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Developing a non-invasive treatment for twin-twin transfusion syndrome

Submission date	**Recruitment status**	[X] Prospectively registered
27/01/2020	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
05/03/2020	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
06/12/2024	Neonatal Diseases	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Approximately 4000 identical (monochorionic diamniotic, MCDA) twin pairs are born in the UK every year. Twin-Twin Transfusion Syndrome (TTTS) affects 10-15% of MCDA twins, and it is a leading cause of mortality, premature delivery and morbidity. Fetoscopic laser ablation (closing) of the abnormal blood vessel connections in the placenta is an invasive procedure performed after 18 weeks gestation. With this treatment there are risks of preterm rupture of membranes, labour/miscarriage, infection and maternal complications. However, in up to 25% cases of TTTS, there is a need for treatment before 18 weeks. High-Intensity Focused Ultrasound (HIFU) is a non-invasive therapeutic technique, so may avoid these laser risks, and can be used before 18 weeks gestation. It uses precisely aimed ultrasound beams to destroy tissue within the body without damage to surrounding tissues or the need for surgery. The researchers have previously used it to safely and effectively block blood flow in the vessels in sheep placentas. In this study they will use ultrasound-guided HIFU to treat TTTS diagnosed at less than 18 weeks. This is a first in human clinical study of using ultrasound-guided HIFU to selectively block abnormal blood vessel connections in the placentae of identical twins which cause TTTS.

Who can participate?
Women with monochorionic MCDA twins between 12+0 and 17+6 weeks of pregnancy, diagnosed with TTTS, in whom the abnormal blood vessel connections can be seen using ultrasound

What does the study involve?
All participants undergo ultrasound-guided HIFU. The participant will be observed overnight as an inpatient. Free overnight accommodation for the accompanying person (if any) will be provided. Participants are assessed on the day following the completion of a treatment cycle (which can be spaced over 72 hours if needed). An interview will be conducted with the participant at this assessment. Study participants will be given a symptom and appointment diary to keep for the following 14 days. This will include a self-reporting of red-flag symptoms for which they should seek urgent medical care including contact details for clinical members of the research. Unless ongoing inpatient care is required, participants will be discharged and return home following this study visit. A third study assessment will take place three days (72 hours) following the completion of a treatment cycle. If recurrent TTTS is identified a repeat

treatment cycle may be offered (following the same pattern as the first and second study visits). The participant will be examined by a member of the research team and the symptom diary will be reviewed. Participants will return home following this study visit unless inpatient admission is required. The fourth study assessment will take place 7 days following the completion of a treatment cycle and will be the same as the third study assessment. The fifth study assessment will take place 14 days following the completion of a treatment cycle and will the same as the third study assessment. After the fifth study assessment participants will return to standard UK care as per NICE clinical guidance CG129 and local policy of the unit providing their maternity care. Following delivery patient medical records will be accessed (with explicit patient consent) to determine pregnancy outcomes. Details of recurrence and stage of TTTS, any further interventions for TTTS, survival of one or both twins until delivery, gestational age and mode of delivery, as well as details of other pregnancy complications will be entered onto the study database. If the participant delivers within Imperial College Healthcare NHS Trust hospital the placental surface will be photographed following delivery and then the placental tissue will be either disposed of or send for analysis according to standard hospital policy by the direct clinical care team present for the delivery. If the participant delivers at a maternity unit other than Imperial College Healthcare NHS Trust, this unit will be contacted to provide the information listed above (using secure NHS email or secure fax) – permission to do this will be included in the consent form. Between 4 - 6 months after the participants EDD (estimated due date), participants will be contacted for a second round of semi-structured interviews. The nature of TTTS means that the twins would have been delivered for between 8 and 16 weeks prior to the EDD. The exact timing will be determined by the needs and preferences of the participant.

What are the possible benefits and risks of participating?
Participation may allow women to have a treatment for TTTS where no other treatment could be offered because of the early gestational age at which the TTTS was diagnosed. This study may also allow women to have a treatment for TTTS which is non-invasive, avoiding the risks of miscarriage, infection and preterm rupture of membranes associated with fetoscopic laser or selective termination. This treatment aims to keep both babies alive until delivery. Ultrasound scans are not believed to have any side effects and are a routine part of the care of pregnant women. Women pregnant with twins usually have quite frequent ultrasound scans in pregnancy. However, participants will need to travel back and forth between their home and Queen Charlotte’s and Chelsea Hospital in London on at least four occasions, and be away from home around the time of the HIFU treatment. The study will reimburse participants financially for their travel and provide accommodation where required. Women will need to lie flat and still for the ultrasound scans and USgHIFU treatments, which can cause discomfort. Although the researchers have studied this technique in laboratory models and believe the treatment will work very well based on this work, they do not know if it is going to be possible to block blood vessels in the human placenta, so participants may not experience any clinical benefit. Potential minor complications resulting from the HIFU treatment are: pain and/or reddening of the skin at the treated area during treatment, or pain due to lying in one position for an extended period. Medication or other treatment needed to control these symptoms will be offered if they occur. Potential major complications from the HIFU treatment are second- or third-degree abdominal skin burns, nerve damage (e.g. sciatica), injury to internal organs (the bladder and the bowel), bleeding from the placenta, and burns to one or both of the twins. The researchers will try to avoid all these complications by careful planning and monitoring of the treatment. If they suspect any of these complications have occurred, participants will be admitted to hospital for further tests and/or treatments.

Where is the study run from?
This study will be conducted at Queen Charlotte's and Chelsea Hospital, Imperial College NHS Trust, London, but participants will be referred from UK-wide NHS maternity hospitals.

When is the study starting and how long is it expected to run for?
March 2018 to March 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
260359

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 44380, IRAS 260359

Study information

Scientific Title
Ultrasound-guided High-Intensity Focused Ultrasound to treat Twin-Twin Transfusion Syndrome (USgHIFU-TTTS study)

Acronym
USgHIFU-TTTS

Study objectives
Null hypothesis: It is not possible to occlude human placental anastomoses using ultrasound-guided high intensity focused ultrasound (USgHIFU).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/01/2020, London - Riverside Research Ethics Committee (Level 3 Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207104 8204; nrescommittee.london-riverside@nhs.net), REC ref: 20/LO/0029

Study design

Non-randomized; Interventional; Design type: Treatment, Other

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Twin-twin transfusion syndrome

Interventions
Design: Phase 1a safety/efficacy (Bryant Day model).

Recruitment:
Potential participants will be identified from:
1. Women booked for obstetric care at Queen Charlotte's and Chelsea Hospital (QCCH), or referred to QCCH from other UK NHS maternity centres. These women will need to enroll in the Twin Placental Mapping study.
2. Women enrolled in the clinical research study "Investigating the feasibility of using Doppler ultrasound imaging to map placental vasculature and anastomoses in monochorionic diamniotic (MCDA) twin pregnancies, IRAS 242564" (the Twin Placental Mapping study)

Study Design:
To address the primary research objective the study is designed as a phase 1a safety/efficacy study using the Bryant and Day model. Bryant and Day's Two-Stage design will be used to incorporate a formal check of the number of positive responses as well as the number of patients experiencing significant iatrogenic harm in each successive participant before recruiting further patients into the study. The researchers will require five participants to be recruited into Stage 1, with 13 patients being the maximum number of patients to be accrued for the study in Stage 1 and Stage 2 combined.

Study methodology:
Prior to entry into the USgHIFU-TTTS study, the following procedures need to have been completed:
1. Twin Placental Mapping study (separate study)
2. Assessment of fetal wellbeing (staging of TTTS)
3. Assessment of maternal medical and obstetric history

Time from Placental Mapping study to USgHIFU-TTTS study
The window of opportunity for any type of treatment for TTTS can be very small. Potential participants will be allowed 24-72 hours to decide whether or not they want to take part in the study, unless there is an urgent clinical need to proceed, when 12-24 hours of consideration will be allowable if the woman feels this sufficient (i.e. same or next day enrolment).

If the USgHIFU treatment is planned for the day following the pre-study procedures described above, the participant will be offered the opportunity to remain in London overnight. Free overnight accommodation for the participant and accompanying person will be provided.

Entry to USgHIFU-TTTS study:
If potential participants are willing to consider enrolling in the USgHIFU-TTTS study, and are

eligible, they will meet with a member of the research team. The study will be explained in detail, and participants will be asked to provide written informed consent to enrol in the TTTS study. Consent will be taken by a consultant, a clinical fellow, or a clinical senior registrar (specialist fetal medicine doctors).

If potential participants decline consent to enroll in the USgHIFU-TTTS study, arrangements for provision of appropriate care according to standard pathways will be made.

First study assessment for USgHIFU-TTTS study:
This will take place usually on the same day as entry into the USgHIFU-TTTS study, and the day following the visit for pre-study procedures to take place.

A repeat obstetric ultrasound will be performed to assess fetal viability/condition and ensure treatment remains indicated. Participants will be informed of this outcome and whether they remain eligible for the study.

Further placental mapping will take place to detail the number and position of the placental anastomoses to be targeted for occlusion with USgHIFU, and to plan the HIFU exposures to be delivered. Based on this, if it is appears appropriate an USgHIFU treatment cycle will be commenced.

A “USgHIFU treatment cycle” will be used to describe a treatment with USgHIFU during which:
1. An attempt to occlude each placental anastomoses identified as a target in placental mapping has been made, and
2. Each placental anastomosis targeted either appears occluded (based on comparison of pre- and post-HIFU exposure colour flow Doppler imaging) or appears to remain present, but a decision to treat/retreat with USgHIFU has been made by the research team.

Following completion of the procedure, fetal viability will be assessed by ultrasound and the participant will be examined for evidence of maternal harm by medically qualified members of the research team. Standard medical care will be provided to the participant as indicated. The participant will be observed overnight as an inpatient at QCCH. Free overnight accommodation for the accompanying person (if any) will be provided.

Second study assessment:
This will take place on the day following the completion of a USgHIFU treatment cycle (which can be spaced over 72 hours if needed) at QCCH.
1. A repeat obstetric ultrasound will be performed by a member of the research team to assess fetal viability/wellbeing and blood flow within targeted placental anastomoses.
2. The participant will be examined by a member of the research team, for evidence of maternal iatrogenic harm. Standard medical care will be provided to the participant as indicated, including referral to other specialists.
3. A semi-structured interview will be conducted with the participant at this assessment. Participants will be asked to maintain a participant diary during the time prior to round two of the interviews, which will take place 4 -6 months after the expected delivery date.
4. Study participants will be given a symptom and appointment diary to keep for the following 14 days. This will include a self-reporting of red-flag symptoms for which they should seek urgent medical care including contact details for clinical members of the research.

Unless ongoing inpatient care is required, participants will be discharged from QCCH and return home following this study visit.

The study participant will be asked to complete a Symptom Journal for the first 14 days after the USgHIFU treatment cycle. This will be collected by a member of the clinical research team.

Once the clinical research team have completed the individual participant's USgHIFU treatment cycle, and the second study visit, a report consisting of the HIFU system report, the pre- and post-HIFU exposure colour flow Dopper imaging for all targeted anastomoses, and a checklist of items related to evidence of iatrogenic harm, maternal and fetal wellbeing will be generated. This report will be analysed by the Independent Oversight Committee.

Third study assessment:
This will take place three days (72 hours) following the completion of a USgHIFU treatment cycle.
1. A repeat obstetric ultrasound will be performed by a member of the research team to assess fetal viability and blood flow within targeted placental anastomoses.
2. If recurrent TTTS is identified a repeat treatment cycle of USgHIFU may be offered (following the same pattern as the first and second study visits). The participant will be asked to provide written confirmation of consent for a repeated USgHIFU treatment cycle.
3. The participant will be examined for evidence of maternal harm by a member of the research team, and the symptom diary will be reviewed. Standard medical care will be provided to the participant as indicated including referral to other specialists.

Participants will return home following this study visit unless inpatient admission is required.

Fourth study assessment:
This will take place 7 days following the completion of a USgHIFU treatment cycle and will be the same as the third study assessment.

Fifth study assessment:
This will take place 14 days following the completion of a USgHIFU treatment cycle and will the same as the third study assessment.

After the fifth study assessment participants will return to standard UK care as per NICE clinical guidance CG129 and local policy of the unit providing their maternity care.

Following delivery:
Patient medical records will be accessed (with explicit patient consent) to determine pregnancy outcomes. Details of recurrence and stage of TTTS, any further interventions for TTTS, survival of one or both twins until delivery, gestational age and mode of delivery, as well as details of other pregnancy complications will be entered onto the study database.

If the participant delivers within Imperial College Healthcare NHS Trust hospital the placental surface will be photographed following delivery and then the placental tissue will be either disposed of or send for histological analysis according to standard hospital policy by the direct clinical care team present for the delivery.

If study participant delivers at a maternity unit other than Imperial College Healthcare NHS Trust, this unit will be contacted to provide the information listed above (using secure NHS email or secure fax) – permission to do this will be included in the consent form.

Between 4 - 6 months after the participants EDD (estimated due date), participants will be contacted for a second round of semi-structured interviews. The nature of TTTS means that the twins would have been delivered for between 8 and 16 weeks prior to the EDD. The exact timing will be determined by the needs and preferences of the participant.

Qualitative work package (optional):
A complementary qualitative work package (QWP) will run alongside the main study. This will be utilised primarily to i) address questions relating to overall treatment acceptability, and ii) inform the study process evaluation. Additionally, the QWP will be used to generate data exploring wider issues related to participants' experiences of i) being diagnosed with and treated for TTTS and ii) participating in a phase 1a safety/efficacy study during pregnancy.

The option of consenting to participation in the QWP will be offered whilst consent to the main study is taken.

Prior to each interview/interaction the qualitative researcher will review the status of participants' understanding of the QWP and relevant aspects of the consent form, to ensure consent remains valid throughout. The researcher will remain alert to any signs of participant distress throughout, and prior to each interview/interaction participants will be reminded that they are able to withdraw from the QWP at any time, without having to provide a reason. Information on relevant support services will be signposted (e.g. TAMBA, Multiple Birth Foundation).

Interviews will be conducted in-person/face-to-face, or via telephone/videoconference, depending on the needs and preferences of each participant. It is anticipated that each interview will take no longer than 60 minutes. The first round of interviews will be conducted soon after USgHIFU treatment (at the second study visit, typically before discharge from QCCH). As such, the researcher will remain highly responsive to any signs of participant distress throughout all interactions (pre, during and post-interview). This approach is considered essential to appropriate engagement with this post-treatment population, where personal, sensitive issues (relating to pregnancy, motherhood/parenthood, prenatal diagnoses and the potential for fetal loss, for example) may be discussed.

Subsequent to round one, interviewees will be asked to maintain a participant notes journal during the time prior to round two, within which they would be able to record key thoughts, events, and/or experiences that they would like to communicate to the research team, for inclusion in the qualitative dataset. In order to maximise opportunities for inclusion, participants would be given the option of using paper-based diaries (supplied by the research team), and/or audio/video recordings. The research team will provide secure electronic and/or postal delivery methods for the return of participant diaries, and original copies of paper-based diaries will be returned to participants subsequent to data analysis (once a copy has been made) (electronic copies will be securely stored as part of the qualitative dataset). The second round of interviews will be conducted 4 - 6 months after the round one interviews have taken place (exact timing will be determined by the needs and preferences of the participant). This will be regarded as the endpoint of the study.

Interim analyses:
After each participant has completed the second study assessment, an interim report will be completed with the findings of the Independent Oversight Committee review to determine if stopping criteria have been met. This will detail the number of participants with a positive response and the number suffering significant iatrogenic harm. Those who are free of significant iatrogenic harm will be calculated with an exact 95% confidence interval calculated using the Clopper-Pearson method.

PPI:
The researchers have conducted PPI focus groups comprised of families with experience of TTTS and online questionnaires of members of the Twin and Multiple Birth Association (TAMBA).

Intervention Type
Procedure/Surgery

Primary outcome(s)
1. Safety: Number/rate of patients experiencing significant iatrogenic harm, measured using clinical examination, review of participant medical records and/or patient symptom diaries, daily for first 14 days after HIFU treatment completed (clinical examination and/or symptom diaries) and after delivery (participant medical records)
2. Efficacy: Number/rate of targeted placental anastomoses which appear occluded at the end of a HIFU treatment cycle, assessed using comparison of colour Doppler imaging of target anastomoses pre- and post-HIFU exposure

Key secondary outcome(s))
1. Feasibility and acceptability of HIFU treatment in terms of study eligibility, recruitment and retention, measured using number of patients who were (i) screened, (ii) recruited and (iii) remained in the study until their delivery at end of the trial period
2. Pregnancy outcomes:
2.1. Rates of regression/persistence/deterioration or recurrence of TTTS measured using Quintero staging at day 1, 3, 7 and 14 after HIFU treatment
2.2. Need for further treatment of TTTS measured using Quintero staging at day 3, 7 and 14 after HIFU treatment
2.3. Pregnancy complications (antepartum bleeding, preterm rupture of membranes, other) measured using review of participant medical records at delivery
2.4. Gestational ages at delivery measured using review of participant medical records at delivery
2.5. Birth weights measured using review of participant medical records at delivery
2.6. Number of live-births measured using review of participant medical records at delivery
3. Placental outcomes:
3.1. Evidence of occlusion of the placenta using photographs of placental surface post-delivery
3.2. Histopathology reports of placenta, if performed, measured using processes adhering to local policy for histopathological placental examination at post-delivery
4. Acceptability of the treatment to participants assessed qualitatively using semi-structured interview and patient diaries at day 1 post HIFU treatment and after delivery

Completion date
31/03/2025

Eligibility

Key inclusion criteria
1. Able to understand patient information sheet (with appropriate support/interpretation if required) and give informed consent
2. Women currently pregnant with monochorionic diamniotic twin pregnancies
3. Gestational age between 12+0 and 17+6 weeks at time of USgHIFU treatment
4. Pregnancy diagnosed with TTTS Stage I-IV (Quintero staging)
5. Aged 18 years or more
6. Enrolled in the "Investigating the feasibility of using Doppler ultrasound imaging to map

placental vasculature and anastomoses in monochorionic diamniotic (MCDA) twin pregnancies, IRAS 242564" (twin placental mapping) study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Total final enrolment
10

Key exclusion criteria
1. Maternal age 51 years or more (average age of menopause in the UK)
2. Pregnancy diagnosed with TTTS Stage V (one or both fetuses dead)
3. Chorionicity assigned at > 14+0 weeks
4. Higher-order pregnancy (even if containing MCDA pair)
5. BMI >35
6. Significant abdominal scarring, subject to medical assessment
7. Unable or unwilling to travel to London for treatment and follow-up
8. Placental anastomoses cannot be identified with ultrasound
9. USgHIFU treatment cannot be planned for technical reasons

Date of first enrolment
08/01/2021

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Imperial College Healthcare NHS Trust
St Mary's Hospital
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Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
Medical Research Council; Grant Codes: MR/R015384/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the Centre for Trials Research (CTR@cardiff.ac.uk). Data will not be made available until after the main results of the study are published. Access will only be permitted to anonymised data.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	version v1	02/12/2019	05/03/2020	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes