Tommy's Net and asks them to consent to storage of their data.

Data Collection

Both partners complete initial baseline questionnaires including demographic details, obstetric and medical history. Investigation results, blood pressure and body mass index (BMI) are recorded by clinic staff and entered into Tommy's Net (supplementary file 2).

The Tommy's Net e-repository and database system, used for data collection and storage in the study, is based on the CURe framework[13,14], a modular system for collecting research data in secondary care settings. The framework includes methods for the standardised, flexible capture and storage of data. The system is intended to link to the participating centre's clinical information

1. * Defined as no pregnancy identified on ultrasound scan

systems where possible to access relevant data already collected, such as laboratory test results. Tommy's Net includes a database to organise data collected as part of the study and a web application for healthcare professionals to use for data entry, review and use in clinic (supplementary file 3). Data in Tommy's Net can be exported for analysis. The development of Tommy's Net has seen continuous improvements based on feedback from clinicians, researchers and patients. The design of the system is intended to promote interoperability with existing hospital systems to allow researchers to use information already collected, collect pregnancy outcomes to benchmark clinics and allow researchers to identify high risk groups of patients for future research.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics. Time to event analysis was performed using Kaplan-Meier curves, a non-parametric method for assessing the probability of an event occurring over time. Multi-variant analysis was conducted using age, BMI, cigarette smoking status, alcohol consumption and use of folic acid.

Retention and Pregnancy Outcomes collection

A variety of methods were assessed to collect patient reported pregnancy outcomes after the first clinic visit. Initially women were encouraged to self-report outcomes by telephoning the clinic or completing an outcome collection form sent by email. Automated invitations to complete this survey are sent via SMS every six months requesting information for follow up. This invitation consists of a single use link allowing the research team to trace the responses back to the patient identifiable baseline information.

Further outcome data are collected through viability scan visits, which can be accessed following initial review in the recurrent miscarriage service and using existing hospital systems. Researchers used a maternity database, Evolution©, and a local intranet service to improve follow up and to validate participant reported information.

Using a variety of methods to collect outcomes improves follow up rate, however this does require researcher vigilance to avoid duplicate data entry. 17.8% of participants are still lost to follow up, therefore more work is needed in this area to encourage continuous engagement of participants (fig 1).

Improving baseline data

In the first three months of recruitment, a number of couples (n=83) consented to the study but did not complete the baseline questionnaire. This resulted in their data being marked as 'inactive' within the database (i.e., consented to the cohort study but not returned initial baseline questionnaires). On receipt of the baseline questionnaires, participants are 'activated' and followed up six monthly (n=10/83 to date). Our process has been updated so critical data items are collected by the clinician from all couples who consent before leaving the initial clinic appointment. Participants are no longer registered within the database until they have completed the initial baseline questionnaire.

Improving pregnancy outcome data collection

Initial pregnancy outcome data collection was poor with only 25% reporting their outcome, mainly due to technical difficulties in completing electronic versions of the forms for the participants. The response rate has gradually improved with development of a text message system. This was followed by other improvements such as a series of changes to the text message wording, by including partners in the messages, and changing the timing of the texts (with the majority sent in the afternoon or evening). Reminder messages are sent after 48 hours and after one week (if no responses from the initial text are received). Changes have been informed by patient and public involvement (PPI) groups, which were used to understand further why participants fail to respond to follow up SMS text message. Some explained that once they had had a baby, they were busy with their baby and forgot to reply. Conversely, repeated reporting of no pregnancy, or miscarriage was felt to be disheartening, or less important. We hope through education and careful wording of the questionnaire the response rate will continue to improve.

These approaches have contributed to an increase in response rate and combined with data from existing hospital systems, the response rate for pregnancy outcomes was 82.2%.

Data linkage with a general practice database was not deemed useful, because few miscarriages are recorded on the local general practice databases. Furthermore, there was a lack of standardisation in pregnancy data in primary care, though automated links with both primary and secondary care electronic health systems are still planned. The maternity services database may provide a fruitful source of pregnancy outcome data in the future.

Results

Analysis of cumulative live birth rate

Between May 2017 and January 2020, 777 women (and 480 partners) who attended the recurrent miscarriage clinic completed a baseline questionnaire and consented for their data to be included in the database (fig 1). One hundred and thirty-eight (17.8%) participants were lost to follow up (no response to SMS, or information obtained for hospital databases), therefore 639 women are active within Tommy's Net. One hundred and thirty-four of these women are within six months of consenting to the study and have not yet received a scheduled SMS. Five of these women have reported conceiving out with the SMS system with the data captured through early pregnancy scan clinics. Of the active women, their mean age was 34 years (table I) and mean number of previous pregnancy losses was 3.5 (range 1-19). Demographic characteristics including age, ethnicity, alcohol intake, folic acid use and previous live births were not statistically different between participants who conceived and those who did not (table I). Statistically more participants who did not conceive smoked and had a BMI over 30.

	Total number active patients continuing in cohort	Those that did not conceive within the continuing cohort	P value
Number	639	106	
Age mean (range)	33.7 (18-46)	34.03 (22-47)	0.092
Ethnicity	White: 84% (436/519) Mixed: 2.1% (11) Asian: 8.9% (46) Black: 3.3% (17) Other: 1.7% (9) Unknown (120)	White 85.5% (65/76) Mixed: 2.6% (2) Asian: 6.6% (5) Black: 3.9% (3) Other: 1.3% (1) Unknown (30)	
Average no. of previous live birth	0.6	0.15	0.36
Average no. of previous miscarriages	3.5	3.6	
BMI over 30	23.8% (n=126/530)	30% (n=26/87)	0.001
Smoking Y/N	Yes:41 (7.4%)	Yes: 12 (13.5%)	0.001
Alcohol Y/N **Units**	Yes: 278 (50%) 5.54 (0.5-30)	Yes: 51 (58%) 5.03 (0.5-35)	0.083 <0.001
Folic acid	Yes: 292 (45.5%)	Yes: 35 (47.17%)	<0.001

Table I: Comparison of demographics for all active participants, participants that did not conceive and those that were lost to follow up

Pregnancy results

Four hundred and four of these women reported conceiving. One hundred and six (16.6%) women reported no pregnancy at least six months following registration, 31 (4%) of whom are no longer trying to conceive. Of those that conceived 72.8% (294/404) had a viable pregnancy (215 live births, 1 stillbirth, remainder currently >24 weeks at time of initial analysis). Analysis of data exported from the database in January 2020, revealed a conception of rate of 81% after two years within the cohort and viable pregnancy rate (pregnancy over 24 weeks or live birth at time of export) of 60% two years after attending the recurrent miscarriage clinic (fig 2). Age does impact on time to conception and time to viable pregnancy, with women of 25-34 years being more likely to have a viable pregnancy two years after initial review than other age groups (fig 3). Partner age within this cohort did not

have a marked effect on time to conception or viable pregnancy, particularly within the first year after initial consultation.

After one year in the cohort there is a 30% difference between the number of couples who conceive and those who reach viable pregnancy. This difference/gap gradually decreases and plateaus after 900 days to a difference of 19% (conception rate 82% with 63% reaching over 24 weeks gestation). The couples within this 'gap' represent those within our clinic who conceive but miscarry prior to viability despite current intervention and support. This gap is maintained within the 30-39 years age group but is less pronounced within those who conceive aged 25-29 years (fig 3). Female BMI over 30 and female smoking status along with miscarriage history increases the time from initial consultation to conception and viable pregnancy within this patient group (fig 4-6). Partner BMI, smoking status or alcohol intake did not impact on time to conception or time to viable pregnancy.

A healthy BMI increases the chance of viable pregnancy, particularly when compared to a maternal BMI over 30kg/m2 (fig 4). Having a BMI over 30 increases the time taken to viable pregnancy by 100-200 days. Within this population BMI does not appear to significantly change the time to conception (fig 7), particularly within the first 300 days.

Couples who have had four or more miscarriages take longer to conceive, compared to couples who have has three or less miscarriages (fig 5). There is a 17% gap within couples who have had four or more losses when comparing the rate of conception with viable pregnancy. This gap represents those that continue to miscarry and should be a population where research should be focused.

Smoking status impacts on time to conception (fig 6). Females that smoke take longer to conceive with significantly more never conceiving.

Discussion

Database

We have developed an electronic method of obtaining outcomes from women following attendance at a recurrent miscarriage clinic. These outcomes can be used to assess recurrent miscarriage care and form a 'benchmark' to compare clinical services and interventions. The electronic cohort provides clinic outcome data in real time (supplementary file 3), and can be used for counselling couples as to both the chance of their next pregnancy succeeding and their cumulative time to live birth. This is novel, as data[3,11,12] identified at literature review could not be generalised to the UK population. Lund and colleagues[11] used a national, Danish registry to collect live birth data from attendees up to five years after their visit to a recurrent miscarriage clinic. Registry data were collected retrospectively and lacks information from couples who moved to other countries. Brigham[3] analysed 716 couples over a 10-year period in their Liverpool clinic, with pregnancy outcome data on 325 patients with unexplained recurrent miscarriage. Data were only reported on those who conceived and had their pregnancy and birth care at the same hospital. These datasets are now over 20 years old. Kling and colleagues[12] published more recent data based on a tertiary referral immunological centre within Germany. Seven hundred and nineteen couples were followed up for a median of 33.7 months, producing time to pregnancy and time to delivery over a five-year period. Whilst this is valuable data the study excluded couples who already had children within the partnership (25% within our clinic) and used immunotherapy in a proportion of couples which is not routinely used within the UK. It also asked for patient reported outcomes between nine months to

four years after the event which could be prone to recall bias. This database will continue to collect and provide prospective outcomes of all those who attend this recurrent miscarriage clinic and, as use increases within the other sites it will allow comparison of outcomes with the aim of sharing good practice to improve patient care.

Infertility

The time to conception curve within our RM population is similar to that in the general population[15,16]. Analysis to date has identified that within our cohort 16.6% (n=106) of couples fail to conceive within the follow up period. These patients are similar ethnicity when compared to all within the active cohort. They do have a trend to a higher BMI and are statistically more likely to smoke. Whist the mean age was similar in those conceived and those who did not, the expected effect of age on conception was demonstrated with a lower conception rate after two years in those over 40years old.

Reasons why couples do not conceive are complex. Couples were encouraged to conceive immediately from first consultation, whilst investigation results are awaited. Anecdotal evidence from the text message system and PPI groups shows some couples feel unable to continue trying to conceive due to the potential risk of miscarriage. Recent research[17] has highlighted an increased risk of post-traumatic stress disorder following pregnancy loss. We hypothesise that the psychological impact of miscarriage may stop couples from trying to conceive again. This is an important area on which to focus research and facilitate additional counselling and support.

Other couples may be unable to conceive despite actively trying. Identifying this subgroup of couples earlier could facilitate prompt referral to fertility services for assessment and treatment. Potentially increasing their chance of conception and ultimately live birth. Within this population, the rate of conception decreases significantly one year after initial consultation (fig 2). 65% of couples conceive within one year of initial consultation, with only an additional 15% conceiving in the second year. In view of this decrease in pace of conception we suggest referral to fertility services should be considered within this population after one year.

Through-out the UK, access to NHS funded fertility treatment is dependent on maternal weight, smoking status, as well as age and parity. Addressing these factors early in the couple's fertility journey may help to manage expectations prior to referral and reduce any delay in starting treatment. We recognise that weight particularly can be a sensitive issue and difficult to manage. Open and honest discussion, without blame, along with support and advice that joining group programmes for exercise and dietary modification can lead to more pregnancies than weight loss alone[17] should be given. Referral to specialised weight management services including bariatric dietetic and surgical teams could be discussed if appropriate.

There may be a role for ovarian reserve assessment for women who have previously taken over 12 months to conceive. Having strong links, or an integrated multi-disciplinary preconception service may allow a more cohesive approach to these couples and increase their chance of having a viable pregnancy as well as providing continuity of medical and psychological care.

Outcome Data

Comparing the 'time to conception' and 'time to viable pregnancy' curves illustrate the importance of assessing cumulative data. There is by definition a lag between conception and reaching 24 weeks pregnant, but following this the difference between the curves represents delay in live birth due to miscarriage. This gap decreases initially and may represent an impact from interventions and support within the recurrent miscarriage service. The importance of support to couples will be studied further during a planned qualitative study using semi-structured interviews of affected couples. After 900 days the gap between the curves is static and represents those whom despite conceiving have not yet had a child. This is a group which resources and research should be targeted to further understand reasons for miscarriage.

Health Education

It is well documented that miscarriage risk increases with BMI over 30kg/m2 and smoking status[16, 18, 19, 20, 21]. Despite this 23.8% of women within the cohort have a BMI over 30kg/m2 and 7.4% smoke tobacco. Modifying these lifestyle factors through pre-conception counselling may reduce the chance of miscarriage and improve pregnancy outcome by reducing the incidence of, for example, gestational diabetes. Future research could be targeted at support in weight loss and smoking cessation.

Limitations and strengths

The Tommy's Net e-repository and associated database contains baseline and prospective pregnancy outcome data from the largest known population of couples with recurrent miscarriage in the UK. It allows calculation of 'time to conception' and 'time to viable pregnancy' using time to event analysis. This large dataset aims to facilitate future studies within a recurrent miscarriage population.

Obtaining follow up data is challenging. Using a variety of methods including self-reporting through the text message link and local hospital systems has improved our follow up rate.

Couples with limited English were unlikely to complete the lengthy questionnaire, which is currently only available in English. This means that this study is likely to miss high risk groups within our community

The introduction of the maternity services database could provide a valuable resource to enable improved follow up. Couples attend this RM clinic from all over the UK. Currently couples who deliver within our trust have at least two ways in which we can capture their outcome (SMS text message and hospital database with or without scan clinic information). These checks are not available to couples who have travelled some distance to attend and therefore may be under-represented within the active participants group.

SMS text message requests for follow up are only sent every six months. This means that for the first six months that participants are within the study we do not expect to collect any outcome data. Some of these participants may go on to become 'inactive' and be removed from analysis.

Conclusion

We have developed a user-friendly electronic database, storing comprehensive data, which can provide accurate time to conception and data on viable pregnancies to facilitate analysis into factors

contributing to recurrent miscarriage. 16.6% of women within our clinic did not conceive and early referral to fertility services should be facilitated. Over 20% of women within the cohort have a BMI of over 30 and 7.4% smoke. Preconception counselling should be targeted at weight and smoking status with an aim of reducing miscarriage.

Contributorship statement

SQ had the initial concept. OK, SLCK and TNA designed and developed Tommy's net database and extracted initial data. RCS analysed the data and interpreted it along with SQ. RCS wrote the initial draft, which was revised by SQ and DB, and reviewed by AH, OK, SNLCK, TNA, AB, AD, SDQ and SK. All commented on initial drafts and approved the final version.

Competing interests

Nil

Funding

Tommy's Baby Charity (award number N/A)

Data sharing statement

Data Available on Reasonable Request (under ethics restrictions).

Ethics statement

Ethical approval for was obtained from West Midlands- South Birmingham Regional Ethics Committee IRAS No: 213740, 2225751 REC Ref: 17/WM/0050: 17/WM/208

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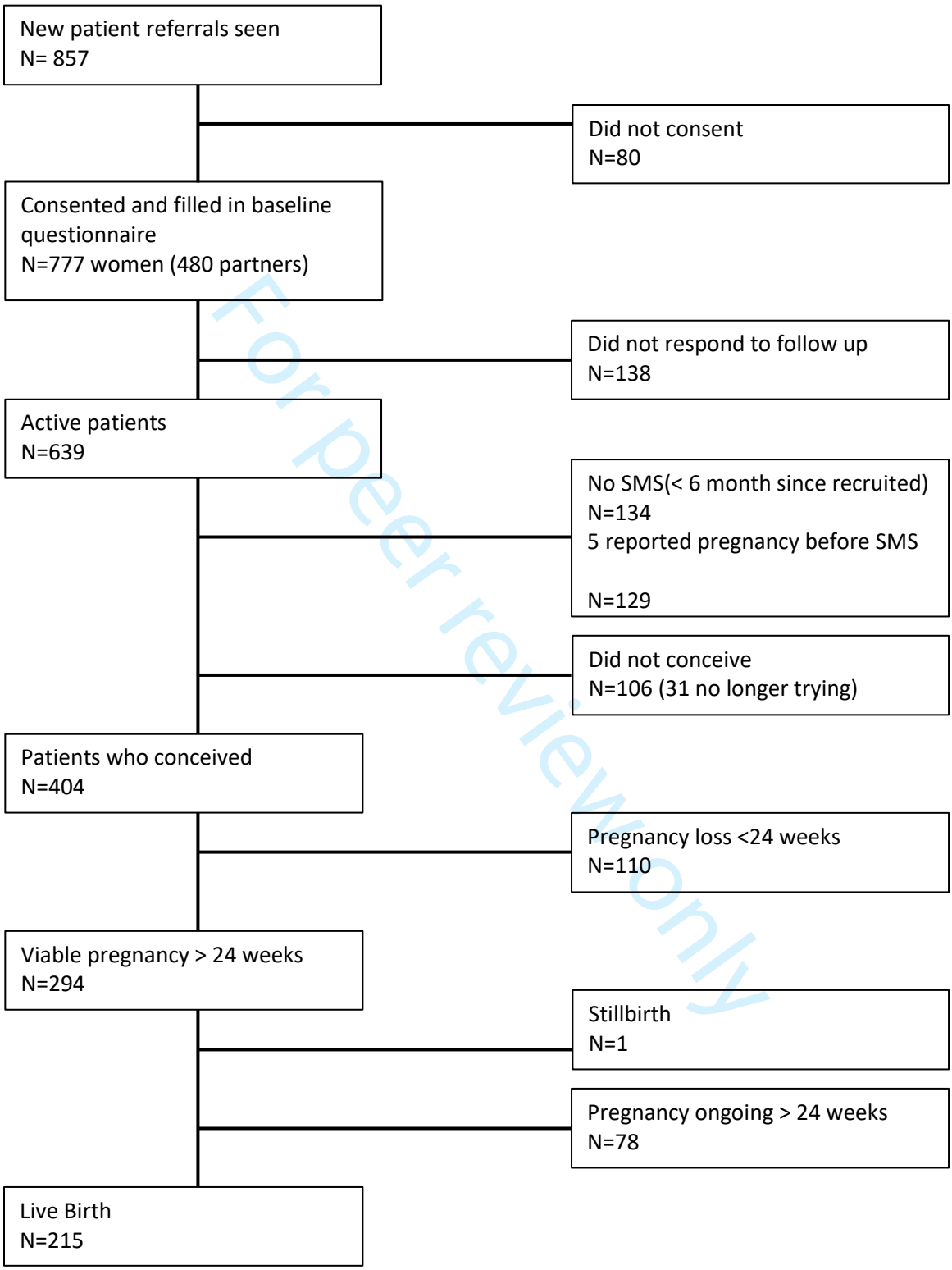
Figure 1: Flow diagram of Cohort



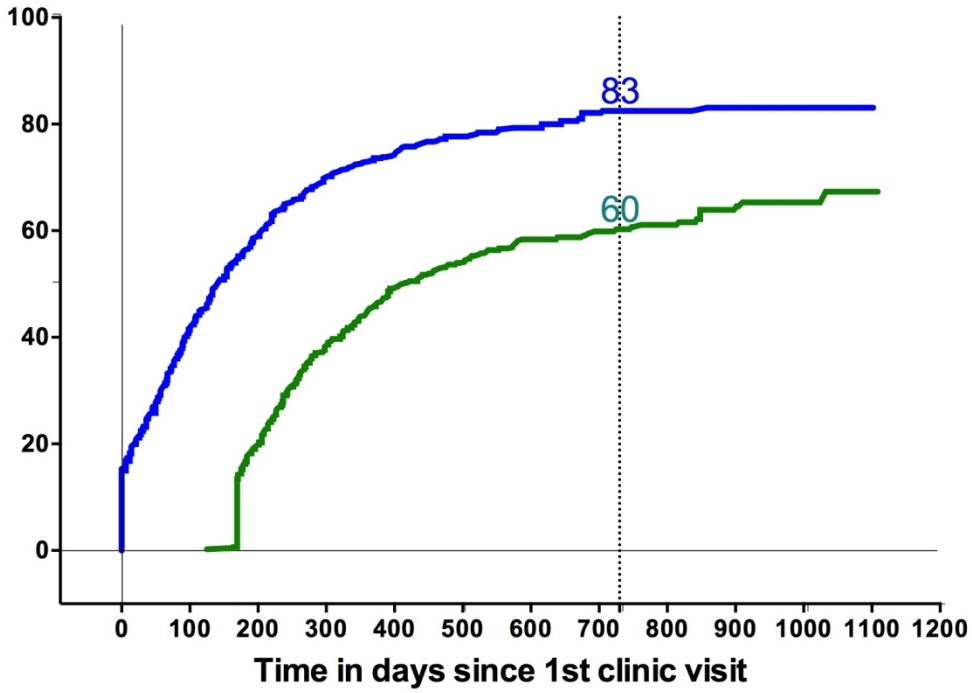


Figure 2: Cumulative rate over time, from initial consultation to conception and viability (>24weeks gestation)
Legend: Blue: conception, Green: viable pregnancy

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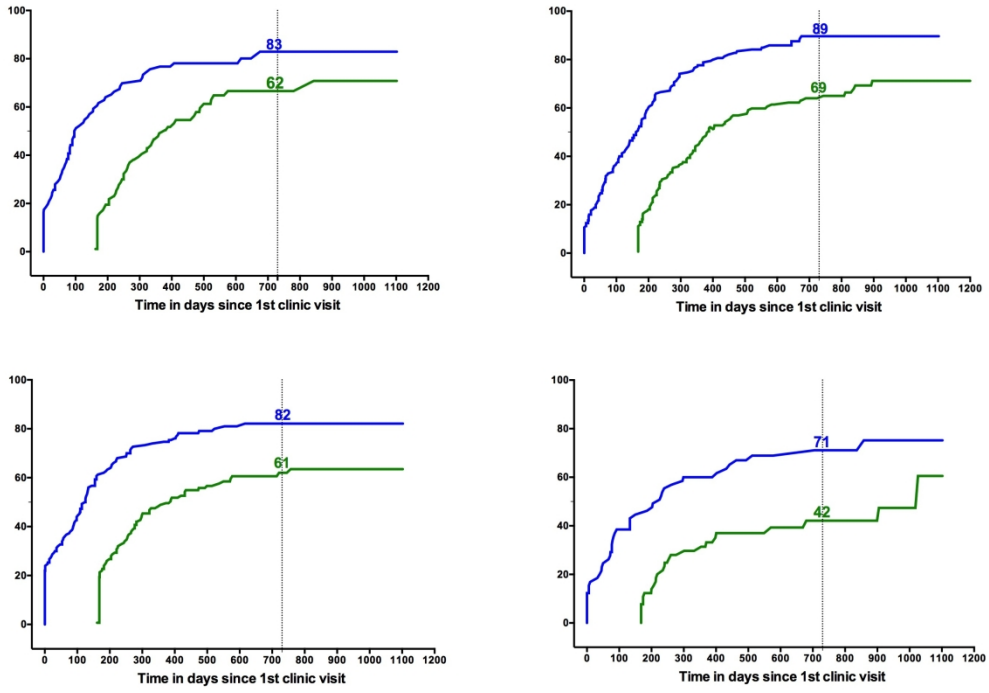

Figure 3: Time from initial consultation to conception/>24 weeks gestation by female age
Legend: Blue = Conception, Green = Viable pregnancy

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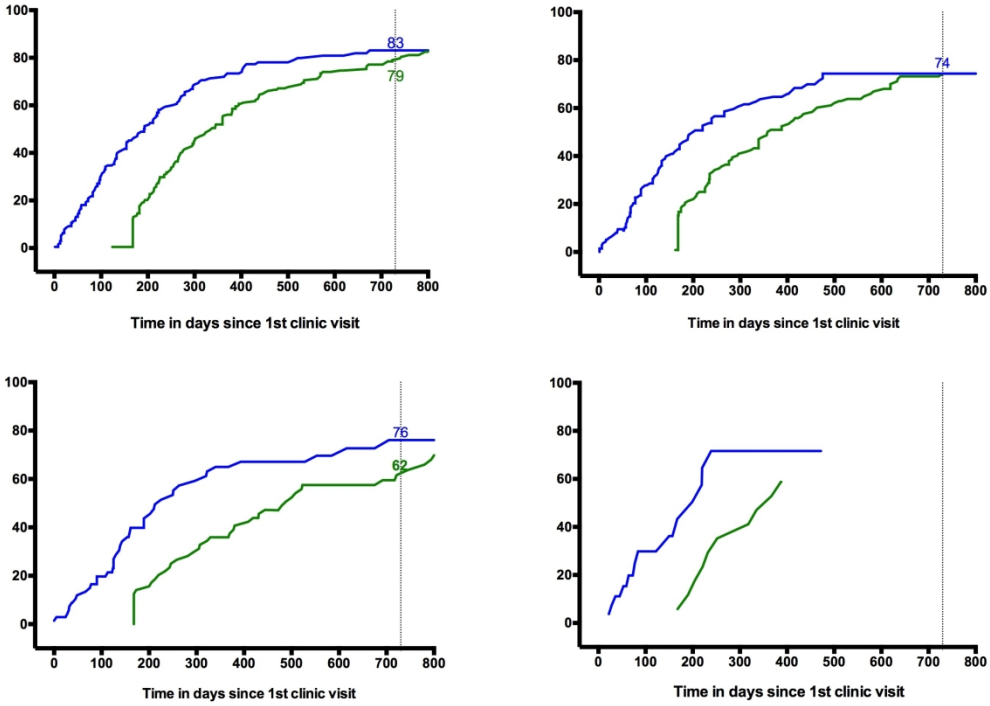

Figure 4: Time from initial consultation to conception/>24 weeks gestation by female BMI range
Legend: Blue = Conception, Green = Viable pregnancy

228x164mm (300 x 300 DPI)

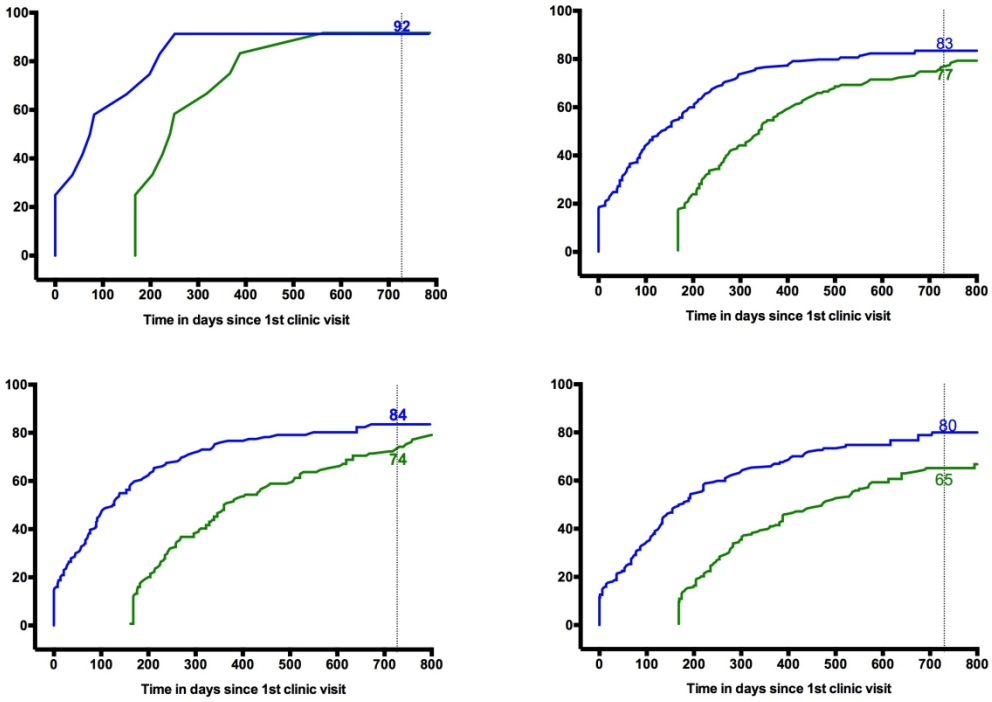

Figure 5: Time from initial consultation to conception/>24weeks gestation by miscarriage history.
Legend: Blue = Conception, Green = Viable pregnancy

228x164mm (300 x 300 DPI)

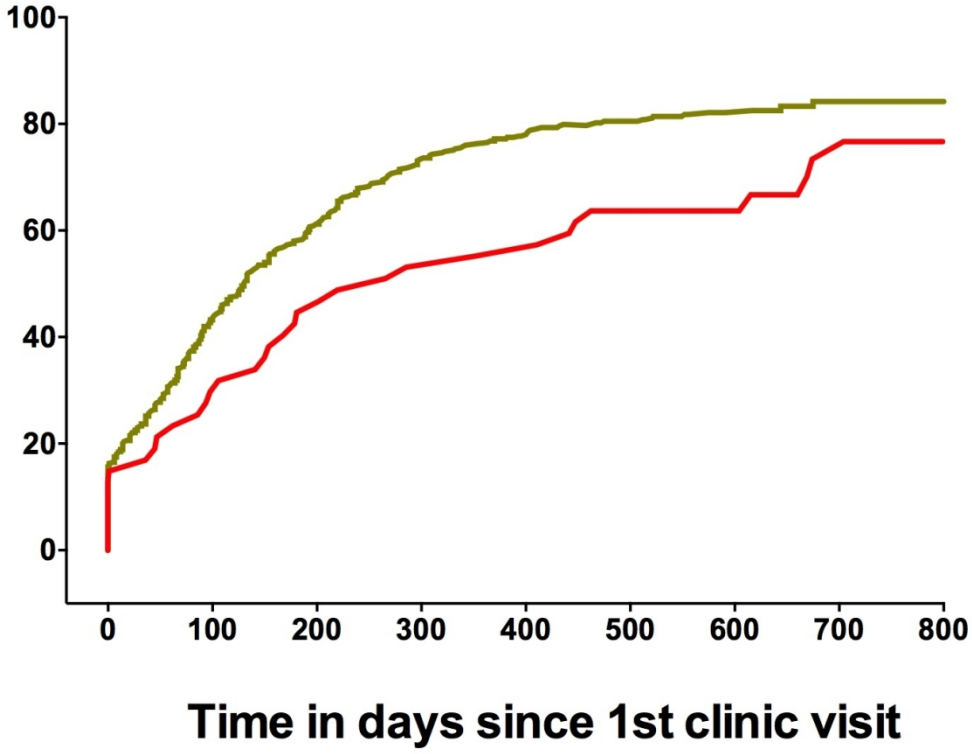

Figure 6: Time from initial consultation to conception by female smoking status.
Legend: Non smoker: Green, Smoker: Red

118x94mm (300 x 300 DPI)

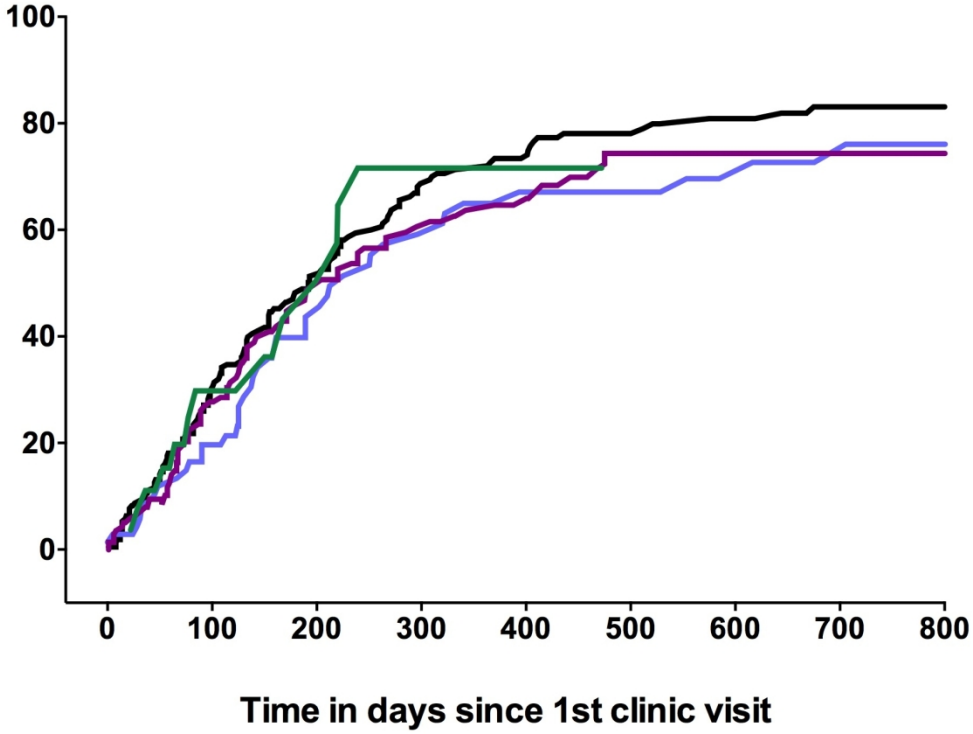

Figure 7: Time from initial consultation to conception by BMI range.Legend: Black: 18.5-25kg/m2, Purple:25.1-29.9kg/m2, Blue: 30-34.9kg/m2, Green: 35-39.9kg/m2

159x123mm (300 x 300 DPI)

Referral criteria for Recurrent miscarriage clinic care UHCW

- Actively trying to conceive
- 2 or more pregnancy losses, including biochemical loss, miscarriage, molar pregnancy, ectopic pregnancy and stillbirth

Tommy's National Centre for Miscarriage Research

University Hospitals Coventry and Warwickshire NHS Trust

Registration form

Male details

Title	**Date of birth**	
Surname	**Ethnic group (see last page)***	
First and forename(s)	**Religion (see last page)***	
Address	**Marital status (see last page)***	
	Education (see last page)*	
	Occupation	
	NHS number	
	Hospital number	
City/town	**GP name**	
County	**GP address**	
Telephone (Home)		
Telephone (Mobile)	**GP telephone**	
E-mail address (we will use this to correspond with you):		

***** - enter the relevant code from the list of tables on the last page of this form

Data Disclosure and Protection: By completing this form, you hereby give your consent for the data to be held within the NHS in accordance with the requirements of the 1998 Data Protection Act (UK).

Male signature:	
Date:	

Tommy's National Centre for Miscarriage Research

Please complete this form with as much information as you are able to. If you are uncertain about any of the questions you will be able to check these with your healthcare provider at your clinic appointment. Please include all medical information in your history even if you think it may be unimportant.

Previous illnesses or medical problems

	Yes	No
Have you had any serious illnesses or medical problems?	☐	☐

If yes, tick all applicable:

Diabetes	☐	Rheumatism or painful joints	☐
Thyroid problems	☐	Skin rashes or other skin disorders	☐
Cancer	☐	Irritable Bowel Syndrome	☐
Heart problems	☐	Coeliac disease	☐
Liver problems	☐	Crohn's disease	☐
Migraines	☐	Autoimmune disease	☐
Epilepsy	☐	Other inflammatory disorder	☐
Depression	☐	Thrombosis (clot in the leg or chest)	☐
High blood pressure	☐	Candida	☐
Lupus (SLE)	☐	Bacterial urethritis	☐
		Abnormal urethral discharge	☐

Other illnesses ☐ Please state: _____

If you have ticked any of the boxes above, please provide further details below:

Current medications and allergies

Please provide details on any allergies you have and medication you are currently taking below:

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Andrological history

Have you had a testicular examination before? Yes ☐ No ☐

What was found? _____

Have you had any of the following diagnosed?

Please tick all applicable options

Absence of a testicle (cryptorchidism)	☐	Mumps	☐
Testicular pain	☐	Tuberculosis (TB)	☐
Twisted testicles (torsion)	☐	Impotence/erectile dysfunction	☐
Testicular cancer	☐	Ejaculatory dysfunction	☐
Varicose veins in your scrotum	☐	Infertility	☐
		STI's	☐

If you have ticked any of the boxes above, please provide further details below:

Have you had any of the following surgeries?

Please tick all applicable options

Groin surgery	☐
Varicocelectomy	☐
Orchidectomy	☐
Orchidopexy	☐
Surgery for hernia	☐

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Family medical problems

Has your mother, father, siblings or maternal aunt(s) had any medical complications? Yes ☐ No ☐

If yes, tick all applicable:

- Miscarriage ☐
- Recurrent (3 or more) miscarriages ☐

If yes: Number of 1st trimester losses (<12 weeks) ☐☐ Number of 2nd trimester losses (>12 weeks) ☐☐ ☐ I don't know

- Obstetric complications (such as pre-eclampsia and growth restriction) ☐
- Genetic or developmental problems ☐
- Heart problems under the age of 50 ☐
- Stroke under the age of 50 ☐
- Still birth ☐
- Pre-term birth ☐
- Infertility ☐
- High blood pressure ☐
- Diabetes ☐
- Blood clots (thrombosis) ☐
- Depression ☐
- Other ☐

Please state: _____

If you have ticked any of the boxes above, please provide further details below:

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National Centre for
Miscarriage Research

Previous paternal history

	Yes	No
Have you had children in another relationship?	☐	☐
If yes, number of children:	☐☐	
Have you ever had a delay (>12 months) trying to father a child?	☐	☐

What age did you enter puberty? ☐☐ years

What is your current average ejaculatory frequency per week? ☐☐☐ times/week

What is your usual ejaculatory frequency per month (4 weeks)? ☐☐☐ times/month

Occupational exposure

	Yes	No
Have you been exposed to any harmful substances during your current or previous jobs? (see below for examples of such substances)	☐	☐

Exposure Type/Substance: (Years of exposure)

Dust	☐☐	Asbestos	☐☐
Fumes	☐☐	Noxious Gases	☐☐
Harmful vapours	☐☐	Chemicals	☐☐

Other (please specify): _____

Please provide further details:

_____

_____

_____

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Type of underwear

What type of underwear do you wear?

Tick one option

Boxer shorts ☐
Boxer briefs/trunks ☐
Briefs ☐
Thongs/Bikinis/G-strings ☐
Long underwear ☐
Jockstraps ☐
None ☐

What type of fabric is the underwear most commonly made from?

Tick one option

Cotton ☐
Synthetic ☐
Lycra ☐
Other (please specify) ☐ _____

Do they hold your testicles to the body, or are they loose?

Tick one option

Tight ☐
Loose ☐
Unsure ☐

Is the tightness of your underwear similar to before the last time your partner fell pregnant?

Tick one option

Yes ☐ No ☐ Don't know ☐

Technology habits

Do you ever sit with a laptop computer on your lap? Yes ☐ No ☐

↓

How many hours per day? ☐☐ hours ☐☐ minutes

Do you keep your mobile phone (that's switched on) in your trouser pocket?

Front pocket? Yes ☐ No ☐

↓

How many hours a day? ☐☐ hours/day

Back pocket? Yes ☐ No ☐

↓

How many hours a day? ☐☐ hours/day

Tommy's National Centre for Miscarriage Research

Diet and supplements

How many days a week do you eat the following foods:

Tick one box per food type

	Number of days per week							
	0	1	2	3	4	5	6	7
Red meat	☐	☐	☐	☐	☐	☐	☐	☐
White meat	☐	☐	☐	☐	☐	☐	☐	☐
Fish	☐	☐	☐	☐	☐	☐	☐	☐
Eggs	☐	☐	☐	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐	☐	☐	☐
Dairy products	☐	☐	☐	☐	☐	☐	☐	☐
Soya products	☐	☐	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐	☐	☐
Nuts (almonds/walnuts)	☐	☐	☐	☐	☐	☐	☐	☐

Do you consume sugar substitutes daily or most days of the week? ☐ Yes ☐ No

How many cups of coffee* do you drink in a typical day? ☐ cups of coffee/day

How many cups of tea* do you drink in a typical day? ☐ cups of tea/day

How many cans (or equivalent) of soft drink do you consume per day (e.g. energy drinks, cola)? ☐ cans/day

Do you currently take any vitamins or supplements? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	How long have you been taking it? (weeks)
1			
2			
3			
4			

* Do not count decaffeinated drinks

Tommy's National Centre for Miscarriage Research

Diet and supplements

If you are not taking vitamins or minerals currently but have taken them in the last four months please complete this table.

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Are you currently taking any protein shakes or protein bars? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Exercise

Do you follow a regular routine of physical exercise? ☐ Yes ☐ No

How many days a week do you exercise?

Tick one option

0 ☐
1-2 ☐
3-4 ☐
5-6 ☐
7 ☐

If you exercise, how many hours a day do you exercise?

Tick one option

< 30 min ☐
30 min - 1 hr ☐
1 hr - 1.5 hrs ☐
1.5 hrs - 2 hrs ☐
2 hrs - 2.5 hrs ☐
> 2.5 hrs ☐

On average how many hours do you spend sitting on a chair per day?

Sofa or armchair ☐ hours/day Work chair ☐ hours/day

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Miscarriage Research

Recreational drug use

Do you currently drink alcohol? Yes ☐ No ☐

How many units per week? ☐☐ units per week

Do you currently smoke? Yes ☐ No ☐

If yes:

How many cigarettes? ☐☐ per day **or** ☐☐ per week

How many vaping sessions? *One session is classified as 5 or more inhalations* ☐☐ per day **or** ☐☐ per week

If no:

Have you recently stopped? ☐ Yes ☐ No

If yes, how recently did you stop? ☐ < 1 month ☐ 1-6 months ☐ > 6 months

Do you take any other recreational drugs? Yes ☐ No ☐

If yes, please complete table:

Type	**Frequency of use (tick one option)**
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months

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Tests and investigations

Please give details of any tests or investigations you've had as a part of your treatment.

Test/investigations	Date of test	Result	Which hospital or clinic did you have the test at?
Semen analysis			
Sexually transmitted infection screening			

If other tests, please state below:

Test/investigation	Date of test	Result	Which hospital or clinic did you have the test at?

Tommy's National Centre for Miscarriage Research

Treatments

Please give details of any treatments you've previously received or are currently receiving as a part of your miscarriage management. Please also include any medications that you've bought yourself.

Treatment (please include medicines and operations)	Dose	Date from*	Date to	Tick if ongoing	Additional clinician's notes
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	

* If an operation, please give the date of operation

Tommy's National Centre for Miscarriage Research

Examination

This section should be completed in conjunction with the a member of the research team who attends to you in the clinic

Weight: ☐☐☐ kg Height: ☐☐☐ cm BMI: ☐☐.☐

Blood pressure: ☐☐☐ / ☐☐☐ mmHg
Systolic Diastolic

Examination findings (if appropriate)

For Tommy's research office use only if patient is consented and registered to take part in Tommy's research

Date of consent: d d - m m m - y y y y

Patient ID: ☐☐☐☐ - P A T

Recruiting site: _

Date entered onto database: __/___/____ Entered by: Date checked: __/___/____ Checked by:

Ethnicity codes

WHITE		Category includes
A	White British	English, Scottish, Welsh, Cornish
B	White Irish	
C	Any other white background	Former USSR, Baltic States, Former Yugoslavia, Other European, White South African, American, Australian, New Zealander, Mixed White
CF	Greek	
CG	Greek Cypriot	
CH	Turkish	
CI	Mediterranean	Italian, Portuguese and Spanish
CJ	Turkish Cypriot	
CN	Jewish	
CY	Other White European	
MIXED		
D	White & Black Caribbean	
E	White & Black African	
F	White & Asian	
G	Any other mixed background	
ASIAN OR ASIAN BRITISH		
H	Indian	British Indian, Punjabi
J	Pakistani	British Pakistani, Kashmiri
K	Bangladeshi	British Bangladeshi
L	Any other Asian background	British Asian, East African Asian, Sri Lankan, Tamil, Sinhalese, Caribbean Asian, Nepalese, Mixed Asian
BLACK OR BLACK BRITISH		
M	Black Caribbean	Caribbean, West Indian Islands (and also Guyana) apart from Puerto Rican, Dominican and Cuban, which are Latin America
N	Black African	Nigerian, Kenyan, Black South African, Other Black African Countries
P	Other Black background	Black American, Mixed Black
PA	Somali	
PE	Black British	
OTHER ETHNIC GROUPS		
R	Chinese	inc. Hong Kong
S	Any other ethnicity	Japanese, Filipino, Malaysian, Aborigine, Afghani, Burmese, Fijian, Inuit, Maori, Native American Indian, Thai, Tongan, Samoan, Iranian, Israeli, Kurdish, Latin American (inc. Cuban, Puerto Rican, Dominican, Hispanic), Moroccan, Multi Ethnic Islands (inc. Seychellois, Maldivian, St. Helena), Other Middle Eastern (inc. Iraqi, Lebanese, Yemeni), Other North African, South American (inc. Central America).
SA	Africa—colour not defined	
SC	Arab	
SD	Vietnamese	
Z	Not stated	

Religion codes

A	Christian (all denominations)
B	Buddhist
C	Hindu
D	Jewish
E	Muslim
F	Sikh
G	Agnostic
H	Atheist
I	I'd rather not say
J	Other (please specify)

Marital status codes

A	Single
B	Married
C	Separated
D	Divorced
E	Widowed

Education codes

A	No formal qualifications
B	1-4 GCSEs (A*-C) or equivalent
C	5+ GCSEs (A*-C) or equivalent
D	Apprenticeship
E	2+ A-levels or equivalent
F	Degree or above
G	Other (please specify)

Tommy's National Centre for Miscarriage Research

University Hospitals Coventry and Warwickshire NHS Trust

Registration form

Female details

Title	**Date of birth**	
Surname	**Ethnic group (see last page)***	
First and forename(s)	**Religion (see last page)***	
Address	**Marital status (see last page)***	
	Education (see last page)*	
	Occupation	
	NHS number	
	Hospital number	
City/town	**GP name**	
County	**GP address**	
Telephone (Home)		
Telephone (Mobile)	**GP telephone**	
E-mail address (we will use this to correspond with you):		

* - enter the relevant code from the list of tables on the last page of this form

Data Disclosure and Protection: By completing this form, you hereby give your consent for the data to be held within the NHS in accordance with the requirements of the 1998 Data Protection Act (UK).

Female signature:	
Date:	

Tommy's National Centre for Miscarriage Research

Please complete this form with as much information as you are able to. If you are uncertain about any of the questions you will be able to check these with your healthcare provider at your clinic appointment. Please include all medical information in your history even if you think it may be insignificant.

Relationship details

What is the length of your currentrelationship? ☐☐ years ☐☐ months

Are you and your partner blood relatives? Yes ☐ No ☐

Please describe: _

Menstrual period and pregnancy information

What was the first date of your last menstrual period? d d - m m - y y y y

What age did your periods start? ☐☐ years

Are your periods regular? Yes ☐ No ☐

If yes, what is your cycle length (time from the beginning of one period to the beginning of the next)? ☐☐ days

If no, what is your cycle length? **MIN** ☐☐ days

MAX ☐☐ days

How many days do you bleed for? ☐☐ days

Do you get any bleeding in between your periods? ☐ ☐

Do you have any problems with intercourse? ☐ ☐

How frequently do you have intercourse? ☐☐ per/wk

or ☐☐ per/month

Have you ever had a delay (>12 months) in trying to get pregnant? ☐ ☐

Are you currently pregnant? ☐ ☐

Are you currently trying to become pregnant? ☐ ☐

How long have you been trying to conceive? ☐☐ years ☐☐ months

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Contraception and fertility treatment

*Please complete the table below with all forms of contraception you have previously used (e.g. coil (IUCD), Depo-Provera injection, oral contraceptive pill). Use of condoms **DOES NOT** need to be included.*

Type of contraception	How long did you use it (years)?	How long ago did you stop using it (years)?

Have you ever used fertility treatment to try and get pregnant? Yes ☐ No ☐

Please tick all treatments you've had, and enter the number of attempts

Clomid/other ovary stimulation ☐ ☐☐ attempts

IVF/ICSI ☐ ☐☐ attempts

IUI ☐ ☐☐ attempts

Donor sperm treatment ☐ ☐☐ attempts

Donor egg treatment ☐ ☐☐ attempts

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Previous pregnancies

*Use the key opposite to complete the fields marked with *. If year or gestation are not known, state NK in the relevant box*

Year	Gestation (wks)	Time taken to get pregnant (months)	Method of conception*	Any ultrasound scan findings? (e.g. please tell us if the baby's heart-beat was seen)	Sex (M or F, if known)	Outcome** (enter code)	If miscarriage, type of management*** (enter code)	Mode of delivery**** (enter code)	With current partner (Yes or No)	Additional clinician's notes

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*** Method of conception**

1	Natural
2	IVF/ICSI
3	IUI
4	Donor sperm treatment
5	Donor egg treatment
6	Ovarian stimulation

****Outcome**

1	Live birth
2	Stillbirth
3	Pregnancy loss without ultrasound confirmation of pregnancy
4	Miscarriage after ultrasound confirmation of pregnancy
5	Late miscarriage (>12 weeks to <24 weeks)
6	Ectopic pregnancy
7	Molar pregnancy
8	Resolved pregnancy of unknown location
9	Termination

*****Type of management**

1	Expectant (waited for nature to take its course)
2	Surgical (operation)
3	Medical (took a tablet(s))

****** Mode of delivery**

1	Unassisted vaginal
2	Instrumental vaginal (forceps or suction cup delivery)
3	Elective caesarean section
4	Emergency caesarean section
5	Vaginal breech
6	Not applicable

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Previous pregnancy-related complications

	Yes	No
Do you have a history of polycystic ovaries?	☐	☐
Do you have a history of fibroids?	☐	☐

If yes: Distorting womb cavity ☐
Not distorting womb cavity ☐
I don't know ☐

	Yes	No
Do you have a history of endometriosis?	☐	☐
Do you have a history of pelvic inflammatory disease?	☐	☐
Do you have a history of uterine (womb) abnormalities?	☐	☐
Have you ever had a sexually transmitted disease?	☐	☐
If yes, when: m m - y y y y Was it treated?	☐	☐
Have you ever had any previous gynaecological surgeries?	☐	☐

If yes, tick all applicable:

Laser or loop excision of the cervix (LLETZ)	☐ →	If yes, how many operations? ☐☐ operations
Removal of fibroids	☐	Removal of scar tissues in the womb ☐
Endometriosis surgery	☐	Womb septum removal ☐
Fallopian tube surgery	☐	Other gynaecological surgeries ☐ If yes, state: _____
Removal of ovarian cyst(s)	☐	Other gynaecological disorders ☐ If yes, state: _____
Surgical management of miscarriage	☐	I don't know ☐

Date of last cervical smear test? m m - y y y y

Result? ☐ Normal ☐ Abnormal

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Recreational drug use

	Yes	No
Do you currently drink alcohol?	☐	☐

How many units per week? ☐☐ units per week

	Yes	No
Do you currently smoke?	☐	☐

If yes:

How many cigarettes? ☐☐ per day **or** ☐☐ per week

How many vaping sessions? ☐☐ per day **or** ☐☐ per week

One session is classified as 5 or more inhalations

If no:

Have you recently stopped? ☐ Yes ☐ No

If yes, how recently did you stop? ☐ < 1 month ☐ 1-6 months ☐ > 6 months

	Yes	No
Do you take any other recreational drugs?	☐	☐

If yes, please complete table:

Type	Frequency of use (tick one option)
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months

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Diet and supplements

How many days a week do you eat the following foods:

Tick one box per food type

	Number of days per week							
	0	1	2	3	4	5	6	7
Red meat	☐	☐	☐	☐	☐	☐	☐	☐
White meat	☐	☐	☐	☐	☐	☐	☐	☐
Fish	☐	☐	☐	☐	☐	☐	☐	☐
Eggs	☐	☐	☐	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐	☐	☐	☐
Dairy products	☐	☐	☐	☐	☐	☐	☐	☐
Soya products	☐	☐	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐	☐	☐
Nuts (almonds/walnuts)	☐	☐	☐	☐	☐	☐	☐	☐

Do you consume sugar substitutes daily or most days of the week? ☐ Yes ☐ No

How many cups of coffee* do you drink in a typical day? ☐ cups of coffee/day

How many cups of tea* do you drink in a typical day? ☐ cups of tea/day

How many cans (or equivalent) of soft drink do you consume per day (e.g. energy drinks, cola)? ☐ cans/day

Do you currently take any vitamins or supplements? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	How long have you been taking it? (weeks)
1			
2			
3			
4			

* Do not count decaffeinated drinks

Tommy's National Centre for Miscarriage Research

Diet and supplements

If you are not taking vitamins or minerals currently but have taken them in the last four months please complete this table.

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Are you currently taking any protein shakes or protein bars? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Exercise

Do you follow a regular routine of physical exercise? ☐ Yes ☐ No

How many days a week do you exercise?

Tick one option

- 0 ☐
- 1-2 ☐
- 3-4 ☐
- 5-6 ☐
- 7 ☐

If you exercise, how many hours a day do you exercise?

Tick one option

- < 30 min ☐
- 30 min - 1 hr ☐
- > 1 hr - 1.5 hrs ☐
- > 1.5 hrs - 2 hrs ☐
- > 2 hrs - 2.5 hrs ☐
- > 2.5 hrs ☐

On average how many hours do you spend sitting on a chair per day?

Sofa or armchair ☐ hours/day Work chair ☐ hours/day

Tommy's National Centre for Miscarriage Research

Previous illnesses or medical problems

Have you had any serious illnesses or medical problems? Yes ☐ No ☐

If yes, tick all applicable:

Diabetes	☐	Rheumatism or painful joints	☐
Thyroid problems	☐	Skin rashes or other skin disorders	☐
Cancer	☐	Irritable Bowel Syndrome	☐
Heart problems	☐	Coeliac disease	☐
Liver problems	☐	Crohn's disease	☐
Migraines	☐	Autoimmune disease	☐
Epilepsy	☐	Other inflammatory disorder	☐
Depression	☐	Thrombosis (clots in legs or chest)	☐
High blood pressure	☐	Candida (thrush)	☐
Lupus (SLE)	☐	Bacterial vaginosis	☐
Abnormal vaginal discharge	☐		
Other illnesses	☐	Please state: _____	

If you have ticked any of the boxes above, please provide further details below:

Current medications and allergies

Please provide details on any allergies you have and medication you are currently taking below:

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Family medical problems

Has your mother, father, siblings or maternal aunt(s) had any medical complications? Yes ☐ No ☐

If yes, tick all applicable:

- Miscarriage ☐
- Recurrent (3 or more) miscarriages ☐
  - If yes: Number of 1st trimester losses (<12 weeks) ☐☐ Number of 2nd trimester losses (>12 weeks) ☐☐ ☐ I don't know
- Obstetric complications (such as pre-eclampsia and growth restriction) ☐
- Genetic or developmental problems ☐
- Heart problems under the age of 50 ☐
- Stroke under the age of 50 ☐
- Still birth ☐
- Pre-term birth ☐
- Infertility ☐
- High blood pressure ☐
- Diabetes ☐
- Blood clots (thrombosis) ☐
- Depression ☐
- Other ☐

Please state: _____

If you have ticked any of the boxes above, please provide further details below:

Tommy's National Centre for Miscarriage Research

Tests and investigations

Please give details of any tests or investigations you've had as a part of your miscarriage treatment.

Test/investigations	Date of test	Result	Which hospital or clinic did you have the test at?
FSH			
LH			
Oestradiol			
Haemoglobin			
Platelets			
Rubella immunity			
Thrombophilia screening			
Thyroid antibodies			
Thyroid function test			
Sexually transmitted disease			
Ultrasound			

If you've had any other tests, please state below:

Test/investigation	Date of test	Result	Which hospital or clinic did you have the test at?

Tommy's National Centre for Miscarriage Research

Treatments

Please give details of any treatments you've previously received or are currently receiving as a part of your miscarriage management. Please also include any medications that you've bought yourself.

Treatment (please include medicines and operations)	Dose	Date from*	Date to	Tick if ongoing	Additional clinician's notes
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	

* If an operation, please give the date of operation

Tommy's National Centre for Miscarriage Research

Examination

This section should be completed in conjunction with a member of the research team who attends to you in the clinic

Weight: ☐☐☐ kg Height: ☐☐☐ cm BMI: ☐☐.☐

Blood pressure: ☐☐☐ / ☐☐☐ mmHg
Systolic Diastolic

Examination findings (if appropriate)

For Tommy's research office use only if patient is consented and registered to take part in Tommy's research

Date of consent: d d - m m m - y y y y

Patient ID: ☐☐☐☐ - M A T

Recruiting site: _

Date entered onto database: __/___/____ Entered Date checked: __/___/____ Checked by:

Tommy's National Centre for Miscarriage Research

Ethnicity codes

		Category includes
WHITE		**Category includes**
A	White British	English, Scottish, Welsh, Cornish
B	White Irish	
C	Any other white background	Former USSR, Baltic States, Former Yugoslavia, Other European, White South African, American, Australian, New Zealander, Mixed White
CF	Greek	
CG	Greek Cypriot	
CH	Turkish	
CI	Mediterranean	Italian, Portuguese and Spanish
CJ	Turkish Cypriot	
CN	Jewish	
CY	Other White European	
MIXED		
D	White & Black Caribbean	
E	White & Black African	
F	White & Asian	
G	Any other mixed background	
ASIAN OR ASIAN BRITISH		
H	Indian	British Indian, Punjabi
J	Pakistani	British Pakistani, Kashmiri
K	Bangladeshi	British Bangladeshi
L	Any other Asian background	British Asian, East African Asian, Sri Lankan, Tamil, Sinhalese, Caribbean Asian, Nepalese, Mixed Asian
BLACK OR BLACK BRITISH		
M	Black Caribbean	Caribbean, West Indian Islands (and also Guyana) apart from Puerto Rican, Dominican and Cuban, which are
N	Black African	Nigerian, Kenyan, Black South African, Other Black African Countries
P	Other Black background	Black American, Mixed Black
PA	Somali	
PE	Black British	
OTHER ETHNIC GROUPS		
R	Chinese	inc. Hong Kong
S	Any other ethnicity	Japanese, Filipino, Malaysian, Aborigine, Afghani, Burmese, Fijian, Inuit, Maori, Native American Indian, Thai, Tongan, Samoan, Iranian, Israeli, Kurdish, Latin American (inc. Cuban, Puerto Rican, Dominican, Hispanic), Moroccan, Multi Ethnic Islands (inc. Seychellois, Maldivian, St. Helena), Other Middle Eastern (inc. Iraqi, Lebanese, Yemeni), Other North African, South American (inc. Central America).
SA	Africa—colour not defined	
SC	Arab	
SD	Vietnamese	
Z	Not stated	

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Miscarriage Research

Religion codes

A	Christian (all denominations)
B	Buddhist
C	Hindu
D	Jewish
E	Muslim
F	Sikh
G	Agnostic
H	Atheist
I	I'd rather not say
J	Other (please specify)

Marital status codes

A	Single
B	Married
C	Separated
D	Divorced
E	Widowed

Education codes

A	No formal qualifications
B	1-4 GCSEs (A*-C) or equivalent
C	5+ GCSEs (A*-C) or equivalent
D	Apprenticeship
E	2+ A-levels or equivalent
F	Degree or above
G	Other (please specify)

1

1 Dashboard

Historic Data (Pre Registration)

Trust	No of Couples	No of Women	No of Men	No of Pregnancies
University Hospitals Coventry and Warwickshire	897	897	736	3768

Age at Registration (female only)

	No of Patients	% of Patients
<35	445	50
35-40	318	35
>40	124	14

History of miscarriage/live births

Patients	No of Patient	% of Patients
2 miscarriages	221	25
3 miscarriages	248	28
4 miscarriages	173	19
5 miscarriages	87	10
>5 miscarriages	118	13
1 or more live births	335	37

Ongoing Miscarriage Outcomes (Post Registration)

Trust	Pregnancies Post Registration
University Hospitals Coventry and Warwickshire	634

Miscarriage/Live Birth Rates by conception type (percentages by row)

	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
All conception types	634	32	1	40	2	20	4	0
Natural conception only	538	33	1	40	2	20	4	0

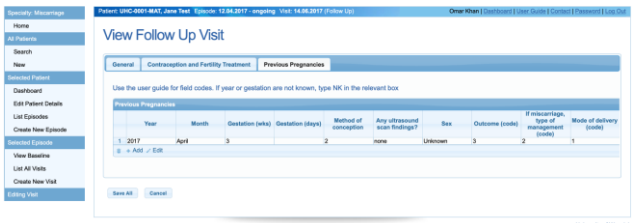
Miscarriage/Live Birth Rates by age of mother at delivery (percentages by row)

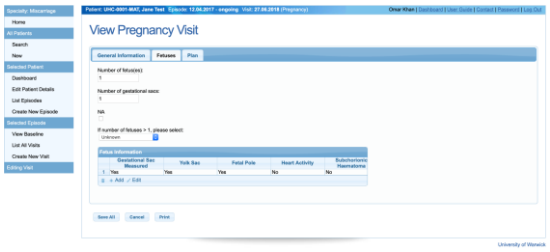
	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
<35	315	32	1	42	3	18	4	0
35-40	247	30	1	41	2	23	3	0
>40	71	39	0	31	1	20	8	0

Miscarriage/Live Birth Rates by history of miscarriage (percentages by row)

	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
2	178	24	1	48	1	26	1	0
3	172	29	1	45	2	18	4	0
4	118	36	0	35	3	19	7	1
5	71	41	1	34	0	17	7	0
>5	81	42	4	31	7	12	4	0

2





3

4

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods	5

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	n/a
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	
6			
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6
Statistical methods	#12c	Explain how missing data were addressed	n/a
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	
7			
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	7

		included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	
14			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
7			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
7			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
7			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
n/a			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			

Key results	#18	Summarise key results with reference to study objectives	3
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	3
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	8
Generalisability	#21	Discuss the generalisability (external validity) of the study results	8
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

This checklist was completed on 19. April 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Version 5.0, 21-Jan-2020

University Hospitals Coventry and Warwickshire NHS Trust

STUDY PROTOCOL

Tommy's Net

A cohort study of pregnancy outcome in couples who miscarry

Sponsor: University Hospitals Coventry and Warwickshire NHS trust
Sponsor reference: SQ186916

Funder: Tommy's Charity

REC reference: 17/WM/0050 for data collection
Reference for database: 17/NW/0208

IRAS No: 213740 for data collection
IRAS No: 225751 for database
ISRCTN: 17732518

Parts with no fill relate to both projects
Part in light grey refers to data collection 17/WM/0050
Parts in light yellow refer to database application

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Research Governance Framework, the ICH Good Clinical Practice guidelines and the Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

Position:

.....

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Funder	Tommy's Charity Nicholas House, 3 Laurence Pountney Hill, London, EC4R 0BB Email: mailbox@tommys.org.
Trial Co-ordinator / Co-ordination centre	Institute of Digital Healthcare University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL

INDEX

1. Aims and Objectives

We seek to achieve the following objectives:

- To undertake a large cohort study of pregnancy outcome following miscarriage.
- To facilitate the development and validation of tests and prediction models that could determine pregnancy outcome.
- To stratify couples with history of miscarriages into distinct phenotypes, allowing targeted management.
- To enable population-based epidemiological studies on miscarriage.
- To facilitate randomised controlled trials in terms of identifying eligible recruits and managing the trials.
- To enable participating hospitals to work together in a way that brings added benefits to all parties and the populations whom they serve.
- To facilitate the clinical/research interface.

We aim to do this by creating an online electronic patient record system, which will be designed and constructed by our specialist team within the University of Warwick, Institute of Digital Healthcare, for use by early pregnancy services.

2. Introduction

Miscarriage, defined as the loss of pregnancy before the fetus reaches viability, is the most common complication of pregnancy. As many as 15-25% of pregnancies end in miscarriage, and 25-50% of women experience at least one sporadic miscarriage in their reproductive life.(1) The number of miscarriages in the UK is estimated to be approximately 200,000 per year.(2) Most miscarriages are sporadic and occur before 12 weeks of gestation.(3) They frequently involve numeric chromosome errors in the conceptus.(4)

Recurrent miscarriage is generally viewed as a condition distinct from sporadic miscarriages. It is estimated that 5% of women experience two consecutive miscarriages, and approximately 1% suffer three or more consecutive miscarriages. (5,6) In recurrent miscarriage, the incidence of euploidic fetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases.(7) Recurrent miscarriage is a debilitating disorder, associated with considerable psychological morbidity, for which there is no effective medical intervention. Fortunately, the cumulative live birth rate for most recurrent miscarriage patients is high; more than around 65% of women with recurrent losses go on to have a successful subsequent pregnancy.(8–14)

The risk factors associated with miscarriage include maternal age, previous pregnancy history, body mass index (BMI), maternal medical conditions, thrombophilia's, parental structural chromosome abnormities, uterine anomalies and lifestyle factors such as smoking.

There are no robustly developed and widely validated prediction models in current clinical use. Couples are currently not provided with accurate estimates of their future risk of miscarriage, or obstetric and perinatal outcomes.

Effective management of miscarriage requires the rigorous study of risk factors and test outcomes, as well as the development of new tests to allow stratification of patients according to the likelihood of future reproductive failure. The development and assessment of prognostic tests require effective and long-term follow-up work with accurate recording and analysis of future pregnancy outcomes. To facilitate such recording, we will establish an online data and record management system that will allow patients to continuously update their reproductive history.

Currently couples suffering miscarriage are stratified according to the number of previous losses. Many clinics in the UK will only investigate women after 3 losses.(11) Our aim is to change this counting of losses as an indicator of disease to an approach that takes multiple risk factors into account, producing distinct miscarriage phenotypes that allow targeted tests and interventions to improve outcomes.

For example, sporadic miscarriages frequently result from aneuploidy, whereas recurrent miscarriage, defined by consecutive miscarriages, is generally viewed as a distinct disorder in which the incidence of euploidic fetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases. Currently affected couples are routinely screened for various anatomical, endocrine, immunological, thrombophilic and genetic risk factors,(11) but the ability of these tests to stratify women in terms of pregnancy outcome and appropriate treatment has not been vigorously tested.

The Tommy's National Centre for Miscarriage Research is a Research Centre which brings together an interdisciplinary Translational Medicine research grouping jointly at the University of Warwick, University of Birmingham and Imperial College London. The Centre is dedicated to research across all aspects of miscarriage and early pregnancy complications including medical, basic scientific, social and ethical issues. In facilitating this research portfolio, one aspect includes the centralised secure storage of all data relating to the research from every participating site, which is to be known as Tommy's Net.

3. **Methods & Design**

3.1 Overview

In this project we plan to use digital technology to store information about the patient's and their partner's demographic details history, investigation results and pregnancy outcome. Thus we will create a large cohort study of women presenting with miscarriage. The crucial feature of the cohort will be the ascertainment of pregnancy outcome. Analysis of this cohort will allow us to assess the utility of existing investigations and new test in predicting pregnancy outcome.

3.2 Centres

This project will initially involve three centres with specialist clinics:

- University Hospitals Coventry and Warwickshire NHS trust (UHCW)
- Birmingham Women's Hospital Foundation Trust (BWH)

- Imperial College Healthcare NHS Trust (Imperial)

Any additional centres will be notified to the responsible REC as a substantial amendment.

3.3 Population

Women attending specialist services at the participating trusts will be invited to participate:

- UHCW; it will include couples attending, early pregnancy, implantation, recurrent miscarriage and preterm prevention clinics.
- BWH; will include individuals attending early pregnancy assessment unit and recurrent miscarriage clinic.
- Imperial; will include individuals attending early pregnancy assessment unit and recurrent miscarriage clinic.

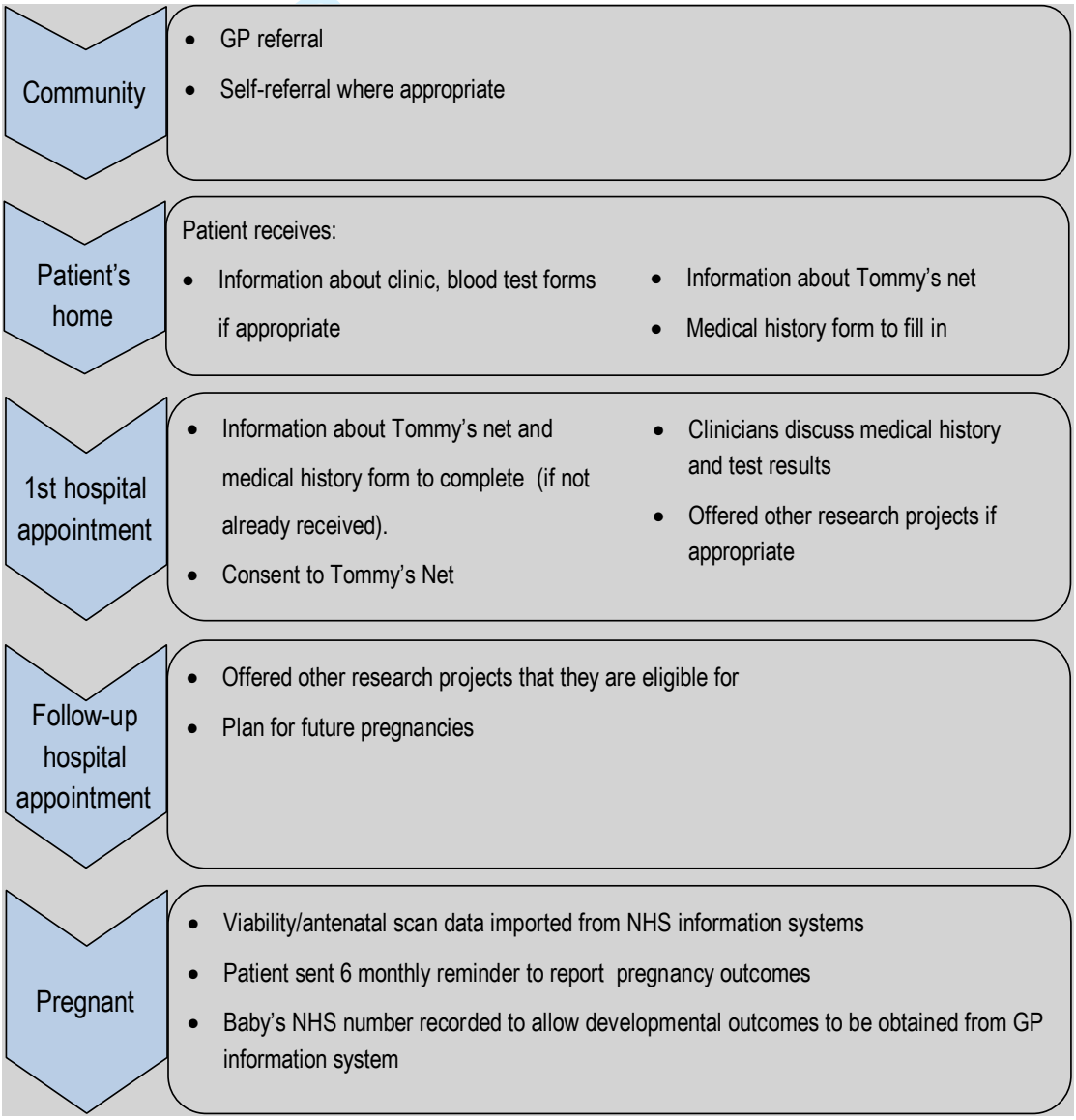

Figure 1. Tommy's Net flow diagram for recurrent miscarriage clinic patients

Pregnant:

- Update of demographics including weight, smoking status, alcohol intake and folic acid use.

May also receive 6-12 information/support text messages annually

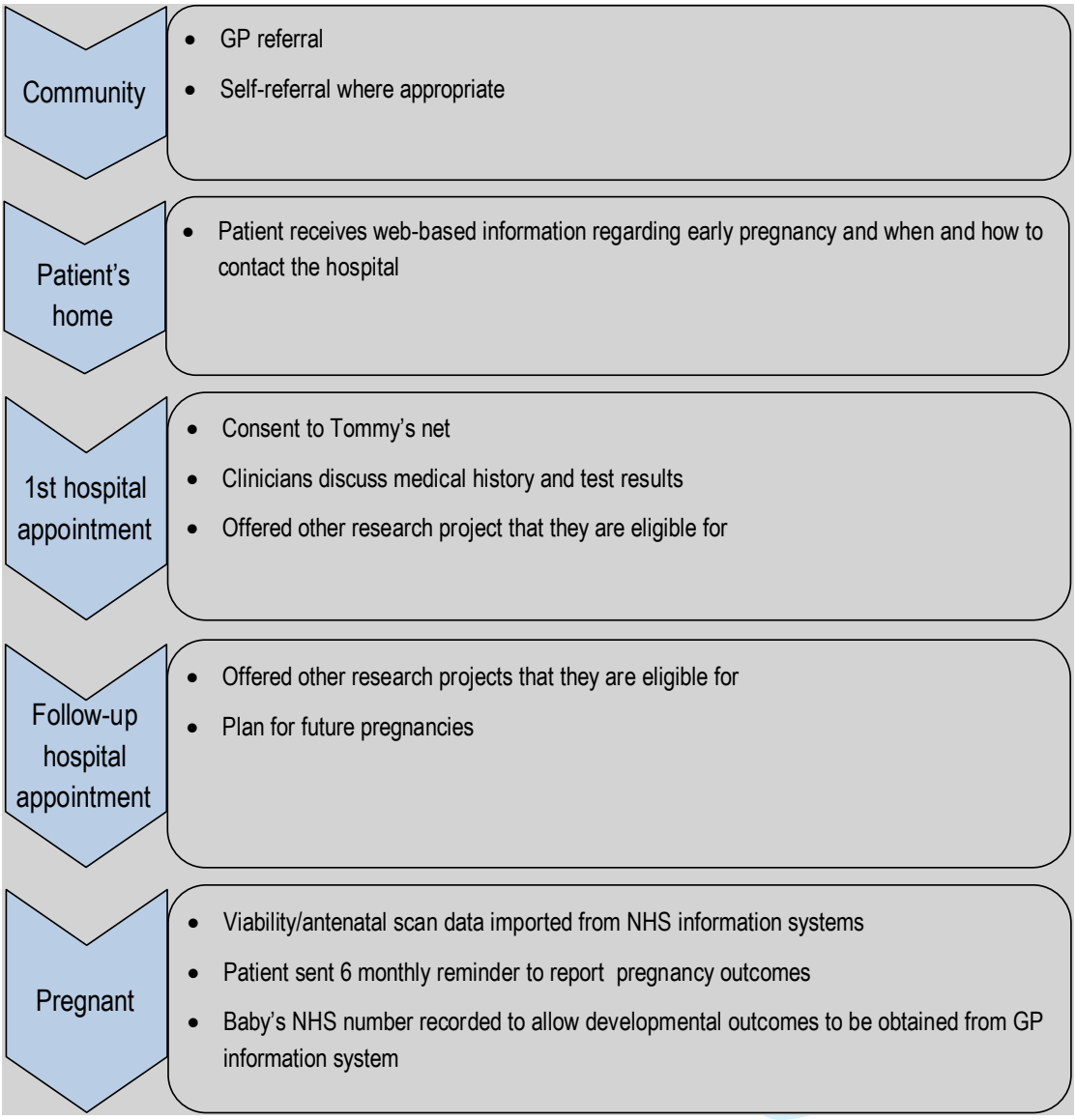

Figure 2. Tommy's Net flow diagram for emergency patients

3.4 Duration

This project is funded for 5 years initially but we would hope this to be renewed.

3.5 Inclusion criteria

- Couples with a history of one or more pregnancy losses;
  - Miscarriage
  - Molar pregnancy
  - Ectopic pregnancy

- Stillbirth
- Bleeding in early pregnancy

3.6 Exclusion criteria

Decline to consent to having their information stored.

3.7 Methods

Couples will be referred by their GP or self-refer. They will then be sent information about Tommy's Net by post and directed to websites (PIS) as well as other trials, the standard NHS information about the clinic and a history sheet. Patients can attend in person or have a telephone consultation:

When they arrive at the clinic a member of the research team will explain Tommy's Net and ask them to consent to the study. If they consent they will be asked to fill the Tommy's Net registration form on paper, after which, their data will be entered on an online system, this will include demographics information, reproductive history, delivery details and related test results. They will then see the clinician who will discuss their history and advise on further investigations and eligibility for other studies and trials.

Prior to telephone consultation the patient will be contacted by telephone and directed to Tommy';s net online consent form. If consented they will be directed to an online registration form and asked to complete this prior to review in the telephone consultation.

All existing relevant investigation results will be imported into the trial database system (Tommy's Net) from existing hospital systems (for example CRRS/Lorenzo). Where investigations relate only to the trial, the data from these will be entered directly into the trial system. Tommy's Net will assist in the production of the clinic letter to the GP and patient as a record of this visit. Thus as well as being a research tool the Tommy's net will facilitate the clinical service. Other related trials will have separate ethical approvals.

Follow up appointments will be offered by telephone or in person to discuss investigation results and plan future pregnancies. Tommy's Net will produce a letter to the GP and patient as a record of this visit which will fit into existing NHS systems this will be in place of the current letter to the GP following an appointment.

In future pregnancies, patients will be offered viability scans in the first trimester and information about these scans, as well as the anonymized scans themselves, will be stored on Tommy's Net. These will be imported from the current Viewpoint, digital, ultrasound results storage system. Participants' details will be updated during these visits (including BMI, smoking status, alcohol intake and folic acid use).

Patients and their partners will be asked to complete an optional anxiety questionnaire (Generalised Anxiety Disorder Questionnaire, GAD-7) prior to the initial ultrasound in each pregnancy and following each subsequent ultrasound. Scores will be recorded on Tommy's net. Any patient scoring over 10 will be offered additional support from the staff at the Biomedical research unit and referred to their GP if required.

Information about antenatal care including, serum screening, booking scans, anomaly scans and growth scans will be recorded (imported from Viewpoint where they exist or entered directly into the research system if inappropriate for the clinical record).

Pregnancy outcome details will be requested from the patient either by filling in a paper copy, which can then be entered into the system via an authorized researcher or by direct patient entry into an online, link anonymised, patient accessible system, hosted at the University of Warwick, every 6 months. The data collected by this system will be transferred to the Tommy's Net system hosted at the hospital, and deleted from the University system, after review by the research midwives. Women will be sent reminders to update us regarding their reproductive outcomes 6 monthly (these can be automated if the patient consents to having their email address or mobile phone number registered on the system to be used for reminders). They may also receive information/support text messages 6-12 times annually.

The baby's NHS number will be requested through appropriate consent so that follow up of the baby's development could be facilitated. Information regarding developmental follow up will be requested from GP records. During the project, direct connections to GP sockets will be developed to facilitate sharing of information, and avoid duplicate data entry, in the presence of approved data sharing agreements.

3.8 Recruitment and consent

The underlying principle of the Centre is that patients should give informed generic consent to use their data in the medical research relating to the Tommy's National Centre for Miscarriage Research. Consent will be obtained within the clinical setting, or over the telephone via an online consent form, by a trained member of the team in accordance with Good Clinical Practice.

For male participants, they will either be consented face to face in a clinical setting if they attend with their partner, or over the telephone via an online consent form. If not, the documents will be posted out to them and they will be asked to complete the questionnaires and consent form at home and return it with their partners at the next clinic appointment or post it straight back to the study office. They will be offered the opportunity to speak to a member of the research team on the phone if they are uncertain about any aspect of the questionnaire or consent form.

In some cases participants fill in the registration form with their clinical details which are stored in the clinical notes but have not signed the consent forms. In these cases participants will have the PIS and consent forms posted to them and they will receive a telephone call from by a research nurse or midwife to ensure they understand the study and to ask them to sign the consent form online or post it back.

Standard Operating Procedures will be used that clearly set out the processes of obtaining consent, data collection and storage, and define the roles and responsibilities of the parties involved. All documentation associated with obtaining informed consent, e.g. patient information sheets and consent forms, will be approved by the Host institution, REC and HRA. The responsible team member will confirm eligibility, encourage open discussion and answer any questions that patient(s) may have. The consent discussion will be noted in the medical record along with the signed consent form which should be retained in support of data collection. A copy of the consent form will be given to the patient.

3.9 cohort multiple Randomised Controlled Trial (cmRCT) design

In addition to providing consent for the Tommy's Net cohort study, participants will also be invited to join a cohort multiple Randomised Controlled Trial (cmRCT), which is embedded in Tommy's Net. cmRCT is a relatively new trial design that simplifies the recruitment and conduct of trials compared with current RCTs (12). In this trial design, participants are asked to agree to participate in the control arm of any future trials that will be conducted by the research team. Once a substantial cohort of participants has been established that have given their consent to participate in the cmRCT, one is able to conduct a trial by identifying and selecting a random sample of participants who will receive the intervention, and another group that will continue to receive standard care. Those patients that are allocated to the intervention will be invited to give their written, informed consent to participate in the intervention arm. However, those allocated to standard care (control arm), can continue to be followed up in the usual way with no additional contact required. Relevant outcomes and other measures are taken on all patients in both arms as part of the regular follow-up process. A large benefit of this trial design is that the same cohort can be used for multiple interventions, so are large number of clinical trials can be conducted within the same core cohort of patients.

The detailed description of each trial will be provided in Appendix 1 of this protocol. A substantial amendment will be submitted to the responsible REC each time a new trial is embedded within this cohort and added to the protocol.

3.10 Withdrawal

A patient is entitled to withdraw consent at any time. They should either inform the clinician responsible for their care, contact the Centre directly, or contact the Research and Development Office within their Trust. Withdrawal of consent, and details of all data involved, will be recorded by the Centre. They will also be able to leave their data but decline to receive reminders to update us with their reproductive history outcomes. Any data on explicitly withdrawn patients will be removed from the database.

3.11 Documentation and confidentiality

The clinical information system will reside within the University Hospital Coventry and Warwickshire NHS trust (UHCW). At UHCW there is an Information Governance

Framework in place that represents itself as the annual Information Governance Tool Kit assessment. This is a key performance measurement for the trust and comprises of the following;

- Robust management and accountability for all aspects of information governance.
- An information governance committee with direct accountability to the quality and Governance committee, that is chaired by the Director of Corporate affairs and has access to appropriately skilled expertise across the entire Information Governance Agenda
- There is a register of all major information assets with assigned responsibility for each asset.
- Information risks are managed, were applicable though owners of information assets and linked to established risk management processes and governance arrangements.
- There is an effective information security even reporting and management processes and governance arrangements
- There is an effective information security event reporting and management procedures in line with Department of Health policies and guidelines
- There are formal contractual arrangements in place with all contractors and support organizations and that these include compliance with information governance requirements.
- Policies and procedures are documented to ensure compliance with common law obligations of confidentiality, Current Data Protection legislation and the NHS Care Record Guarantee . Key areas include but are not limited to:
    - Consent and management and ethical practice
    - Information sharing protocols
    - Fair processing
    - Subject access request and other GDPR requirements
    - Confidentiality code of conduct
    - Business continuity and disaster recovery
    - Physical security
    - Network security
    - Remote/home/teleworking
    - Secure data transfer
    - Access controls and access management
    - Data and media destruction
    - Local data warehousing
    - Cross boundary information sharing
    - Records management
    - Data flow mapping
    - Record retention
    - Archiving
    - Data quality including NHS number implementation

The database will be hosted at University Hospitals Coventry and Warwickshire on secure servers, specific members of the Institute of Digital Healthcare, WMG, and

University of Warwick will be given access to the server to administer the system. Information from other sites will be transferred through the secure NHS N3 network (n3.nhs.uk). Data stored will remain on the UHCW network and no data will be transferred to the IDH. Any patient identifiable data required for the trial will, similarly, be kept at the Trust sites, linked to the data stored within the system via a unique identifier, all data stored outside the trusts, e.g. for the purposes of statistical analysis, will be appropriately anonymised.

Certain information from participants consented to the Tommy's National Centre for Miscarriage Research study (Trial IDs, mobile numbers and email addresses) will be transferred securely to the University of Warwick hosted online survey system in order to collect follow up information. Only the IDH administrators and hospital research team will have access to the system. Automated invitations will be sent via SMS (or email if a mobile phone number is not available). A welcome message will be sent asking to confirm mobile phone number, followed by 6monthly requests for information. This invitation will consist of a one-time use link allowing the Tommy's team to trace the responses back to the patient identifiable baseline information, stored at UHCW. No identifiable information will be sent out in communications and no participants or members of the public will be able to access stored information (unless through a data subject request). The data collected, through the secure patient portal, will not be identifiable (will not contain the patient details section of the follow-up form) and will be transferred to the hospital and subsequently deleted from the system after review by an authorised research midwife. Patient may also receive up to 6-12 text messages a year for support/information.

The initial SMS will read: Thank you for joining Tommy's net. You will receive 6monthly texts with a link to a short questionnaire. Click here (LINK) to confirm your number. Tommy's
The 6monthly follow up will read: Update your record quickly by completing this questionnaire (LINK). All information will be used to improve our understanding of miscarriage. Tommy's
A reminder message will be sent around 48hours and 96hours.

Examples of the information text messages:

- Emotional well-being is important when trying to conceive and when pregnant. See tommys.org for support (LINK)
- Tommy's net has been looking at weight in couple's who are trying to conceive. For support in optimizing your weight visit tommys.org (LINK)
- It can be difficult to stop smoking. See tommys.org (LINK) for help and advice
- Folic acid is important when preparing for a pregnancy and in the first 12 weeks to help the baby's spine develop. See tommys.org (LINK)

Management of the database will be subject to the NHS IG Tool kit and Standard Operating Procedures in place at the IDH. Specifically, access to the clinician/research portal will be limited to authorised users on NHS computers, access to the data will be allowed according to the user's role:

- Principal Investigators will have access to all patient information at their site, including patient identifiable information stored at their trust. They will also have access to anonymised data originating from other sites. They will be able to create new records and modify records they have entered (all of which will be logged by the system)
- Researchers will only have access to anonymised data but will be able to view information across sites. They will not be able to modify data.
- Data Managers, such as the database administrators at the IDH will not have access to the web portal and will not be able to read the raw data.
- Once a patient portal is developed, this will be accessible through a secure web login by registered patients. Patients logging in to the patient portal will only be able to see their own data and will be able to submit new data for review by the site PI.

Access to existing hospital systems from Tommy's Net will be restricted to those results relevant to the trial and only the treating clinician will be authorized to view and import this data from any hospital or healthcare system. Any data copied to or from the trial system will only be transferred through encrypted channels to ensure data is kept secure at all times.

The research system has been validated through functional and user testing and approved use cases have been documented. An approved process for failure recovery is also in place which ensures that, even in the event of catastrophic failure, the system can be restored within 2 working days and, at most, 1 days' worth of data will be lost.

3.12 MHRA Compliance

The trial database developed complies with MHRA requirements as detailed in the Annex 11 guidelines published under Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and the electronic record requirements for Good Clinical Practice:

- Data integrity is ensured via ongoing data review.
- There is a clear and documented change control process which ensures all changes are approved and have a clear audit trail.
- Any changes to the data within the system is logged automatically, time stamped and recorded along with the user who made the change.
- All information entered into the system can be reviewed by the investigator regardless of who entered the data.
- Originals of any scans or images imported into the system will be kept on their respective clinical systems and appropriate quality controlled procedures will be used to anonymize the images.
- Access to trial data and audit trails can be granted to inspectors and sponsor representatives for auditing and monitoring purposes.

- Data and metadata on the system can be archived in accordance with Clinical Trials Regulations for up to 25 years.
- Written procedures are in place to cover all the above processes.

In addition to the above mentioned procedures, Trust R&D will be granted oversight access to the research system allowing them to detect and report any breaches of GCP.

Customisation of the trial system for Tommy's will be conducted in collaboration with the investigators to ensure the sponsor's established requirements for completeness, accuracy, reliability and performance are met. The design process and user requirements will be documented. Standard Operating Procedures (SOPs) will be drafted and maintained for the use of the system.

3.13 Data access and sharing

The underlying principle of the Tommy's National Centre for Miscarriage Research is that data stored within Tommy's Net is made available to all the research centres that have been granted approval by the responsible ethics committee. This provides a reciprocal arrangement whereby anonymised data can be uploaded to Tommy's Net and then shared between all approved parties within the Centre. The Centre has procedures in place to ensure the security, confidentiality and data protection of the collection. The aim is to ensure that researchers do not have access to personal identifiers through these data.

All stored data that relates to specific research projects within the Tommy's National Centre for Miscarriage Research will have obtained separate ethical and regulatory approval where appropriate. This will have been obtained for the site responsible for each specific research project with approval for the data access and sharing arrangements described above.

3.14 Analysis

The data will be interrogated so that all clinics will have anonymized information on:

- Numbers and demographic of attendees.
- Running live birth rates per clinic and per subgroup.
  For each investigation undertaken by the NHS clinical service the investigation will be assessed for its ability to predict pregnancy outcome. Mathematical models will be created in liaison with appropriate statisticians to construct outcome prediction using demographic data and investigation results. Aurelio Tobias a statistician with significant expertise in outcome prediction will advise on the outcome prediction models used.
- A semantically enabled query tool will be developed alongside the research database to allow clinicians and researchers to query anonymized information stored in the database for initial hypothesis testing.

- Further ethical approval will be sought for other studies involving tissue collection. Once results from these new test are available they will we assess with the outcome prediction models that have been developed.

4. Study supervision

The investigators who will receive progress reports every 4 months will oversee the study. The Warwick investigators and representative from Birmingham and Imperial and will have twice monthly virtual meetings to report on the progress.

5. Ethics and Sponsorship & indemnity

The study will be conducted in compliance the principles of the ICH GCP guidelines and in accordance with all applicable regulatory guidance, including, but not limited to, the Research Governance Framework. Ethical approval for this study will be sought from the Research Ethics Committee combined with Health Research Authority (HRA) approval. No study activities will commence until favorable ethical opinion and HRA approval has been obtained. Progress reports and a final report at the conclusion of the trial will be submitted to the approving REC within the timelines defined by the committee. Confirmation of capacity and capability will be obtained from the R&D departments obtained prior to commencement of the study at all participating sites.

UHCW NHS Trust has agreed to act as sponsor for this trial and will undertake the responsibilities of sponsor as defined by the UK Policy Framework for Health and Social Care Research and ICH Good Clinical Practice. An authorised representative of the Sponsor has approved the final version of this protocol with respect to the trial design, conduct, data analysis and interpretation and plans for publication and dissemination of results.

“The study will be monitored by the Research and Development Department at UHCW as representatives of the Sponsor, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study.”

As sponsor, UHCW provides indemnity for this trial and, as such, will be responsible for claims for any negligent harm suffered by anyone as a result of participating in

this trial. The indemnity is renewed on an annual basis and will continue for the duration of this trial."

6. Publications policy

All publications arising from this data will be agreed by all investigators prior to submission.

7. Intellectual property

The legal arrangements relating to intellectual property (IP) will be adhered as per the signed agreement between Tommy's Charity and the University of Birmingham (lead site for the Tommy's National Centre for Miscarriage Research).

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Appendix 1. cmRCT protocols

BMJ Open

Quantitative assessment of pregnancy outcome following recurrent miscarriage clinic care: a prospective cohort study

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Quantitative assessment of pregnancy outcome following recurrent miscarriage clinic care: a prospective cohort study

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Quantitative assessment of pregnancy outcome following recurrent miscarriage clinic care: a prospective cohort study

Abstract

Objectives

To measure pregnancy outcome following attendance at a recurrent miscarriage service and identify factors that influence outcome.

Design

Prospective, observational electronic cohort study.

Setting

Participants attending a specialist recurrent miscarriage clinic, with a history of two or more pregnancy losses. 857 new patients attended over a 30month period and were invited to participate. Participant data were recorded on a bespoke study database, 'Tommy's Net'.

Participants

777 women consented to participate (90.7% of new patients). 639 (82%) women continued within the cohort, and 138 were lost to follow up. Mean age of active participants was 34 years for women and 37 years for partners, with a mean of 3.5 (1-19) previous pregnancy losses. Rates of obesity (maternal: 23.8%, paternal: 22.4%), smoking (maternal:7.4%, paternal: 19.4%) and alcohol consumption (maternal: 50%, paternal: 79.2%) were high and 55% of participants were not taking folic acid.

Outcome measures

Biannual collection of pregnancy outcomes, either through prompted self-reporting, or existing hospital systems.

Results

639 (82%) women were followed up. 404 (83.4%) reported conception and 106 (16.6%) reported no pregnancy, at least six months following registration. Of those that conceived, 72.8% (294/404) had a viable pregnancy. Maternal smoking and BMI over 30 were significantly higher in those who did not conceive (p=0.001)

Conclusions

Tommy's Net provides a secure electronic repository on data for couples with recurrent pregnancy loss and associated outcomes. The study identified that subfertility, as well as repeated miscarriage, maternal BMI and smoking status, contributed to failure to achieve live birth. Study findings may enable comparison of clinic outcomes and inform the development of a personalized holistic care package.

Strengths and Limitations of this study (related to the method)

- The 'Tommy's Net' e-repository and associated database contains baseline and prospective pregnancy outcome data from the largest known population of couples with recurrent miscarriage in the UK.
- Time to conception and viable pregnancy can be calculated from this data using time to event analysis.
- Obtaining follow up data is challenging but can be improved by using a variety of data collection methods.
- Follow up data is only requested biannually, therefore this is an inevitable lag in data collection.
- Limited use of the English language can be a barrier for participants completing the initial lengthy questionnaire.

Introduction

Miscarriage, the loss of a pregnancy prior to viability (24 weeks gestation) is common, with 15% of pregnancies ending in miscarriage[1,2]. Most miscarriages are sporadic and occur before 12 weeks gestation[3]. Recurrent miscarriage (RM) is defined as two or three (or more) consecutive miscarriages[4,5]. It is estimated that 1.9% of women experience two consecutive miscarriages, and approximately 0.7% suffer three or more consecutive miscarriages [1,6,7]. In recurrent miscarriage, the incidence of euploid fetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases[8]. Recurrent miscarriage is a debilitating disorder, associated with considerable psychological morbidity[9].

European and national miscarriage care guidelines recognise the importance of providing good physical care and psychological support[4,5] however there are no standardised outcomes to assess care within clinics. The recent Lancet series[1] on miscarriage which brought together best evidence and expert opinion, clearly outlines essential investigations for couples, dependent on their history, together with a graded model of care to optimise outcome. This could address deficiencies identified by couples in a systematic review by MMJ van den Berg and colleagues (2018)[10], which evaluated features of care that couples valued within miscarriage services, identified that explaining potential causes of pregnancy loss and planning for future pregnancies were specific areas for improvement.

Accurate information following attendance at a recurrent miscarriage clinic is important for couples' counselling, stratifying care and directing research. Whilst data does exist around outcomes in a recurrent miscarriage setting[3,11,12] it requires prospective update from clinics working under standardised guidance[4], including all couples regardless of their outcome and not only those who conceived or who participate within a research trial.

The Tommy's National Centre for Miscarriage Research brings together an interdisciplinary Translational Medicine research grouping jointly at the University of Warwick, University of Birmingham and Imperial College London. The Centre is dedicated to research across all aspects of miscarriage and early pregnancy complications including medical, basic scientific, social and ethical issues. A secure electronic data collection tool and e-repository (with associated database), Tommy's Net, has been developed to facilitate recording of participant data, including follow up[13].

Objectives

Our objective was to quantify the long term cumulative live birth rate after first attendance at a recurrent miscarriage clinic. A cohort of couples was developed, with prospective data collection of the medical and obstetric histories of both partners, investigation results and pregnancy and neonatal outcomes. The tool for collecting data on this cohort is designed to be used in multiple clinics so that success rates between clinics can be benchmarked. This objective will also allow clinics to support and assess new care pathways, identify areas needing further research, develop outcome prediction modelling and investigate new tests in future clinical trials.

Methods

The e-repository and associated database has been developed over several years by a team with representation from University Hospital Coventry and Warwickshire (UHCW) NHS Trust and University of Warwick, Imperial College and University of Birmingham. The cohort was initiated at UHCW but designed so other clinics can join. This paper summarises data collected only from couples attending UHCW recurrent miscarriage service.

Sponsorship, Ethics, Data management and Information Governance

Sponsorship (from primary hospital Trust), ethical permissions (IRAS No: 213740, 2225751 REC Ref: 17/WM/0050: 17/WM/208) and adherence to information technology governance standards was obtained. The study database complies with the regulatory requirements for Good Clinical Practice.

Patient and public involvement

An established patient and public involvement (PPI) group from within the Tommy's centre at UHCW was consulted during initial protocol development. Two further PPI sessions with 10 service users, each including 9 women and 1 partner, where consulted to ensure follow up methods where acceptable to participants and to optimise response rates.

Setting

This cohort is from a specialist recurrent miscarriage clinic in a tertiary referral centre (UHCW) within the UK. Miscarriage care followed European Society of Human Reproduction and Embryology (ESHRE) guidelines[4].

Eligibility

All couples with a history of two or more pregnancy losses (including biochemical loss[1]*, miscarriage, molar pregnancy, ectopic pregnancy and stillbirth) were eligible (supplementary file 1).

Recruitment

Couples are referred to the recurrent miscarriage clinic by their General Practitioner (family doctor). Signposting prior to referral can occur from other hospital departments (e.g., Early Pregnancy Assessment Unit, Acute Gynaecology, Fertility unit) or charities (e.g., Tommy's, The Miscarriage Association). Couples are then sent information about Tommy's Net by post along with a baseline questionnaire (supplementary file 2). At their first clinic visit a member of the research team explains Tommy's Net and asks them to consent to storage of their data.

Data Collection

Both partners complete initial baseline questionnaires including demographic details, obstetric and medical history. Investigation results, blood pressure and body mass index (BMI) are recorded by clinic staff and entered into Tommy's Net (supplementary file 2).

The Tommy's Net e-repository and database system, used for data collection and storage in the study, is based on the CURe framework[13,14], a modular system for collecting research data in secondary care settings. The framework includes methods for the standardised, flexible capture and

1. * Defined as no pregnancy identified on ultrasound scan

storage of data. The system is intended to link to the participating centre's clinical information systems where possible to access relevant data already collected, such as laboratory test results. Tommy's Net includes a database to organise data collected as part of the study and a web application for healthcare professionals to use for data entry, review and use in clinic (supplementary file 3). Data in Tommy's Net can be exported for analysis. The development of Tommy's Net has seen continuous improvements based on feedback from clinicians, researchers and patients. The design of the system is intended to promote interoperability with existing hospital systems to allow researchers to use information already collected, collect pregnancy outcomes to benchmark clinics and allow researchers to identify high risk groups of patients for future research.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics. Time to event analysis was performed using Kaplan-Meier curves, a non-parametric method for assessing the probability of an event occurring over time. Multi-variant analysis was conducted using age, BMI, cigarette smoking status, alcohol consumption and use of folic acid.

Retention and Pregnancy Outcomes collection

A variety of methods were assessed to collect patient reported pregnancy outcomes after the first clinic visit. Initially women were encouraged to self-report outcomes by telephoning the clinic or completing an outcome collection form sent by email. Automated invitations to complete this survey are sent via SMS every six months requesting information for follow up. This invitation consists of a single use link allowing the research team to trace the responses back to the patient identifiable baseline information.

Further outcome data are collected through viability scan visits, which can be accessed following initial review in the recurrent miscarriage service and using existing hospital systems. Researchers used a maternity database, Evolution©, and a local intranet service to improve follow up and to validate participant reported information.

Using a variety of methods to collect outcomes improves follow up rate, however this does require researcher vigilance to avoid duplicate data entry. 17.8% of participants are still lost to follow up, therefore more work is needed in this area to encourage continuous engagement of participants (fig 1).

Improving baseline data

In the first three months of recruitment, a number of couples (n=83) consented to the study but did not complete the baseline questionnaire. This resulted in their data being marked as 'inactive' within the database (i.e., consented to the cohort study but not returned initial baseline questionnaires). On receipt of the baseline questionnaires, participants are 'activated' and followed up six monthly (n=10/83 to date). Our process has been updated so critical data items are collected by the clinician from all couples who consent before leaving the initial clinic appointment. Participants are no longer registered within the database until they have completed the initial baseline questionnaire.

Improving pregnancy outcome data collection

Initial pregnancy outcome data collection was poor with only 25% reporting their outcome, mainly due to technical difficulties in completing electronic versions of the forms for the participants. The response rate has gradually improved with development of a text message system. This was followed by other improvements such as a series of changes to the text message wording, by including partners in the messages, and changing the timing of the texts (with the majority sent in the afternoon or evening). Reminder messages are sent after 48 hours and after one week (if no responses from the initial text are received). Changes have been informed by patient and public involvement (PPI) groups, which were used to understand further why participants fail to respond to follow up SMS text message. Some explained that once they had had a baby, they were busy with their baby and forgot to reply. Conversely, repeated reporting of no pregnancy, or miscarriage was felt to be disheartening, or less important. We hope through education and careful wording of the questionnaire the response rate will continue to improve.

These approaches have contributed to an increase in response rate and combined with data from existing hospital systems, the response rate for pregnancy outcomes was 82.2%.

Data linkage with a general practice database was not deemed useful, because few miscarriages are recorded on the local general practice databases. Furthermore, there was a lack of standardisation in pregnancy data in primary care, though automated links with both primary and secondary care electronic health systems are still planned. The maternity services database may provide a fruitful source of pregnancy outcome data in the future.

Results

Analysis of cumulative live birth rate

Between May 2017 and January 2020, 777 women (and 480 partners) who attended the recurrent miscarriage clinic completed a baseline questionnaire and consented for their data to be included in the database (fig 1). One hundred and thirty-eight (17.8%) participants were lost to follow up (no response to SMS, or information obtained for hospital databases), therefore 639 women are active within Tommy's Net. One hundred and thirty-four of these women are within six months of consenting to the study and have not yet received a scheduled SMS. Five of these women have reported conceiving out with the SMS system with the data captured through early pregnancy scan clinics. Of the active women, their mean age was 34 years (table I) and mean number of previous pregnancy losses was 3.5 (range 1-19). Demographic characteristics including age, ethnicity, alcohol intake, folic acid use and previous live births were not statistically different between participants who conceived and those who did not (table I). Statistically more participants who did not conceive smoked and had a BMI over 30.

	Total number active patients continuing in cohort	Those that did not conceive within the continuing cohort	P value
Number	639	106	
Age mean (range)	33.7 (18-46)	34.03 (22-47)	0.092
Ethnicity	White: 84% (436/519) Mixed: 2.1% (11) Asian: 8.9% (46) Black: 3.3% (17) Other: 1.7% (9) Unknown (120)	White 85.5% (65/76) Mixed: 2.6% (2) Asian: 6.6% (5) Black: 3.9% (3) Other: 1.3% (1) Unknown (30)	
Average no. of previous live birth	0.6	0.15	0.36
Average no. of previous miscarriages	3.5	3.6	
BMI over 30	23.8% (n=126/530)	30% (n=26/87)	0.001
Smoking Y/N	Yes:41 (7.4%)	Yes: 12 (13.5%)	0.001
Alcohol Y/N **Units**	Yes: 278 (50%) 5.54 (0.5-30)	Yes: 51 (58%) 5.03 (0.5-35)	0.083 <0.001
Folic acid	Yes: 292 (45.5%)	Yes: 35 (47.17%)	<0.001

Table I: Comparison of demographics for all active participants, participants that did not conceive and those that were lost to follow up

Pregnancy results

Four hundred and four of these women reported conceiving. One hundred and six (16.6%) women reported no pregnancy at least six months following registration, 31 (4%) of whom are no longer trying to conceive. Of those that conceived 72.8% (294/404) had a viable pregnancy (215 live births, 1 stillbirth, remainder currently >24 weeks at time of initial analysis). Analysis of data exported from the database in January 2020, revealed a conception of rate of 81% after two years within the cohort and viable pregnancy rate (pregnancy over 24 weeks or live birth at time of export) of 60% two years after attending the recurrent miscarriage clinic (fig 2). Age does impact on time to conception and time to viable pregnancy, with women of 25-34 years being more likely to have a viable pregnancy two years after initial review than other age groups (fig 3). Partner age within this cohort did not

have a marked effect on time to conception or viable pregnancy, particularly within the first year after initial consultation.

After one year in the cohort there is a 30% difference between the number of couples who conceive and those who reach viable pregnancy. This difference/gap gradually decreases and plateaus after 900 days to a difference of 19% (conception rate 82% with 63% reaching over 24 weeks gestation). The couples within this 'gap' represent those within our clinic who conceive but miscarry prior to viability despite current intervention and support. This gap is maintained within the 30-39 years age group but is less pronounced within those who conceive aged 25-29 years (fig 3). Female BMI over 30 and female smoking status along with miscarriage history increases the time from initial consultation to conception and viable pregnancy within this patient group (fig 4-6). Partner BMI, smoking status or alcohol intake did not impact on time to conception or time to viable pregnancy.

A healthy BMI increases the chance of viable pregnancy, particularly when compared to a maternal BMI over 30kg/m2 (fig 4). Having a BMI over 30 increases the time taken to viable pregnancy by 100-200 days. Within this population BMI does not appear to significantly change the time to conception (fig 7), particularly within the first 300 days.

Couples who have had four or more miscarriages take longer to conceive, compared to couples who have has three or less miscarriages (fig 5). There is a 17% gap within couples who have had four or more losses when comparing the rate of conception with viable pregnancy. This gap represents those that continue to miscarry and should be a population where research should be focused.

Smoking status impacts on time to conception (fig 6). Females that smoke take longer to conceive with significantly more never conceiving.

Discussion

Database

We have developed an electronic method of obtaining outcomes from women following attendance at a recurrent miscarriage clinic. These outcomes can be used to assess recurrent miscarriage care and form a 'benchmark' to compare clinical services and interventions. The electronic cohort provides clinic outcome data in real time (supplementary file 3), and can be used for counselling couples as to both the chance of their next pregnancy succeeding and their cumulative time to live birth. This is novel, as data[3,11,12] identified at literature review could not be generalised to the UK population. Lund and colleagues[11] used a national, Danish registry to collect live birth data from attendees up to five years after their visit to a recurrent miscarriage clinic. Registry data were collected retrospectively and lacks information from couples who moved to other countries. Brigham[3] analysed 716 couples over a 10-year period in their Liverpool clinic, with pregnancy outcome data on 325 patients with unexplained recurrent miscarriage. Data were only reported on those who conceived and had their pregnancy and birth care at the same hospital. These datasets are now over 20 years old. Kling and colleagues[12] published more recent data based on a tertiary referral immunological centre within Germany. Seven hundred and nineteen couples were followed up for a median of 33.7 months, producing time to pregnancy and time to delivery over a five-year period. Whilst this is valuable data the study excluded couples who already had children within the partnership (25% within our clinic) and used immunotherapy in a proportion of couples which is not routinely used within the UK. It also asked for patient reported outcomes between nine months to

four years after the event which could be prone to recall bias. This database will continue to collect and provide prospective outcomes of all those who attend this recurrent miscarriage clinic and, as use increases within the other sites it will allow comparison of outcomes with the aim of sharing good practice to improve patient care.

Infertility

The time to conception curve within our RM population is similar to that in the general population[15,16]. It is often assumed that the reason couples do not have a baby after attendance at recurrent miscarriage services is because they have miscarried again. This however is only part of the picture. Analysis to date has identified that within our cohort 16.6% (n=106) of couples fail to conceive within the follow up period. These patients are similar ethnicity when compared to all within the active cohort. They do have a trend to a higher BMI and are statistically more likely to smoke. Whist the mean age was similar in those conceived and those who did not, the expected effect of age on conception was demonstrated with a lower conception rate after two years in those over 40years old.

Reasons why couples do not conceive are complex. Couples were encouraged to conceive immediately from first consultation, whilst investigation results are awaited. Anecdotal evidence from the text message system and PPI groups shows some couples feel unable to continue trying to conceive due to the potential risk of miscarriage. Recent research[17] has highlighted an increased risk of post-traumatic stress disorder following pregnancy loss. We hypothesise that the psychological impact of miscarriage may stop couples from trying to conceive again. This is an important area on which to focus research and facilitate additional counselling and support.

Other couples may be unable to conceive despite actively trying. Identifying this subgroup of couples earlier could facilitate prompt referral to fertility services for assessment and treatment. Potentially increasing their chance of conception and ultimately live birth. Within this population, the rate of conception decreases significantly one year after initial consultation (fig 2). 65% of couples conceive within one year of initial consultation, with only an additional 15% conceiving in the second year. In view of this decrease in pace of conception we suggest referral to fertility services should be considered within this population after one year.

Through-out the UK, access to NHS funded fertility treatment is dependent on maternal weight, smoking status, as well as age and parity. Addressing these factors early in the couple's fertility journey may help to manage expectations prior to referral and reduce any delay in starting treatment. We recognise that weight particularly can be a sensitive issue and difficult to manage. Open and honest discussion, without blame, along with support and advice that joining group programmes for exercise and dietary modification can lead to more pregnancies than weight loss alone[17] should be given. Referral to specialised weight management services including bariatric dietetic and surgical teams could be discussed if appropriate.

There may be a role for ovarian reserve assessment for women who have previously taken over 12 months to conceive. Having strong links, or an integrated multi-disciplinary preconception service including miscarriage and fertility specialists along with psychologist and counsellors may allow a

more cohesive approach to these couples and increase their chance of having a viable pregnancy as well as providing continuity of medical and psychological care.

Outcome Data

Comparing the 'time to conception' and 'time to viable pregnancy' curves illustrate the importance of assessing cumulative data. There is by definition a lag between conception and reaching 24 weeks pregnant, but following this the difference between the curves represents delay in live birth due to miscarriage. This gap decreases initially and may represent an impact from interventions and support within the recurrent miscarriage service. The importance of support to couples will be studied further during a planned qualitative study using semi-structured interviews of affected couples. After 900 days the gap between the curves is static and represents those whom despite conceiving have not yet had a child. This is a group which resources and research should be targeted to further understand reasons for miscarriage.

Health Education

It is well documented that miscarriage risk increases with BMI over 30kg/m2 and smoking status[16, 18, 19, 20, 21]. Despite this 23.8% of women within the cohort have a BMI over 30kg/m2 and 7.4% smoke tobacco. Modifying these lifestyle factors through pre-conception counselling may reduce the chance of miscarriage and improve pregnancy outcome by reducing the incidence of, for example, gestational diabetes. Future research could be targeted at support in weight loss and smoking cessation.

Limitations and strengths

The Tommy's Net e-repository and associated database contains baseline and prospective pregnancy outcome data from the largest known population of couples with recurrent miscarriage in the UK. It allows calculation of 'time to conception' and 'time to viable pregnancy' using time to event analysis. This large dataset aims to facilitate future studies within a recurrent miscarriage population.

Obtaining follow up data is challenging. Using a variety of methods including self-reporting through the text message link and local hospital systems has improved our follow up rate.

Couples with limited English were unlikely to complete the lengthy questionnaire, which is currently only available in English. This means that this study is likely to miss high risk groups within our community

The introduction of the maternity services database could provide a valuable resource to enable improved follow up. Couples attend this RM clinic from all over the UK. Currently couples who deliver within our trust have at least two ways in which we can capture their outcome (SMS text message and hospital database with or without scan clinic information). These checks are not available to couples who have travelled some distance to attend and therefore may be under-represented within the active participants group.

SMS text message requests for follow up are only sent every six months. This means that for the first six months that participants are within the study we do not expect to collect any outcome data. Some of these participants may go on to become 'inactive' and be removed from analysis.

Conclusion

We have developed a user-friendly electronic database, storing comprehensive data, which can provide accurate time to conception and data on viable pregnancies to facilitate analysis into factors contributing to recurrent miscarriage. 16.6% of women within our clinic did not conceive and early referral to fertility services should be facilitated. Over 20% of women within the cohort have a BMI of over 30 and 7.4% smoke. Preconception counselling should be targeted at weight and smoking status with an aim of reducing miscarriage.

Contributorship statement

SQ had the initial concept. OK, SLCK and TNA designed and developed Tommy's net database and extracted initial data. RCS analysed the data and interpreted it along with SQ. RCS wrote the initial draft, which was revised by SQ and DB, and reviewed by AH, OK, SNLCK, TNA, AB, AD, SDQ and SK. All commented on initial drafts and approved the final version.

Competing interests

Nil

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Tommy's Baby Charity (award number N/A)

Data sharing statement

Data Available on Reasonable Request (under ethics restrictions).

Ethics statement

Ethical approval for was obtained from West Midlands- South Birmingham Regional Ethics Committee IRAS No: 213740, 2225751 REC Ref: 17/WM/0050: 17/WM/208

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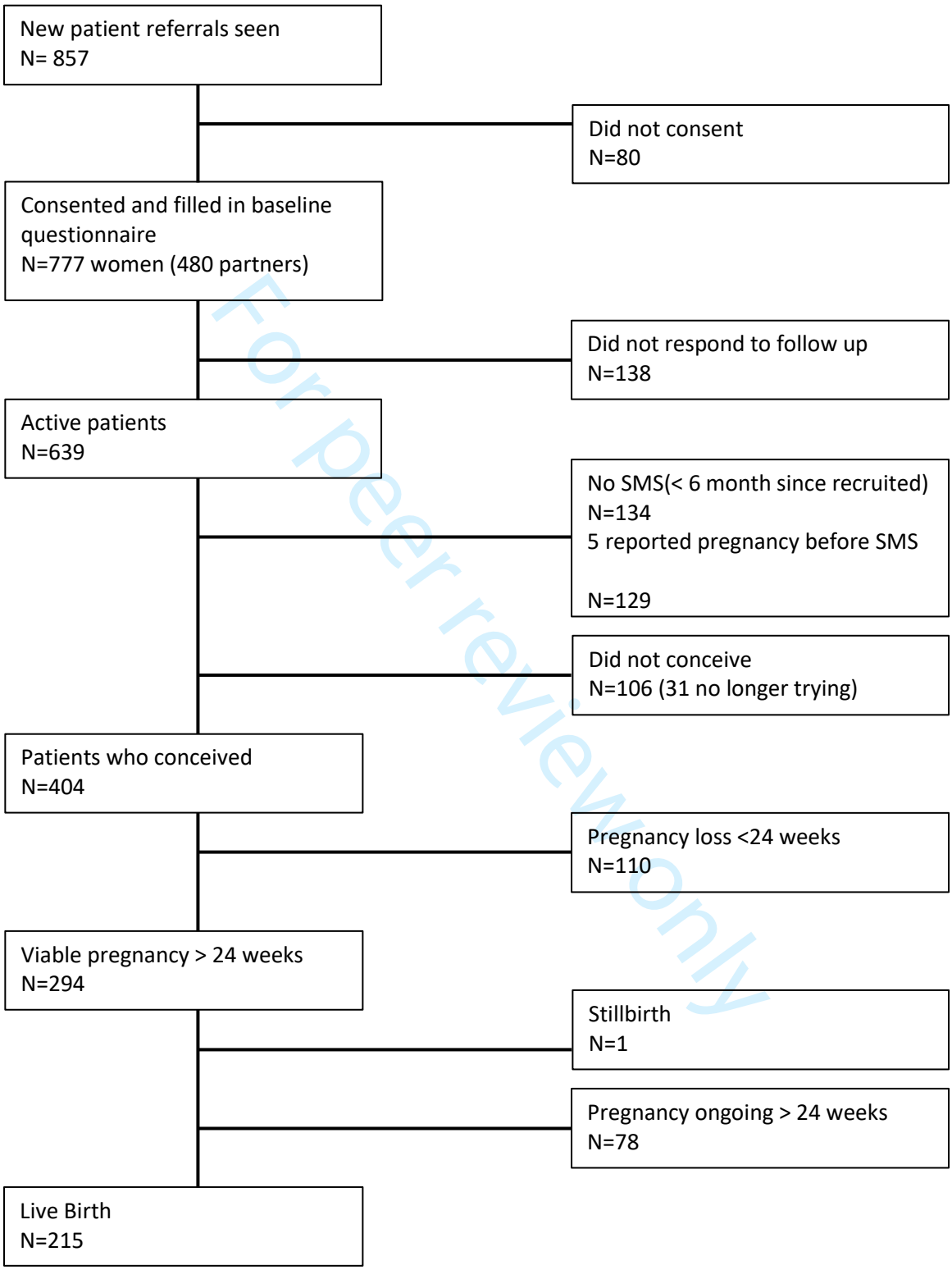
Figure 1: Flow diagram of Cohort



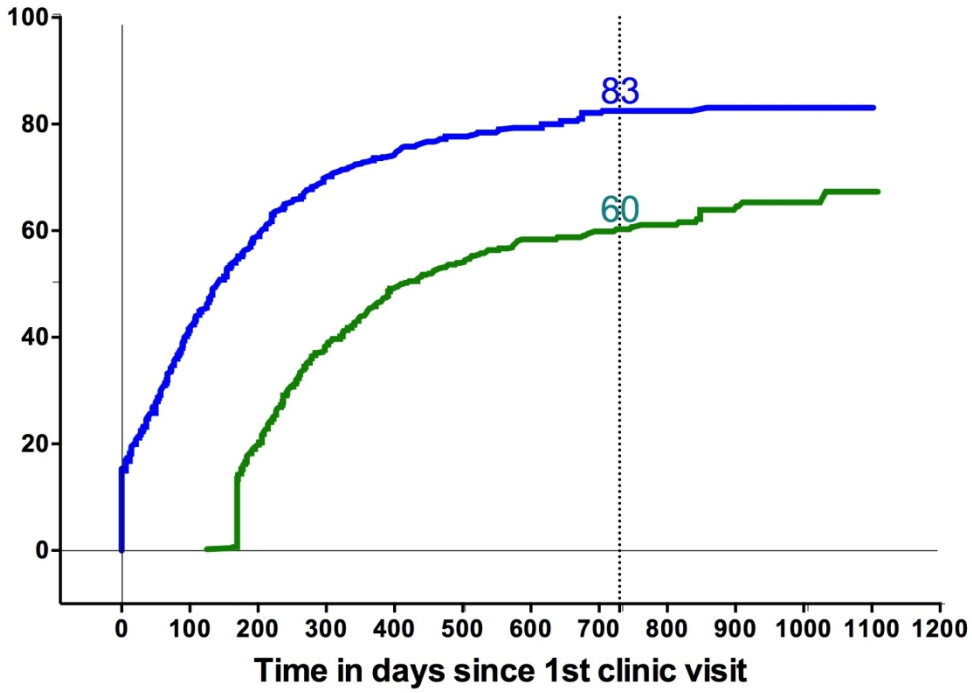


Figure 2: Cumulative rate over time, from initial consultation to conception and viability (>24weeks gestation)
Legend: Blue: conception, Green: viable pregnancy

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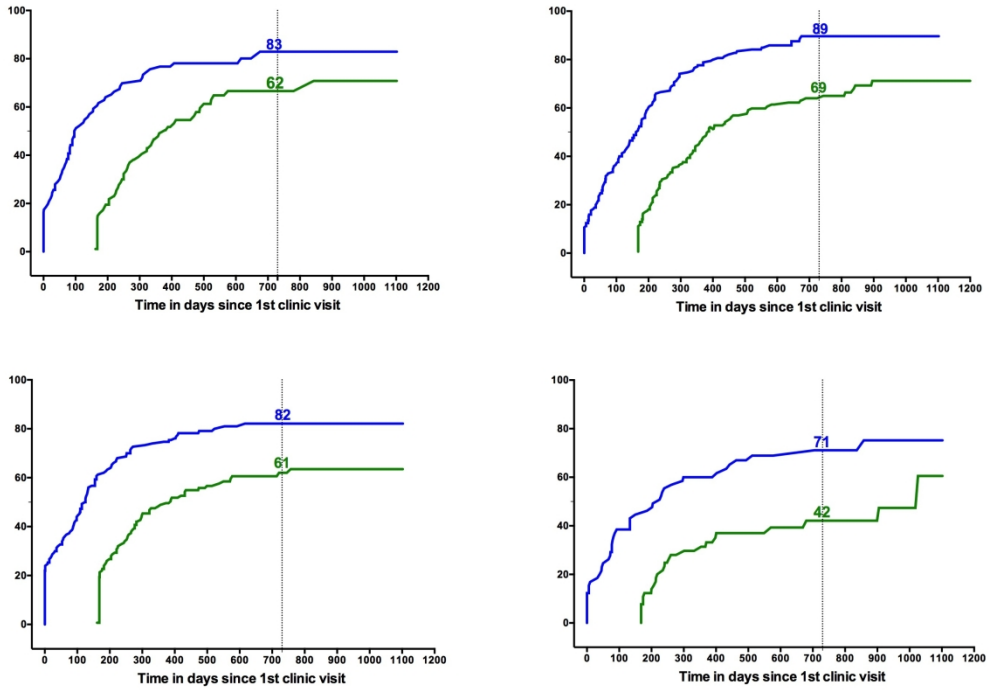

Figure 3: Time from initial consultation to conception/>24 weeks gestation by female age
Legend: Blue = Conception, Green = Viable pregnancy

229x165mm (300 x 300 DPI)

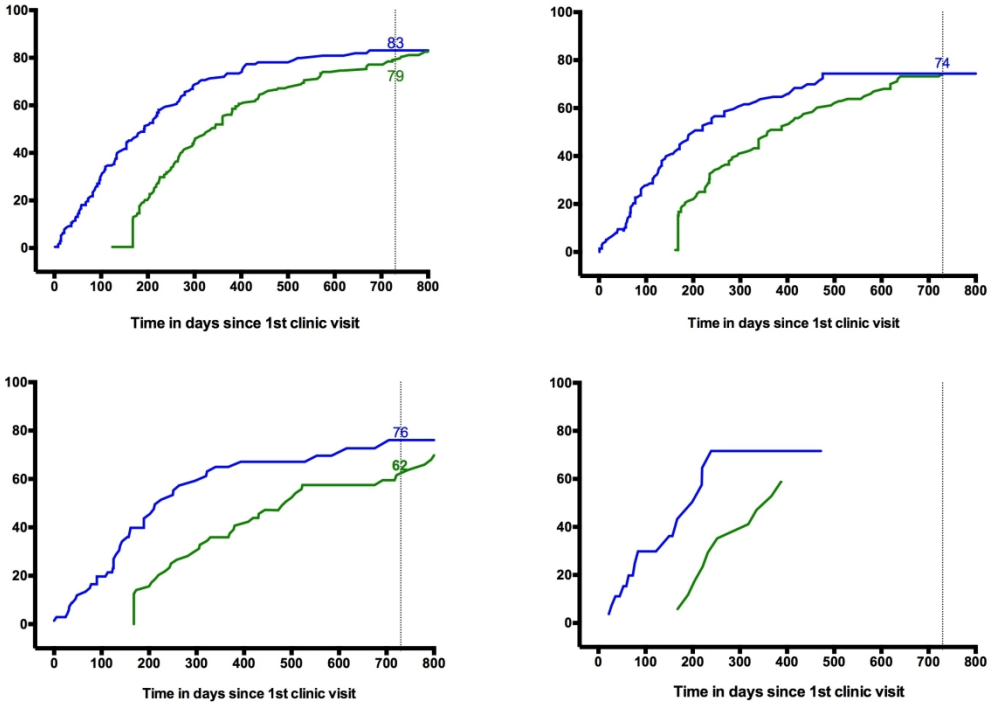

Figure 4: Time from initial consultation to conception/>24 weeks gestation by female BMI range
Legend: Blue = Conception, Green = Viable pregnancy

228x164mm (300 x 300 DPI)

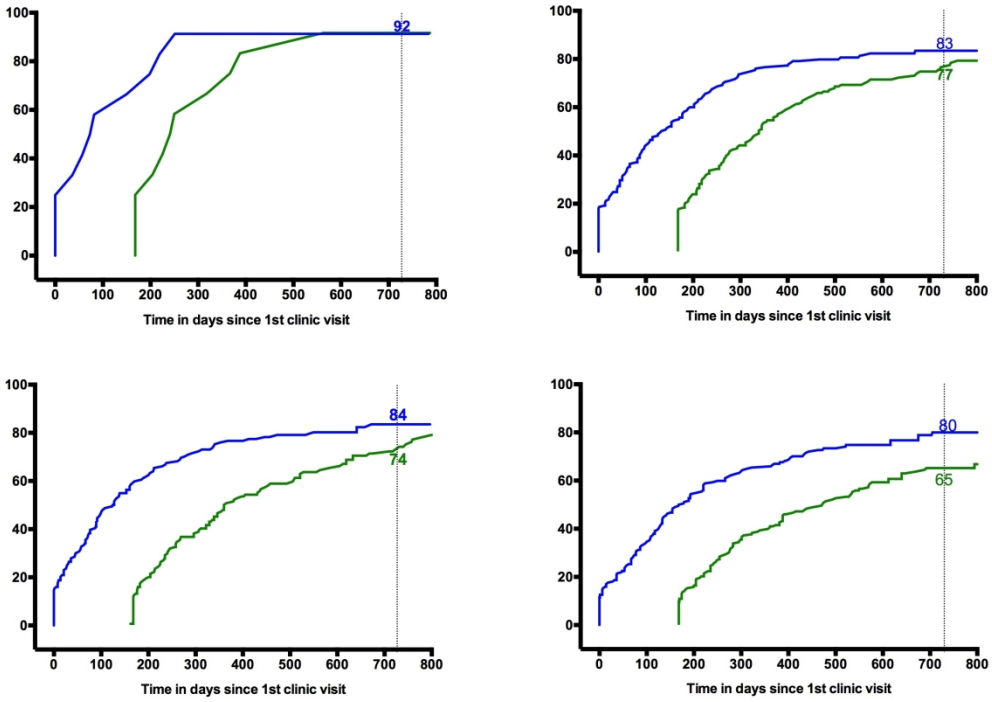

Figure 5: Time from initial consultation to conception/>24weeks gestation by miscarriage history.
Legend: Blue = Conception, Green = Viable pregnancy

228x164mm (300 x 300 DPI)

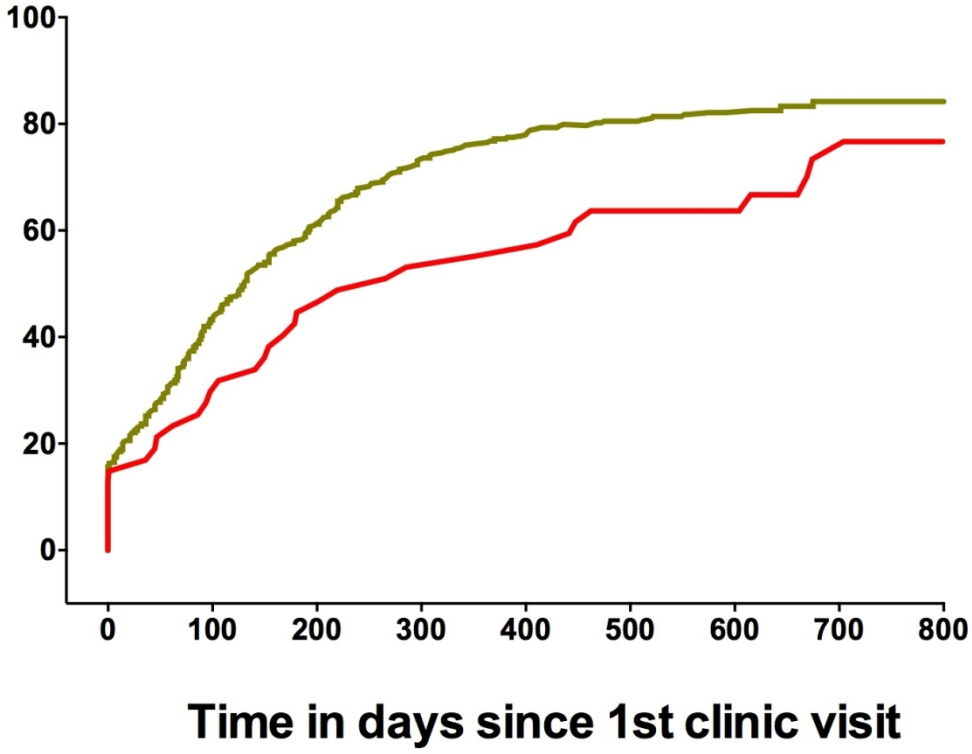

Figure 6: Time from initial consultation to conception by female smoking status.
Legend: Non smoker: Green, Smoker: Red

118x94mm (300 x 300 DPI)

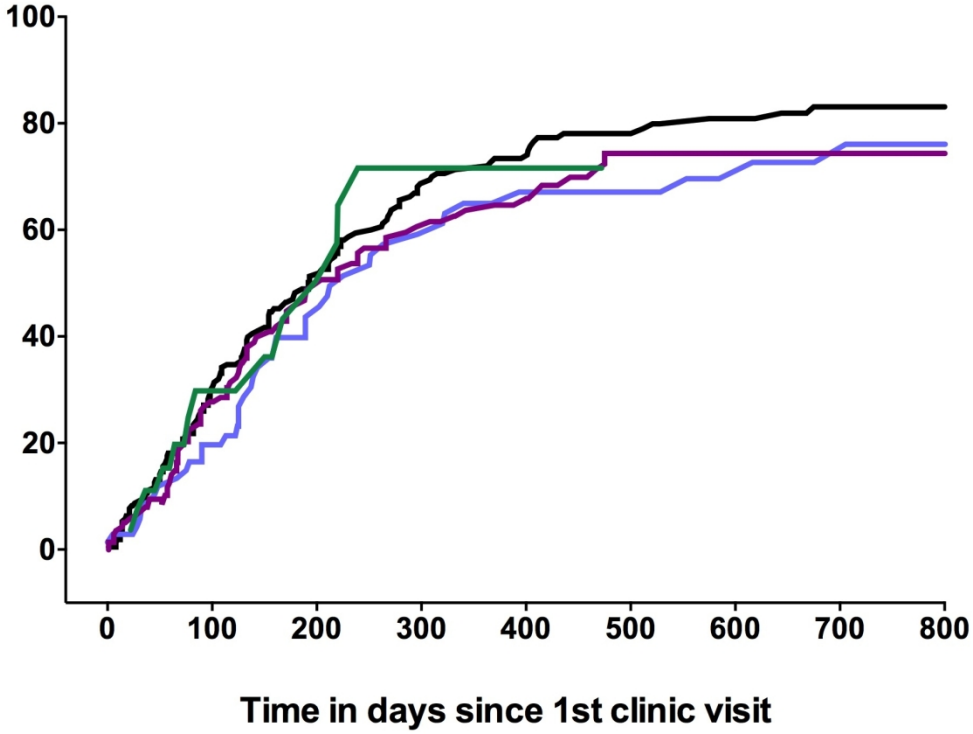

Figure 7: Time from initial consultation to conception by BMI range.Legend: Black: 18.5-25kg/m2, Purple:25.1-29.9kg/m2, Blue: 30-34.9kg/m2, Green: 35-39.9kg/m2

159x123mm (300 x 300 DPI)

Referral criteria for Recurrent miscarriage clinic care UHCW

- Actively trying to conceive
- 2 or more pregnancy losses, including biochemical loss, miscarriage, molar pregnancy, ectopic pregnancy and stillbirth

Tommy's National Centre for Miscarriage Research

University Hospitals Coventry and Warwickshire NHS Trust

Registration form

Male details

Title	**Date of birth**	
Surname	**Ethnic group (see last page)***	
First and forename(s)	**Religion (see last page)***	
Address	**Marital status (see last page)***	
	Education (see last page)*	
	Occupation	
	NHS number	
	Hospital number	
City/town	**GP name**	
County	**GP address**	
Telephone (Home)		
Telephone (Mobile)	**GP telephone**	
E-mail address (we will use this to correspond with you):		

***** - enter the relevant code from the list of tables on the last page of this form

Data Disclosure and Protection: By completing this form, you hereby give your consent for the data to be held within the NHS in accordance with the requirements of the 1998 Data Protection Act (UK).

Male signature:	
Date:	

Tommy's National Centre for Miscarriage Research

Please complete this form with as much information as you are able to. If you are uncertain about any of the questions you will be able to check these with your healthcare provider at your clinic appointment. Please include all medical information in your history even if you think it may be unimportant.

Previous illnesses or medical problems

	Yes	No
Have you had any serious illnesses or medical problems?	☐	☐

If yes, tick all applicable:

Diabetes	☐	Rheumatism or painful joints	☐
Thyroid problems	☐	Skin rashes or other skin disorders	☐
Cancer	☐	Irritable Bowel Syndrome	☐
Heart problems	☐	Coeliac disease	☐
Liver problems	☐	Crohn's disease	☐
Migraines	☐	Autoimmune disease	☐
Epilepsy	☐	Other inflammatory disorder	☐
Depression	☐	Thrombosis (clot in the leg or chest)	☐
High blood pressure	☐	Candida	☐
Lupus (SLE)	☐	Bacterial urethritis	☐
		Abnormal urethral discharge	☐

Other illnesses ☐ Please state: _____

If you have ticked any of the boxes above, please provide further details below:

Current medications and allergies

Please provide details on any allergies you have and medication you are currently taking below:

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Andrological history

Have you had a testicular examination before? Yes ☐ No ☐

What was found? _____

Have you had any of the following diagnosed?

Please tick all applicable options

Absence of a testicle (cryptorchidism)	☐	Mumps	☐
Testicular pain	☐	Tuberculosis (TB)	☐
Twisted testicles (torsion)	☐	Impotence/erectile dysfunction	☐
Testicular cancer	☐	Ejaculatory dysfunction	☐
Varicose veins in your scrotum	☐	Infertility	☐
		STI's	☐

If you have ticked any of the boxes above, please provide further details below:

Have you had any of the following surgeries?

Please tick all applicable options

Groin surgery	☐
Varicocelectomy	☐
Orchidectomy	☐
Orchidopexy	☐
Surgery for hernia	☐

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Family medical problems

Has your mother, father, siblings or maternal aunt(s) had any medical complications? Yes ☐ No ☐

If yes, tick all applicable:

- Miscarriage ☐
- Recurrent (3 or more) miscarriages ☐

If yes: Number of 1st trimester losses (<12 weeks) ☐☐ Number of 2nd trimester losses (>12 weeks) ☐☐ ☐ I don't know

- Obstetric complications (such as pre-eclampsia and growth restriction) ☐
- Genetic or developmental problems ☐
- Heart problems under the age of 50 ☐
- Stroke under the age of 50 ☐
- Still birth ☐
- Pre-term birth ☐
- Infertility ☐
- High blood pressure ☐
- Diabetes ☐
- Blood clots (thrombosis) ☐
- Depression ☐
- Other ☐

Please state: _____

If you have ticked any of the boxes above, please provide further details below:

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National Centre for
Miscarriage Research

Previous paternal history

	Yes	No
Have you had children in another relationship?	☐	☐
If yes, number of children:	☐☐	
Have you ever had a delay (>12 months) trying to father a child?	☐	☐

What age did you enter puberty? ☐☐ years

What is your current average ejaculatory frequency per week? ☐☐☐ times/week

What is your usual ejaculatory frequency per month (4 weeks)? ☐☐☐ times/month

Occupational exposure

	Yes	No
Have you been exposed to any harmful substances during your current or previous jobs? (see below for examples of such substances)	☐	☐

Exposure Type/Substance: (Years of exposure)

Dust	☐☐	Asbestos	☐☐
Fumes	☐☐	Noxious Gases	☐☐
Harmful vapours	☐☐	Chemicals	☐☐

Other (please specify): _____

Please provide further details:

_____

_____

_____

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Type of underwear

What type of underwear do you wear?

Tick one option

Boxer shorts ☐
Boxer briefs/trunks ☐
Briefs ☐
Thongs/Bikinis/G-strings ☐
Long underwear ☐
Jockstraps ☐
None ☐

What type of fabric is the underwear most commonly made from?

Tick one option

Cotton ☐
Synthetic ☐
Lycra ☐
Other (please specify) ☐ _____

Do they hold your testicles to the body, or are they loose?

Tick one option

Tight ☐
Loose ☐
Unsure ☐

Is the tightness of your underwear similar to before the last time your partner fell pregnant?

Tick one option

Yes ☐ No ☐ Don't know ☐

Technology habits

Do you ever sit with a laptop computer on your lap? Yes ☐ No ☐

↓

How many hours per day? ☐☐ hours ☐☐ minutes

Do you keep your mobile phone (that's switched on) in your trouser pocket?

Front pocket? Yes ☐ No ☐

↓

How many hours a day? ☐☐ hours/day

Back pocket? Yes ☐ No ☐

↓

How many hours a day? ☐☐ hours/day

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Diet and supplements

How many days a week do you eat the following foods:

Tick one box per food type

	Number of days per week							
	0	1	2	3	4	5	6	7
Red meat	☐	☐	☐	☐	☐	☐	☐	☐
White meat	☐	☐	☐	☐	☐	☐	☐	☐
Fish	☐	☐	☐	☐	☐	☐	☐	☐
Eggs	☐	☐	☐	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐	☐	☐	☐
Dairy products	☐	☐	☐	☐	☐	☐	☐	☐
Soya products	☐	☐	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐	☐	☐
Nuts (almonds/walnuts)	☐	☐	☐	☐	☐	☐	☐	☐

Do you consume sugar substitutes daily or most days of the week? ☐ Yes ☐ No

How many cups of coffee* do you drink in a typical day? ☐ cups of coffee/day

How many cups of tea* do you drink in a typical day? ☐ cups of tea/day

How many cans (or equivalent) of soft drink do you consume per day (e.g. energy drinks, cola)? ☐ cans/day

Do you currently take any vitamins or supplements? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	How long have you been taking it? (weeks)
1			
2			
3			
4			

* Do not count decaffeinated drinks

Tommy's National Centre for Miscarriage Research

Diet and supplements

If you are not taking vitamins or minerals currently but have taken them in the last four months please complete this table.

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Are you currently taking any protein shakes or protein bars? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Exercise

Do you follow a regular routine of physical exercise? ☐ Yes ☐ No

How many days a week do you exercise?

Tick one option

0 ☐
1-2 ☐
3-4 ☐
5-6 ☐
7 ☐

If you exercise, how many hours a day do you exercise?

Tick one option

< 30 min ☐
30 min - 1 hr ☐
1 hr - 1.5 hrs ☐
1.5 hrs - 2 hrs ☐
2 hrs - 2.5 hrs ☐
> 2.5 hrs ☐

On average how many hours do you spend sitting on a chair per day?

Sofa or armchair ☐ hours/day Work chair ☐ hours/day

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Recreational drug use

Do you currently drink alcohol? Yes ☐ No ☐

How many units per week? ☐☐ units per week

Do you currently smoke? Yes ☐ No ☐

If yes:

How many cigarettes? ☐☐ per day **or** ☐☐ per week

How many vaping sessions? ☐☐ per day **or** ☐☐ per week
One session is classified as 5 or more inhalations

If no:

Have you recently stopped? ☐ Yes ☐ No

If yes, how recently did you stop? ☐ < 1 month ☐ 1-6 months ☐ > 6 months

Do you take any other recreational drugs? Yes ☐ No ☐

If yes, please complete table:

Type	Frequency of use (tick one option)
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months

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Tests and investigations

Please give details of any tests or investigations you've had as a part of your treatment.

Test/investigations	Date of test	Result	Which hospital or clinic did you have the test at?
Semen analysis			
Sexually transmitted infection screening			

If other tests, please state below:

Test/investigation	Date of test	Result	Which hospital or clinic did you have the test at?

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Treatments

Please give details of any treatments you've previously received or are currently receiving as a part of your miscarriage management. Please also include any medications that you've bought yourself.

Treatment (please include medicines and operations)	Dose	Date from*	Date to	Tick if ongoing	Additional clinician's notes
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	

* If an operation, please give the date of operation

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Examination

This section should be completed in conjunction with the a member of the research team who attends to you in the clinic

Weight: ☐☐☐ kg Height: ☐☐☐ cm BMI: ☐☐.☐

Blood pressure: ☐☐☐ / ☐☐☐ mmHg
Systolic Diastolic

Examination findings (if appropriate)

For Tommy's research office use only if patient is consented and registered to take part in Tommy's research

Date of consent: d d - m m m - y y y y

Patient ID: ☐☐☐☐ - P A T

Recruiting site: _

Date entered onto database: __/___/____ Entered by: Date checked: __/___/____ Checked by:

Ethnicity codes

WHITE		Category includes
A	White British	English, Scottish, Welsh, Cornish
B	White Irish	
C	Any other white background	Former USSR, Baltic States, Former Yugoslavia, Other European, White South African, American, Australian, New Zealander, Mixed White
CF	Greek	
CG	Greek Cypriot	
CH	Turkish	
CI	Mediterranean	Italian, Portuguese and Spanish
CJ	Turkish Cypriot	
CN	Jewish	
CY	Other White European	
MIXED		
D	White & Black Caribbean	
E	White & Black African	
F	White & Asian	
G	Any other mixed background	
ASIAN OR ASIAN BRITISH		
H	Indian	British Indian, Punjabi
J	Pakistani	British Pakistani, Kashmiri
K	Bangladeshi	British Bangladeshi
L	Any other Asian background	British Asian, East African Asian, Sri Lankan, Tamil, Sinhalese, Caribbean Asian, Nepalese, Mixed Asian
BLACK OR BLACK BRITISH		
M	Black Caribbean	Caribbean, West Indian Islands (and also Guyana) apart from Puerto Rican, Dominican and Cuban, which are Latin America
N	Black African	Nigerian, Kenyan, Black South African, Other Black African Countries
P	Other Black background	Black American, Mixed Black
PA	Somali	
PE	Black British	
OTHER ETHNIC GROUPS		
R	Chinese	inc. Hong Kong
S	Any other ethnicity	Japanese, Filipino, Malaysian, Aborigine, Afghani, Burmese, Fijian, Inuit, Maori, Native American Indian, Thai, Tongan, Samoan, Iranian, Israeli, Kurdish, Latin American (inc. Cuban, Puerto Rican, Dominican, Hispanic), Moroccan, Multi Ethnic Islands (inc. Seychellois, Maldivian, St. Helena), Other Middle Eastern (inc. Iraqi, Lebanese, Yemeni), Other North African, South American (inc. Central America).
SA	Africa—colour not defined	
SC	Arab	
SD	Vietnamese	
Z	Not stated	

Religion codes

A	Christian (all denominations)
B	Buddhist
C	Hindu
D	Jewish
E	Muslim
F	Sikh
G	Agnostic
H	Atheist
I	I'd rather not say
J	Other (please specify)

Marital status codes

A	Single
B	Married
C	Separated
D	Divorced
E	Widowed

Education codes

A	No formal qualifications
B	1-4 GCSEs (A*-C) or equivalent
C	5+ GCSEs (A*-C) or equivalent
D	Apprenticeship
E	2+ A-levels or equivalent
F	Degree or above
G	Other (please specify)

Tommy's National Centre for Miscarriage Research

University Hospitals Coventry and Warwickshire NHS Trust

Registration form

Female details

Title	**Date of birth**	
Surname	**Ethnic group (see last page)***	
First and forename(s)	**Religion (see last page)***	
Address	**Marital status (see last page)***	
	Education (see last page)*	
	Occupation	
	NHS number	
	Hospital number	
City/town	**GP name**	
County	**GP address**	
Telephone (Home)		
Telephone (Mobile)	**GP telephone**	
E-mail address (we will use this to correspond with you):		

* - enter the relevant code from the list of tables on the last page of this form

Data Disclosure and Protection: By completing this form, you hereby give your consent for the data to be held within the NHS in accordance with the requirements of the 1998 Data Protection Act (UK).

Female signature:	
Date:	

Tommy's National Centre for Miscarriage Research

Please complete this form with as much information as you are able to. If you are uncertain about any of the questions you will be able to check these with your healthcare provider at your clinic appointment. Please include all medical information in your history even if you think it may be insignificant.

Relationship details

What is the length of your currentrelationship? ☐☐ years ☐☐ months

Are you and your partner blood relatives? Yes ☐ No ☐

Please describe: _

Menstrual period and pregnancy information

What was the first date of your last menstrual period? d d - m m - y y y y

What age did your periods start? ☐☐ years

Are your periods regular? Yes ☐ No ☐

If yes, what is your cycle length (time from the beginning of one period to the beginning of the next)? ☐☐ days

If no, what is your cycle length? **MIN** ☐☐ days

MAX ☐☐ days

How many days do you bleed for? ☐☐ days

Do you get any bleeding in between your periods? ☐ ☐

Do you have any problems with intercourse? ☐ ☐

How frequently do you have intercourse? ☐☐ per/wk

or ☐☐ per/month

Have you ever had a delay (>12 months) in trying to get pregnant? ☐ ☐

Are you currently pregnant? ☐ ☐

Are you currently trying to become pregnant? ☐ ☐

How long have you been trying to conceive? ☐☐ years ☐☐ months

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Contraception and fertility treatment

*Please complete the table below with all forms of contraception you have previously used (e.g. coil (IUCD), Depo-Provera injection, oral contraceptive pill). Use of condoms **DOES NOT** need to be included.*

Type of contraception	How long did you use it (years)?	How long ago did you stop using it (years)?

Have you ever used fertility treatment to try and get pregnant? Yes ☐ No ☐

Please tick all treatments you've had, and enter the number of attempts

Clomid/other ovary stimulation ☐ ☐☐ attempts

IVF/ICSI ☐ ☐☐ attempts

IUI ☐ ☐☐ attempts

Donor sperm treatment ☐ ☐☐ attempts

Donor egg treatment ☐ ☐☐ attempts

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Previous pregnancies

*Use the key opposite to complete the fields marked with *. If year or gestation are not known, state NK in the relevant box*

Year	Gestation (wks)	Time taken to get pregnant (months)	Method of conception*	Any ultrasound scan findings? (e.g. please tell us if the baby's heart-beat was seen)	Sex (M or F, if known)	Outcome** (enter code)	If miscarriage, type of management*** (enter code)	Mode of delivery**** (enter code)	With current partner (Yes or No)	Additional clinician's notes

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*** Method of conception**

1	Natural
2	IVF/ICSI
3	IUI
4	Donor sperm treatment
5	Donor egg treatment
6	Ovarian stimulation

****Outcome**

1	Live birth
2	Stillbirth
3	Pregnancy loss without ultrasound confirmation of pregnancy
4	Miscarriage after ultrasound confirmation of pregnancy
5	Late miscarriage (>12 weeks to <24 weeks)
6	Ectopic pregnancy
7	Molar pregnancy
8	Resolved pregnancy of unknown location
9	Termination

*****Type of management**

1	Expectant (waited for nature to take its course)
2	Surgical (operation)
3	Medical (took a tablet(s))

****** Mode of delivery**

1	Unassisted vaginal
2	Instrumental vaginal (forceps or suction cup delivery)
3	Elective caesarean section
4	Emergency caesarean section
5	Vaginal breech
6	Not applicable

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Previous pregnancy-related complications

	Yes	No
Do you have a history of polycystic ovaries?	☐	☐
Do you have a history of fibroids?	☐	☐

If yes: Distorting womb cavity ☐
Not distorting womb cavity ☐
I don't know ☐

	Yes	No
Do you have a history of endometriosis?	☐	☐
Do you have a history of pelvic inflammatory disease?	☐	☐
Do you have a history of uterine (womb) abnormalities?	☐	☐
Have you ever had a sexually transmitted disease?	☐	☐
If yes, when: m m - y y y y Was it treated?	☐	☐
Have you ever had any previous gynaecological surgeries?	☐	☐

If yes, tick all applicable:

Laser or loop excision of the cervix (LLETZ)	☐ →	If yes, how many operations? ☐☐ operations
Removal of fibroids	☐	Removal of scar tissues in the womb ☐
Endometriosis surgery	☐	Womb septum removal ☐
Fallopian tube surgery	☐	Other gynaecological surgeries ☐ If yes, state: _____
Removal of ovarian cyst(s)	☐	Other gynaecological disorders ☐ If yes, state: _____
Surgical management of miscarriage	☐	I don't know ☐

Date of last cervical smear test? m m - y y y y

Result? ☐ Normal ☐ Abnormal

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Recreational drug use

Do you currently drink alcohol? Yes ☐ No ☐

How many units per week? ☐☐ units per week

Do you currently smoke? Yes ☐ No ☐

If yes:

How many cigarettes? ☐☐ per day **or** ☐☐ per week

How many vaping sessions? ☐☐ per day **or** ☐☐ per week
One session is classified as 5 or more inhalations

If no:

Have you recently stopped? ☐ Yes ☐ No

If yes, how recently did you stop? ☐ < 1 month ☐ 1-6 months ☐ > 6 months

Do you take any other recreational drugs? Yes ☐ No ☐

If yes, please complete table:

Type	Frequency of use (tick one option)
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months
	☐ Daily ☐ 2-3 times per week ☐ Weekly ☐ Bi-weekly ☐ Monthly ☐ Every 2-3 months ☐ Every 6 months

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Diet and supplements

How many days a week do you eat the following foods:

Tick one box per food type

	Number of days per week							
	0	1	2	3	4	5	6	7
Red meat	☐	☐	☐	☐	☐	☐	☐	☐
White meat	☐	☐	☐	☐	☐	☐	☐	☐
Fish	☐	☐	☐	☐	☐	☐	☐	☐
Eggs	☐	☐	☐	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐	☐	☐	☐
Dairy products	☐	☐	☐	☐	☐	☐	☐	☐
Soya products	☐	☐	☐	☐	☐	☐	☐	☐
Chocolate	☐	☐	☐	☐	☐	☐	☐	☐
Nuts (almonds/walnuts)	☐	☐	☐	☐	☐	☐	☐	☐

Do you consume sugar substitutes daily or most days of the week? ☐ Yes ☐ No

How many cups of coffee* do you drink in a typical day? ☐ cups of coffee/day

How many cups of tea* do you drink in a typical day? ☐ cups of tea/day

How many cans (or equivalent) of soft drink do you consume per day (e.g. energy drinks, cola)? ☐ cans/day

Do you currently take any vitamins or supplements? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	How long have you been taking it? (weeks)
1			
2			
3			
4			

* Do not count decaffeinated drinks

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Diet and supplements

If you are not taking vitamins or minerals currently but have taken them in the last four months please complete this table.

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Are you currently taking any protein shakes or protein bars? ☐ Yes ☐ No

If yes, please provide details:

	Name of product	Frequency (times/week)	Duration (weeks)
1			
2			
3			
4			

Exercise

Do you follow a regular routine of physical exercise? ☐ Yes ☐ No

How many days a week do you exercise?

Tick one option

- 0 ☐
- 1-2 ☐
- 3-4 ☐
- 5-6 ☐
- 7 ☐

If you exercise, how many hours a day do you exercise?

Tick one option

- < 30 min ☐
- 30 min - 1 hr ☐
- > 1 hr - 1.5 hrs ☐
- > 1.5 hrs - 2 hrs ☐
- > 2 hrs - 2.5 hrs ☐
- > 2.5 hrs ☐

On average how many hours do you spend sitting on a chair per day?

Sofa or armchair ☐ hours/day Work chair ☐ hours/day

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Previous illnesses or medical problems

Have you had any serious illnesses or medical problems? Yes ☐ No ☐

If yes, tick all applicable:

Diabetes	☐	Rheumatism or painful joints	☐
Thyroid problems	☐	Skin rashes or other skin disorders	☐
Cancer	☐	Irritable Bowel Syndrome	☐
Heart problems	☐	Coeliac disease	☐
Liver problems	☐	Crohn's disease	☐
Migraines	☐	Autoimmune disease	☐
Epilepsy	☐	Other inflammatory disorder	☐
Depression	☐	Thrombosis (clots in legs or chest)	☐
High blood pressure	☐	Candida (thrush)	☐
Lupus (SLE)	☐	Bacterial vaginosis	☐
Abnormal vaginal discharge	☐		
Other illnesses	☐	Please state: _____	

If you have ticked any of the boxes above, please provide further details below:

Current medications and allergies

Please provide details on any allergies you have and medication you are currently taking below:

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Family medical problems

Has your mother, father, siblings or maternal aunt(s) had any medical complications? Yes ☐ No ☐

If yes, tick all applicable:

- Miscarriage ☐
- Recurrent (3 or more) miscarriages ☐
  - If yes: Number of 1st trimester losses (<12 weeks) ☐☐ Number of 2nd trimester losses (>12 weeks) ☐☐ ☐ I don't know
- Obstetric complications (such as pre-eclampsia and growth restriction) ☐
- Genetic or developmental problems ☐
- Heart problems under the age of 50 ☐
- Stroke under the age of 50 ☐
- Still birth ☐
- Pre-term birth ☐
- Infertility ☐
- High blood pressure ☐
- Diabetes ☐
- Blood clots (thrombosis) ☐
- Depression ☐
- Other ☐

Please state: _____

If you have ticked any of the boxes above, please provide further details below:

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Tests and investigations

Please give details of any tests or investigations you've had as a part of your miscarriage treatment.

Test/investigations	Date of test	Result	Which hospital or clinic did you have the test at?
FSH			
LH			
Oestradiol			
Haemoglobin			
Platelets			
Rubella immunity			
Thrombophilia screening			
Thyroid antibodies			
Thyroid function test			
Sexually transmitted disease			
Ultrasound			

If you've had any other tests, please state below:

Test/investigation	Date of test	Result	Which hospital or clinic did you have the test at?

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Treatments

Please give details of any treatments you've previously received or are currently receiving as a part of your miscarriage management. Please also include any medications that you've bought yourself.

Treatment (please include medicines and operations)	Dose	Date from*	Date to	Tick if ongoing	Additional clinician's notes
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	
				☐	

* If an operation, please give the date of operation

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Examination

This section should be completed in conjunction with a member of the research team who attends to you in the clinic

Weight: ☐☐☐ kg Height: ☐☐☐ cm BMI: ☐☐.☐

Blood pressure: ☐☐☐ / ☐☐☐ mmHg
Systolic Diastolic

Examination findings (if appropriate)

For Tommy's research office use only if patient is consented and registered to take part in Tommy's research

Date of consent: d d - m m m - y y y y

Patient ID: ☐☐☐☐ - M A T

Recruiting site: _

Date entered onto database: __/___/____ Entered Date checked: __/___/____ Checked by:

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Ethnicity codes

		Category includes
WHITE		**Category includes**
A	White British	English, Scottish, Welsh, Cornish
B	White Irish	
C	Any other white background	Former USSR, Baltic States, Former Yugoslavia, Other European, White South African, American, Australian, New Zealander, Mixed White
CF	Greek	
CG	Greek Cypriot	
CH	Turkish	
CI	Mediterranean	Italian, Portuguese and Spanish
CJ	Turkish Cypriot	
CN	Jewish	
CY	Other White European	
MIXED		
D	White & Black Caribbean	
E	White & Black African	
F	White & Asian	
G	Any other mixed background	
ASIAN OR ASIAN BRITISH		
H	Indian	British Indian, Punjabi
J	Pakistani	British Pakistani, Kashmiri
K	Bangladeshi	British Bangladeshi
L	Any other Asian background	British Asian, East African Asian, Sri Lankan, Tamil, Sinhalese, Caribbean Asian, Nepalese, Mixed Asian
BLACK OR BLACK BRITISH		
M	Black Caribbean	Caribbean, West Indian Islands (and also Guyana) apart from Puerto Rican, Dominican and Cuban, which are
N	Black African	Nigerian, Kenyan, Black South African, Other Black African Countries
P	Other Black background	Black American, Mixed Black
PA	Somali	
PE	Black British	
OTHER ETHNIC GROUPS		
R	Chinese	inc. Hong Kong
S	Any other ethnicity	Japanese, Filipino, Malaysian, Aborigine, Afghani, Burmese, Fijian, Inuit, Maori, Native American Indian, Thai, Tongan, Samoan, Iranian, Israeli, Kurdish, Latin American (inc. Cuban, Puerto Rican, Dominican, Hispanic), Moroccan, Multi Ethnic Islands (inc. Seychellois, Maldivian, St. Helena), Other Middle Eastern (inc. Iraqi, Lebanese, Yemeni), Other North African, South American (inc. Central America).
SA	Africa—colour not defined	
SC	Arab	
SD	Vietnamese	
Z	Not stated	

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Religion codes

A	Christian (all denominations)
B	Buddhist
C	Hindu
D	Jewish
E	Muslim
F	Sikh
G	Agnostic
H	Atheist
I	I'd rather not say
J	Other (please specify)

Marital status codes

A	Single
B	Married
C	Separated
D	Divorced
E	Widowed

Education codes

A	No formal qualifications
B	1-4 GCSEs (A*-C) or equivalent
C	5+ GCSEs (A*-C) or equivalent
D	Apprenticeship
E	2+ A-levels or equivalent
F	Degree or above
G	Other (please specify)

1

1 Dashboard

Historic Data (Pre Registration)

Trust	No of Couples	No of Women	No of Men	No of Pregnancies
University Hospitals Coventry and Warwickshire	897	897	736	3768

Age at Registration (female only)

	No of Patients	% of Patients
<35	445	50
35-40	318	35
>40	124	14

History of miscarriage/live births

Patients	No of Patient	% of Patients
2 miscarriages	221	25
3 miscarriages	248	28
4 miscarriages	173	19
5 miscarriages	87	10
>5 miscarriages	118	13
1 or more live births	335	37

Ongoing Miscarriage Outcomes (Post Registration)

Trust	Pregnancies Post Registration
University Hospitals Coventry and Warwickshire	634

Miscarriage/Live Birth Rates by conception type (percentages by row)

	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
All conception types	634	32	1	40	2	20	4	0
Natural conception only	538	33	1	40	2	20	4	0

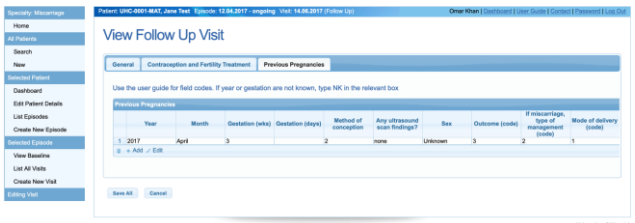
Miscarriage/Live Birth Rates by age of mother at delivery (percentages by row)

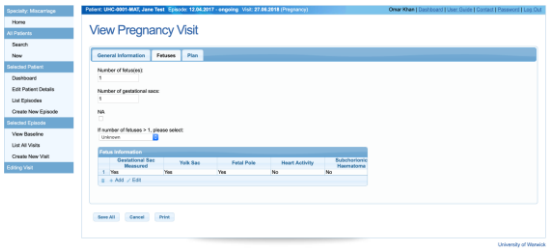
	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
<35	315	32	1	42	3	18	4	0
35-40	247	30	1	41	2	23	3	0
>40	71	39	0	31	1	20	8	0

Miscarriage/Live Birth Rates by history of miscarriage (percentages by row)

	No of Pregnancies	% Miscarriage (preg. loss w/ or w/o US)	% Late Miscarriage (12-24 weeks)	% Live Birth	% Other Loss (still birth, ectopic, molar, resolved PUL, termination)	% Ongoing	% Outcome Unknown	% Outcome Not Applicable
2	178	24	1	48	1	26	1	0
3	172	29	1	45	2	18	4	0
4	118	36	0	35	3	19	7	1
5	71	41	1	34	0	17	7	0
>5	81	42	4	31	7	12	4	0

2





3

4

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods	5

		of recruitment, exposure, follow-up, and data collection	
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	n/a
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	
6			
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6
Statistical methods	#12c	Explain how missing data were addressed	n/a
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	
7			
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible,	7

		included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	n/a
Participants	#13c	Consider use of a flow diagram	
14			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
7			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
7			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
7			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
n/a			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			

Key results	#18	Summarise key results with reference to study objectives	3
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	3
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	8
Generalisability	#21	Discuss the generalisability (external validity) of the study results	8
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

This checklist was completed on 19. April 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Version 5.0, 21-Jan-2020

University Hospitals Coventry and Warwickshire NHS Trust

STUDY PROTOCOL

Tommy's Net

A cohort study of pregnancy outcome in couples who miscarry

Sponsor: University Hospitals Coventry and Warwickshire NHS trust
Sponsor reference: SQ186916

Funder: Tommy's Charity

REC reference: 17/WM/0050 for data collection
Reference for database: 17/NW/0208

IRAS No: 213740 for data collection
IRAS No: 225751 for database
ISRCTN: 17732518

Parts with no fill relate to both projects
Part in light grey refers to data collection 17/WM/0050
Parts in light yellow refer to database application

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Research Governance Framework, the ICH Good Clinical Practice guidelines and the Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

Position:

.....

KEY TRIAL CONTACTS

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Funder	Tommy's Charity Nicholas House, 3 Laurence Pountney Hill, London, EC4R 0BB Email: mailbox@tommys.org.
Trial Co-ordinator / Co-ordination centre	Institute of Digital Healthcare University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL

INDEX

1. Aims and Objectives

We seek to achieve the following objectives:

- To undertake a large cohort study of pregnancy outcome following miscarriage.
- To facilitate the development and validation of tests and prediction models that could determine pregnancy outcome.
- To stratify couples with history of miscarriages into distinct phenotypes, allowing targeted management.
- To enable population-based epidemiological studies on miscarriage.
- To facilitate randomised controlled trials in terms of identifying eligible recruits and managing the trials.
- To enable participating hospitals to work together in a way that brings added benefits to all parties and the populations whom they serve.
- To facilitate the clinical/research interface.

We aim to do this by creating an online electronic patient record system, which will be designed and constructed by our specialist team within the University of Warwick, Institute of Digital Healthcare, for use by early pregnancy services.

2. Introduction

Miscarriage, defined as the loss of pregnancy before the fetus reaches viability, is the most common complication of pregnancy. As many as 15-25% of pregnancies end in miscarriage, and 25-50% of women experience at least one sporadic miscarriage in their reproductive life.(1) The number of miscarriages in the UK is estimated to be approximately 200,000 per year.(2) Most miscarriages are sporadic and occur before 12 weeks of gestation.(3) They frequently involve numeric chromosome errors in the conceptus.(4)

Recurrent miscarriage is generally viewed as a condition distinct from sporadic miscarriages. It is estimated that 5% of women experience two consecutive miscarriages, and approximately 1% suffer three or more consecutive miscarriages. (5,6) In recurrent miscarriage, the incidence of euploidic fetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases.(7) Recurrent miscarriage is a debilitating disorder, associated with considerable psychological morbidity, for which there is no effective medical intervention. Fortunately, the cumulative live birth rate for most recurrent miscarriage patients is high; more than around 65% of women with recurrent losses go on to have a successful subsequent pregnancy.(8–14)

The risk factors associated with miscarriage include maternal age, previous pregnancy history, body mass index (BMI), maternal medical conditions, thrombophilia's, parental structural chromosome abnormities, uterine anomalies and lifestyle factors such as smoking.

There are no robustly developed and widely validated prediction models in current clinical use. Couples are currently not provided with accurate estimates of their future risk of miscarriage, or obstetric and perinatal outcomes.

Effective management of miscarriage requires the rigorous study of risk factors and test outcomes, as well as the development of new tests to allow stratification of patients according to the likelihood of future reproductive failure. The development and assessment of prognostic tests require effective and long-term follow-up work with accurate recording and analysis of future pregnancy outcomes. To facilitate such recording, we will establish an online data and record management system that will allow patients to continuously update their reproductive history.

Currently couples suffering miscarriage are stratified according to the number of previous losses. Many clinics in the UK will only investigate women after 3 losses.(11) Our aim is to change this counting of losses as an indicator of disease to an approach that takes multiple risk factors into account, producing distinct miscarriage phenotypes that allow targeted tests and interventions to improve outcomes.

For example, sporadic miscarriages frequently result from aneuploidy, whereas recurrent miscarriage, defined by consecutive miscarriages, is generally viewed as a distinct disorder in which the incidence of euploidic fetal loss increases with each additional miscarriage, and the likelihood of a future successful pregnancy gradually decreases. Currently affected couples are routinely screened for various anatomical, endocrine, immunological, thrombophilic and genetic risk factors,(11) but the ability of these tests to stratify women in terms of pregnancy outcome and appropriate treatment has not been vigorously tested.

The Tommy's National Centre for Miscarriage Research is a Research Centre which brings together an interdisciplinary Translational Medicine research grouping jointly at the University of Warwick, University of Birmingham and Imperial College London. The Centre is dedicated to research across all aspects of miscarriage and early pregnancy complications including medical, basic scientific, social and ethical issues. In facilitating this research portfolio, one aspect includes the centralised secure storage of all data relating to the research from every participating site, which is to be known as Tommy's Net.

3. **Methods & Design**

3.1 Overview

In this project we plan to use digital technology to store information about the patient's and their partner's demographic details history, investigation results and pregnancy outcome. Thus we will create a large cohort study of women presenting with miscarriage. The crucial feature of the cohort will be the ascertainment of pregnancy outcome. Analysis of this cohort will allow us to assess the utility of existing investigations and new test in predicting pregnancy outcome.

3.2 Centres

This project will initially involve three centres with specialist clinics:

- University Hospitals Coventry and Warwickshire NHS trust (UHCW)
- Birmingham Women's Hospital Foundation Trust (BWH)

- Imperial College Healthcare NHS Trust (Imperial)

Any additional centres will be notified to the responsible REC as a substantial amendment.

3.3 Population

Women attending specialist services at the participating trusts will be invited to participate:

- UHCW; it will include couples attending, early pregnancy, implantation, recurrent miscarriage and preterm prevention clinics.
- BWH; will include individuals attending early pregnancy assessment unit and recurrent miscarriage clinic.
- Imperial; will include individuals attending early pregnancy assessment unit and recurrent miscarriage clinic.

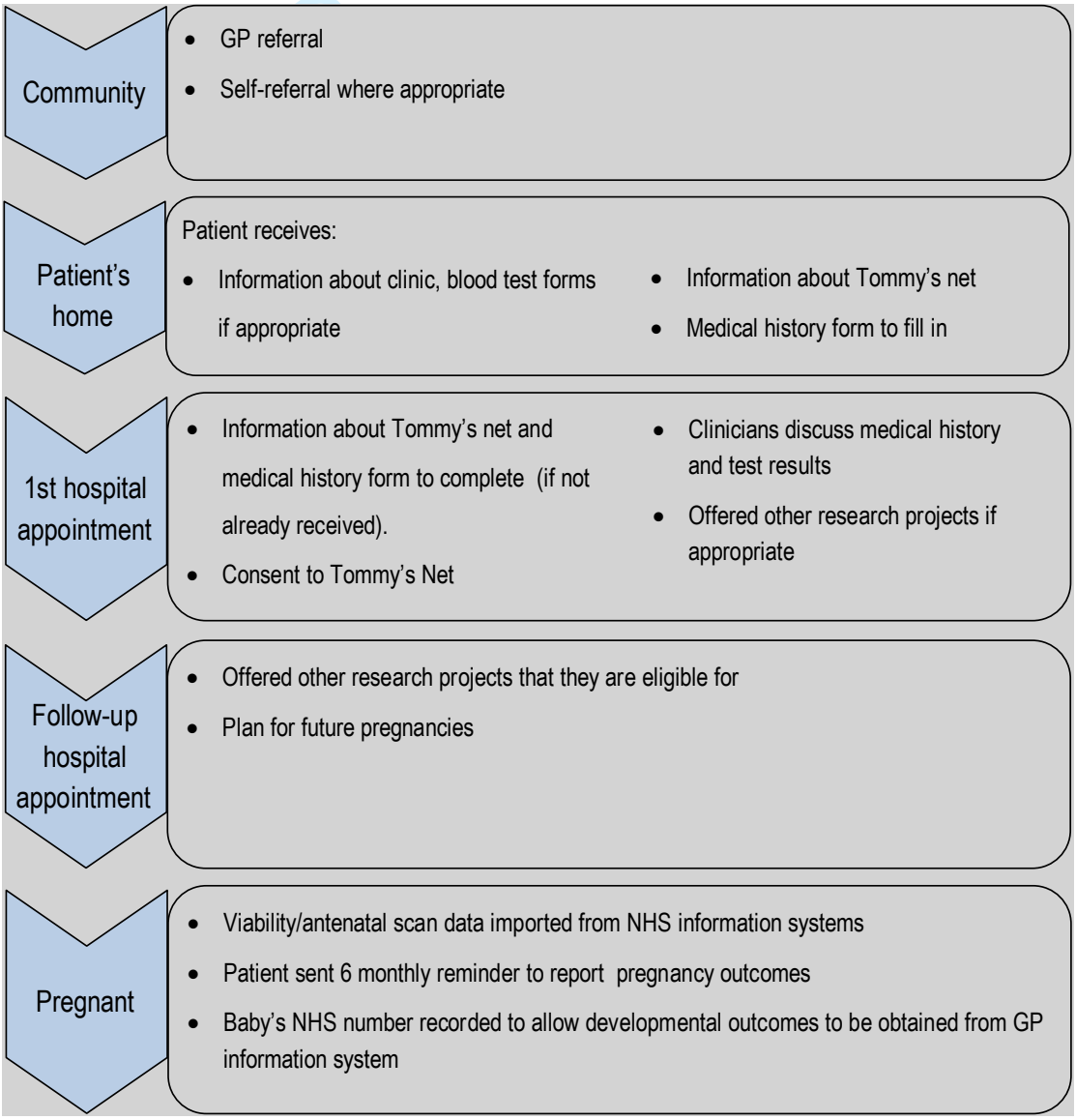

Figure 1. Tommy's Net flow diagram for recurrent miscarriage clinic patients

Pregnant:

- Update of demographics including weight, smoking status, alcohol intake and folic acid use.

May also receive 6-12 information/support text messages annually

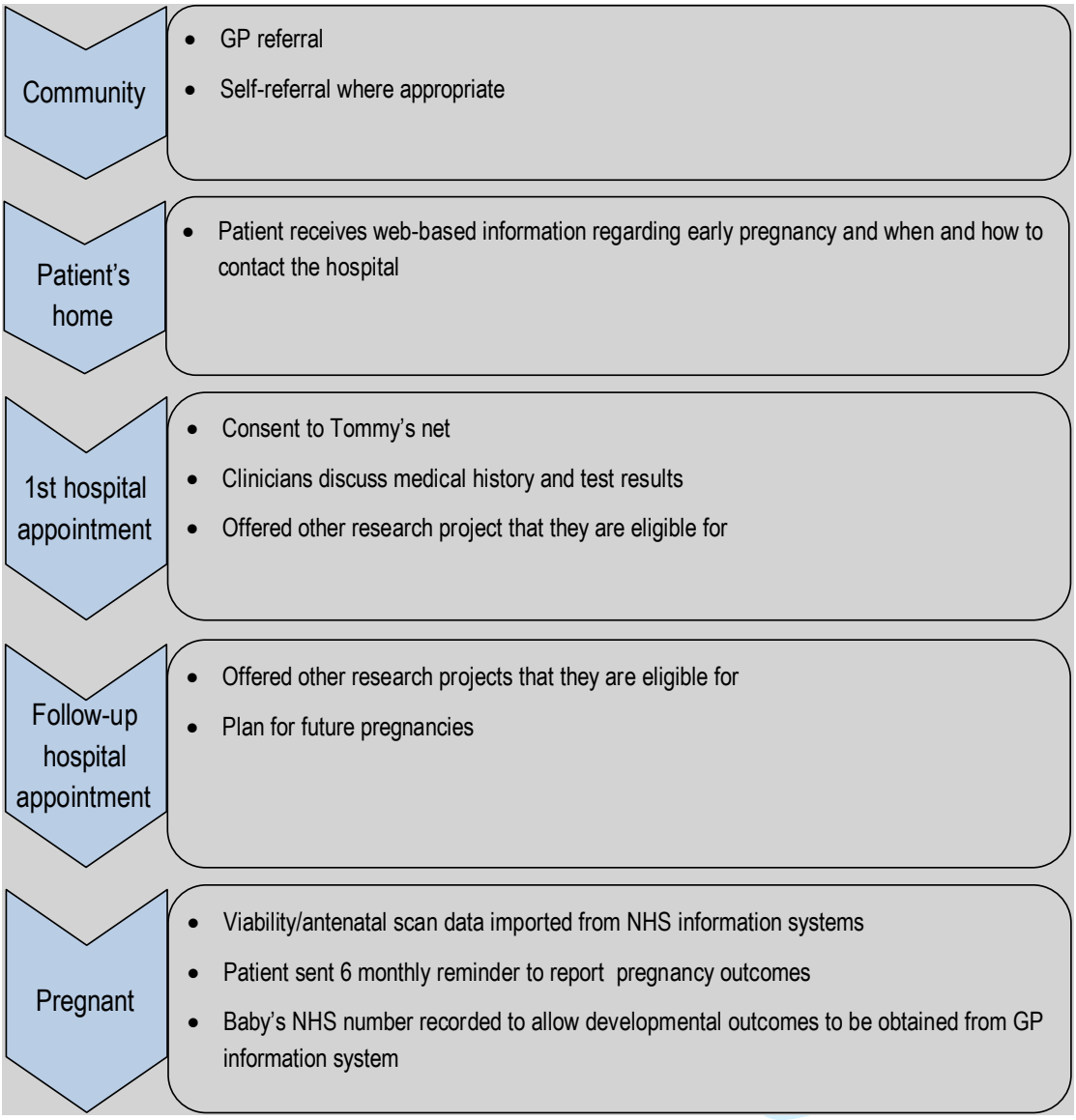

Figure 2. Tommy's Net flow diagram for emergency patients

3.4 Duration

This project is funded for 5 years initially but we would hope this to be renewed.

3.5 Inclusion criteria

- Couples with a history of one or more pregnancy losses;
  - Miscarriage
  - Molar pregnancy
  - Ectopic pregnancy

- Stillbirth
- Bleeding in early pregnancy

3.6 Exclusion criteria

Decline to consent to having their information stored.

3.7 Methods

Couples will be referred by their GP or self-refer. They will then be sent information about Tommy's Net by post and directed to websites (PIS) as well as other trials, the standard NHS information about the clinic and a history sheet. Patients can attend in person or have a telephone consultation:

When they arrive at the clinic a member of the research team will explain Tommy's Net and ask them to consent to the study. If they consent they will be asked to fill the Tommy's Net registration form on paper, after which, their data will be entered on an online system, this will include demographics information, reproductive history, delivery details and related test results. They will then see the clinician who will discuss their history and advise on further investigations and eligibility for other studies and trials.

Prior to telephone consultation the patient will be contacted by telephone and directed to Tommy';s net online consent form. If consented they will be directed to an online registration form and asked to complete this prior to review in the telephone consultation.

All existing relevant investigation results will be imported into the trial database system (Tommy's Net) from existing hospital systems (for example CRRS/Lorenzo). Where investigations relate only to the trial, the data from these will be entered directly into the trial system. Tommy's Net will assist in the production of the clinic letter to the GP and patient as a record of this visit. Thus as well as being a research tool the Tommy's net will facilitate the clinical service. Other related trials will have separate ethical approvals.

Follow up appointments will be offered by telephone or in person to discuss investigation results and plan future pregnancies. Tommy's Net will produce a letter to the GP and patient as a record of this visit which will fit into existing NHS systems this will be in place of the current letter to the GP following an appointment.

In future pregnancies, patients will be offered viability scans in the first trimester and information about these scans, as well as the anonymized scans themselves, will be stored on Tommy's Net. These will be imported from the current Viewpoint, digital, ultrasound results storage system. Participants' details will be updated during these visits (including BMI, smoking status, alcohol intake and folic acid use).

Patients and their partners will be asked to complete an optional anxiety questionnaire (Generalised Anxiety Disorder Questionnaire, GAD-7) prior to the initial ultrasound in each pregnancy and following each subsequent ultrasound. Scores will be recorded on Tommy's net. Any patient scoring over 10 will be offered additional support from the staff at the Biomedical research unit and referred to their GP if required.

Information about antenatal care including, serum screening, booking scans, anomaly scans and growth scans will be recorded (imported from Viewpoint where they exist or entered directly into the research system if inappropriate for the clinical record).

Pregnancy outcome details will be requested from the patient either by filling in a paper copy, which can then be entered into the system via an authorized researcher or by direct patient entry into an online, link anonymised, patient accessible system, hosted at the University of Warwick, every 6 months. The data collected by this system will be transferred to the Tommy's Net system hosted at the hospital, and deleted from the University system, after review by the research midwives. Women will be sent reminders to update us regarding their reproductive outcomes 6 monthly (these can be automated if the patient consents to having their email address or mobile phone number registered on the system to be used for reminders). They may also receive information/support text messages 6-12 times annually.

The baby's NHS number will be requested through appropriate consent so that follow up of the baby's development could be facilitated. Information regarding developmental follow up will be requested from GP records. During the project, direct connections to GP sockets will be developed to facilitate sharing of information, and avoid duplicate data entry, in the presence of approved data sharing agreements.

3.8 Recruitment and consent

The underlying principle of the Centre is that patients should give informed generic consent to use their data in the medical research relating to the Tommy's National Centre for Miscarriage Research. Consent will be obtained within the clinical setting, or over the telephone via an online consent form, by a trained member of the team in accordance with Good Clinical Practice.

For male participants, they will either be consented face to face in a clinical setting if they attend with their partner, or over the telephone via an online consent form. If not, the documents will be posted out to them and they will be asked to complete the questionnaires and consent form at home and return it with their partners at the next clinic appointment or post it straight back to the study office. They will be offered the opportunity to speak to a member of the research team on the phone if they are uncertain about any aspect of the questionnaire or consent form.

In some cases participants fill in the registration form with their clinical details which are stored in the clinical notes but have not signed the consent forms. In these cases participants will have the PIS and consent forms posted to them and they will receive a telephone call from by a research nurse or midwife to ensure they understand the study and to ask them to sign the consent form online or post it back.

Standard Operating Procedures will be used that clearly set out the processes of obtaining consent, data collection and storage, and define the roles and responsibilities of the parties involved. All documentation associated with obtaining informed consent, e.g. patient information sheets and consent forms, will be approved by the Host institution, REC and HRA. The responsible team member will confirm eligibility, encourage open discussion and answer any questions that patient(s) may have. The consent discussion will be noted in the medical record along with the signed consent form which should be retained in support of data collection. A copy of the consent form will be given to the patient.

3.9 cohort multiple Randomised Controlled Trial (cmRCT) design

In addition to providing consent for the Tommy's Net cohort study, participants will also be invited to join a cohort multiple Randomised Controlled Trial (cmRCT), which is embedded in Tommy's Net. cmRCT is a relatively new trial design that simplifies the recruitment and conduct of trials compared with current RCTs (12). In this trial design, participants are asked to agree to participate in the control arm of any future trials that will be conducted by the research team. Once a substantial cohort of participants has been established that have given their consent to participate in the cmRCT, one is able to conduct a trial by identifying and selecting a random sample of participants who will receive the intervention, and another group that will continue to receive standard care. Those patients that are allocated to the intervention will be invited to give their written, informed consent to participate in the intervention arm. However, those allocated to standard care (control arm), can continue to be followed up in the usual way with no additional contact required. Relevant outcomes and other measures are taken on all patients in both arms as part of the regular follow-up process. A large benefit of this trial design is that the same cohort can be used for multiple interventions, so are large number of clinical trials can be conducted within the same core cohort of patients.

The detailed description of each trial will be provided in Appendix 1 of this protocol. A substantial amendment will be submitted to the responsible REC each time a new trial is embedded within this cohort and added to the protocol.

3.10 Withdrawal

A patient is entitled to withdraw consent at any time. They should either inform the clinician responsible for their care, contact the Centre directly, or contact the Research and Development Office within their Trust. Withdrawal of consent, and details of all data involved, will be recorded by the Centre. They will also be able to leave their data but decline to receive reminders to update us with their reproductive history outcomes. Any data on explicitly withdrawn patients will be removed from the database.

3.11 Documentation and confidentiality

The clinical information system will reside within the University Hospital Coventry and Warwickshire NHS trust (UHCW). At UHCW there is an Information Governance

Framework in place that represents itself as the annual Information Governance Tool Kit assessment. This is a key performance measurement for the trust and comprises of the following;

- Robust management and accountability for all aspects of information governance.
- An information governance committee with direct accountability to the quality and Governance committee, that is chaired by the Director of Corporate affairs and has access to appropriately skilled expertise across the entire Information Governance Agenda
- There is a register of all major information assets with assigned responsibility for each asset.
- Information risks are managed, were applicable though owners of information assets and linked to established risk management processes and governance arrangements.
- There is an effective information security even reporting and management processes and governance arrangements
- There is an effective information security event reporting and management procedures in line with Department of Health policies and guidelines
- There are formal contractual arrangements in place with all contractors and support organizations and that these include compliance with information governance requirements.
- Policies and procedures are documented to ensure compliance with common law obligations of confidentiality, Current Data Protection legislation and the NHS Care Record Guarantee . Key areas include but are not limited to:
    - Consent and management and ethical practice
    - Information sharing protocols
    - Fair processing
    - Subject access request and other GDPR requirements
    - Confidentiality code of conduct
    - Business continuity and disaster recovery
    - Physical security
    - Network security
    - Remote/home/teleworking
    - Secure data transfer
    - Access controls and access management
    - Data and media destruction
    - Local data warehousing
    - Cross boundary information sharing
    - Records management
    - Data flow mapping
    - Record retention
    - Archiving
    - Data quality including NHS number implementation

The database will be hosted at University Hospitals Coventry and Warwickshire on secure servers, specific members of the Institute of Digital Healthcare, WMG, and

University of Warwick will be given access to the server to administer the system. Information from other sites will be transferred through the secure NHS N3 network (n3.nhs.uk). Data stored will remain on the UHCW network and no data will be transferred to the IDH. Any patient identifiable data required for the trial will, similarly, be kept at the Trust sites, linked to the data stored within the system via a unique identifier, all data stored outside the trusts, e.g. for the purposes of statistical analysis, will be appropriately anonymised.

Certain information from participants consented to the Tommy's National Centre for Miscarriage Research study (Trial IDs, mobile numbers and email addresses) will be transferred securely to the University of Warwick hosted online survey system in order to collect follow up information. Only the IDH administrators and hospital research team will have access to the system. Automated invitations will be sent via SMS (or email if a mobile phone number is not available). A welcome message will be sent asking to confirm mobile phone number, followed by 6monthly requests for information. This invitation will consist of a one-time use link allowing the Tommy's team to trace the responses back to the patient identifiable baseline information, stored at UHCW. No identifiable information will be sent out in communications and no participants or members of the public will be able to access stored information (unless through a data subject request). The data collected, through the secure patient portal, will not be identifiable (will not contain the patient details section of the follow-up form) and will be transferred to the hospital and subsequently deleted from the system after review by an authorised research midwife. Patient may also receive up to 6-12 text messages a year for support/information.

The initial SMS will read: Thank you for joining Tommy's net. You will receive 6monthly texts with a link to a short questionnaire. Click here (LINK) to confirm your number. Tommy's
The 6monthly follow up will read: Update your record quickly by completing this questionnaire (LINK). All information will be used to improve our understanding of miscarriage. Tommy's
A reminder message will be sent around 48hours and 96hours.

Examples of the information text messages:

- Emotional well-being is important when trying to conceive and when pregnant. See tommys.org for support (LINK)
- Tommy's net has been looking at weight in couple's who are trying to conceive. For support in optimizing your weight visit tommys.org (LINK)
- It can be difficult to stop smoking. See tommys.org (LINK) for help and advice
- Folic acid is important when preparing for a pregnancy and in the first 12 weeks to help the baby's spine develop. See tommys.org (LINK)

Management of the database will be subject to the NHS IG Tool kit and Standard Operating Procedures in place at the IDH. Specifically, access to the clinician/research portal will be limited to authorised users on NHS computers, access to the data will be allowed according to the user's role:

- Principal Investigators will have access to all patient information at their site, including patient identifiable information stored at their trust. They will also have access to anonymised data originating from other sites. They will be able to create new records and modify records they have entered (all of which will be logged by the system)
- Researchers will only have access to anonymised data but will be able to view information across sites. They will not be able to modify data.
- Data Managers, such as the database administrators at the IDH will not have access to the web portal and will not be able to read the raw data.
- Once a patient portal is developed, this will be accessible through a secure web login by registered patients. Patients logging in to the patient portal will only be able to see their own data and will be able to submit new data for review by the site PI.

Access to existing hospital systems from Tommy's Net will be restricted to those results relevant to the trial and only the treating clinician will be authorized to view and import this data from any hospital or healthcare system. Any data copied to or from the trial system will only be transferred through encrypted channels to ensure data is kept secure at all times.

The research system has been validated through functional and user testing and approved use cases have been documented. An approved process for failure recovery is also in place which ensures that, even in the event of catastrophic failure, the system can be restored within 2 working days and, at most, 1 days' worth of data will be lost.

3.12 MHRA Compliance

The trial database developed complies with MHRA requirements as detailed in the Annex 11 guidelines published under Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and the electronic record requirements for Good Clinical Practice:

- Data integrity is ensured via ongoing data review.
- There is a clear and documented change control process which ensures all changes are approved and have a clear audit trail.
- Any changes to the data within the system is logged automatically, time stamped and recorded along with the user who made the change.
- All information entered into the system can be reviewed by the investigator regardless of who entered the data.
- Originals of any scans or images imported into the system will be kept on their respective clinical systems and appropriate quality controlled procedures will be used to anonymize the images.
- Access to trial data and audit trails can be granted to inspectors and sponsor representatives for auditing and monitoring purposes.

- Data and metadata on the system can be archived in accordance with Clinical Trials Regulations for up to 25 years.
- Written procedures are in place to cover all the above processes.

In addition to the above mentioned procedures, Trust R&D will be granted oversight access to the research system allowing them to detect and report any breaches of GCP.

Customisation of the trial system for Tommy's will be conducted in collaboration with the investigators to ensure the sponsor's established requirements for completeness, accuracy, reliability and performance are met. The design process and user requirements will be documented. Standard Operating Procedures (SOPs) will be drafted and maintained for the use of the system.

3.13 Data access and sharing

The underlying principle of the Tommy's National Centre for Miscarriage Research is that data stored within Tommy's Net is made available to all the research centres that have been granted approval by the responsible ethics committee. This provides a reciprocal arrangement whereby anonymised data can be uploaded to Tommy's Net and then shared between all approved parties within the Centre. The Centre has procedures in place to ensure the security, confidentiality and data protection of the collection. The aim is to ensure that researchers do not have access to personal identifiers through these data.

All stored data that relates to specific research projects within the Tommy's National Centre for Miscarriage Research will have obtained separate ethical and regulatory approval where appropriate. This will have been obtained for the site responsible for each specific research project with approval for the data access and sharing arrangements described above.

3.14 Analysis

The data will be interrogated so that all clinics will have anonymized information on:

- Numbers and demographic of attendees.
- Running live birth rates per clinic and per subgroup.
  For each investigation undertaken by the NHS clinical service the investigation will be assessed for its ability to predict pregnancy outcome. Mathematical models will be created in liaison with appropriate statisticians to construct outcome prediction using demographic data and investigation results. Aurelio Tobias a statistician with significant expertise in outcome prediction will advise on the outcome prediction models used.
- A semantically enabled query tool will be developed alongside the research database to allow clinicians and researchers to query anonymized information stored in the database for initial hypothesis testing.

- Further ethical approval will be sought for other studies involving tissue collection. Once results from these new test are available they will we assess with the outcome prediction models that have been developed.

4. Study supervision

The investigators who will receive progress reports every 4 months will oversee the study. The Warwick investigators and representative from Birmingham and Imperial and will have twice monthly virtual meetings to report on the progress.

5. Ethics and Sponsorship & indemnity

The study will be conducted in compliance the principles of the ICH GCP guidelines and in accordance with all applicable regulatory guidance, including, but not limited to, the Research Governance Framework. Ethical approval for this study will be sought from the Research Ethics Committee combined with Health Research Authority (HRA) approval. No study activities will commence until favorable ethical opinion and HRA approval has been obtained. Progress reports and a final report at the conclusion of the trial will be submitted to the approving REC within the timelines defined by the committee. Confirmation of capacity and capability will be obtained from the R&D departments obtained prior to commencement of the study at all participating sites.

UHCW NHS Trust has agreed to act as sponsor for this trial and will undertake the responsibilities of sponsor as defined by the UK Policy Framework for Health and Social Care Research and ICH Good Clinical Practice. An authorised representative of the Sponsor has approved the final version of this protocol with respect to the trial design, conduct, data analysis and interpretation and plans for publication and dissemination of results.

“The study will be monitored by the Research and Development Department at UHCW as representatives of the Sponsor, to ensure that the study is being conducted as per protocol, adhering to Research Governance and GCP. The approach to, and extent of, monitoring will be specified in a trial monitoring plan determined by the risk assessment undertaken prior to the start of the study.”

As sponsor, UHCW provides indemnity for this trial and, as such, will be responsible for claims for any negligent harm suffered by anyone as a result of participating in

this trial. The indemnity is renewed on an annual basis and will continue for the duration of this trial."

6. Publications policy

All publications arising from this data will be agreed by all investigators prior to submission.

7. Intellectual property

The legal arrangements relating to intellectual property (IP) will be adhered as per the signed agreement between Tommy's Charity and the University of Birmingham (lead site for the Tommy's National Centre for Miscarriage Research).

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Appendix 1. cmRCT protocols