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Time Lapse Imaging Trial

Submission date
04/04/2018

Recruitment status
No longer recruiting

Registration date
18/04/2018

Overall study status
Completed

Last Edited
22/07/2024

Condition category
Pregnancy and Childbirth

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
In vitro fertilisation (IVF) techniques can help people with fertility problems to have a baby. In IVF an egg is fertilized by sperm in a test tube to create an embryo. The current methods of selecting the best embryo for replacement into the womb during IVF are imprecise. The resulting success rates for this expensive treatment are less than ideal. Success rates might be improved by a new technology that uses time-lapse imaging, where embryos are grown in a special incubator, and an inbuilt microscope and camera allows embryos to be assessed without having to remove them. In addition, images of the developing embryo are taken every five to fifteen minutes, which can give additional information (morphokinetic parameters) to aid selection. The aim of this study is to find out whether this technology increases the likelihood of live birth following fertility treatment.

Who can participate?
Couples undergoing IVF or ICSI (Intra-Cytoplasmic Sperm Injection) treatment, where the woman is between 18 and 42 years of age and the male partner is at least 18 years of age

What does the study involve?
Participants are randomly allocated to one of three treatment groups. In the first group embryos are grown in the time-lapse incubator using time-lapse imaging for embryo selection. In the second group embryos are grown in the time-lapse incubator using only standard assessment techniques. In the third group embryos are grown in standard incubators. At the end of the incubation (3-6 days after egg collection), the best embryo(s) are transferred. The woman is then followed up until a maximum of 6 weeks after the end of the pregnancy. The number of live births is taken from the patients' medical notes or by contacting the participant.

What are the possible benefits and risks of participating?
There is no guarantee that taking part in this study will increase the chances of IVF/ICSI being successful, but participants will be helping clinicians and policy makers decide whether current IVF/ICSI guidelines need to be changed. There is no added risk using this technology for the growth and monitoring of embryos. The camera captures embryos in red light for a very short period of time – 15 milliseconds. This is the same amount of light exposure as during manual removal of embryos from the standard incubator and their examination under a standard microscope. The time lapse imaging systems are CE marked.

Where is the study run from?
Barts Research Centre for Women's Health, Women's Health Research Unit, Queen Mary University of London, James Cook University Hospital (UK) and The Chinese University of Hong Kong Prince of Wales Hospital (Hong Kong)

When is the study starting and how long is it expected to run for?
September 2017 to September 2023

Who is funding the study?
1. Barts and the London Charity and Related Charities (UK)
2. Pharmasure Ltd (UK)

Who is the main contact?
1. James Heighway
j.heighway@qmul.ac.uk
2. Priya Bhide
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Study website
https://www.barc-research.org/tilt

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
37510

Study information

Scientific Title
A pragmatic, multi-centre, three-arm randomised controlled trial to assess the clinical effectiveness and safety of time lapse imaging in in-vitro fertilisation treatment

Acronym
TILT

Study objectives
Current methods of selecting the best embryo for replacement into the womb during in-vitro fertilisation treatment (IVF) are imprecise. The resulting success rates for this expensive treatment are less than ideal. Success rates might be improved by a new technology that uses time-lapse imaging, where embryos are grown in a special incubator, and an inbuilt microscope and camera allow embryos to be assessed without having to remove them. In addition, images of the developing embryo are taken every five to fifteen minutes, which can give additional information (so-called morphokinetic parameters) to aid selection. Current best evidence for the use of time-lapse imaging is uncertain and of moderate to low quality. The trialists propose to conduct a large-scale study giving high-quality evidence and a definitive answer to whether this technology increases the likelihood of live birth following fertility treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London Central Research Ethics Committee, provisional approval 08/03/2018, ref: 18/LO/0330

Study design
Randomised; Interventional; Design type: Treatment, Device

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
In vitro fertilization

Interventions
A secure, web based randomisation system hosted by the Barts Women's Health Research Centre. The randomisation will be stratified by fertility clinic, and minimised by:
1. Participant's age (<35 years, 35 – 40 years, >40 years)
2. Type of planned first embryo transfer (fresh, frozen).

Participants are randomly allocated to one of three treatment groups:
Time-lapse imaging (intervention group 1): incubation and assessment of embryos within time-lapse imaging systems, using morphokinetic parameters in addition to conventional morphological assessment
Undisturbed culture (intervention group 2): incubation of embryos in undisturbed culture conditions within time-lapse imaging incubators, using conventional morphological embryo assessment only
Standard care (control group): incubation of embryos in standard incubators, using conventional morphological embryo assessment only

At the end of the incubation (3-6 days after egg collection), the best embryo(s) will be transferred. The woman will then be followed up until a maximum of 6 weeks after the end of the pregnancy.

The sample size calculation was based upon the primary outcome of live birth. With a 5% overall significance level (2.5% for each of the two main treatment comparisons: TLI vs. standard care, and undisturbed culture vs. standard care), 514 participants would be required per treatment arm to detect an absolute increase in the primary outcome from 26.5% to 35.25% with 80% power. Allowing for 2% loss-to-follow-up or withdrawal of consent would require 525 participants per treatment arm (1575 in total). The comparison between experimental treatment arms (TLI vs. undisturbed culture) will be performed with no impact on sample size

because this statistical test will be carried out conditional to the rejection of at least one of the primary comparisons planned (TLI vs. standard care, or undisturbed culture vs. standard care). This hierarchical approach permits to maintain the overall type I error rate of 5%.

Intervention Type
Other

Primary outcome measure
Number of live births, taken from medical notes/contacting the participant; Timepoint(s): Delivery

Secondary outcome measures
Current secondary outcome measures as of 06/04/2020:
Clinical efficacy outcomes:
1. Pregnancy rate measured by pregnancy test taken from medical notes; Timepoint(s): 2 weeks after embryo transfer
2. Successful implantation of embryo(s) into womb measured by total number of gestational sacs seen on ultrasound scan/total number of embryos replaced into the womb taken from medical notes; Timepoint(s): 6-8 weeks after embryo transfer.
3. Successful clinical pregnancy measured by at least one intrauterine gestational sac taken from medical notes/contacting the participant; Timepoint(s): 6-8 weeks after embryo transfer
4. Use of elective single embryo transfer (e-SET) recorded per participant, taken from medical notes; Timepoint(s): At embryo transfer
5. Embryo utilization rate (% of total embryos either transferred or frozen), taken from medical notes; Timepoint: 2-6 days after date of fertilisation check.

Clinical safety outcomes:
1. Multiple pregnancy measured by two or more gestational sacs seen on ultrasound scan taken from medical notes/contacting the participant; Timepoint(s): 6-8 weeks after embryo transfer
2. Pregnancy loss recorded from medical notes/contacting the participant; Timepoint(s):
2.1. Between positive pregnancy test and 6-8 week scan
2.2. Between 6-8 week scan and 12 weeks (early miscarriage)
2.3. Between 12 and 24 weeks
2.4. Stillbirth
3. Incidence of major congenital abnormality at birth recorded as a Serious Adverse Event taken from medical notes/contacting the participant; Timepoint(s): Within 6 weeks of delivery
4. Birth weight, taken from medical notes; Timepoint: Delivery
5. Gestational age, taken from medical notes; Timepoint: Delivery
6. Ectopic pregnancy, taken from medical notes/contacting the participant; Timepoint(s): early pregnancy scan (6-8 weeks) & 24 weeks assessment

Previous secondary outcome measures:
Clinical efficacy outcomes:
1. Pregnancy rate measured by pregnancy test taken from medical notes; Timepoint(s): 2 weeks after embryo transfer
2. Successful implantation of embryo(s) into womb measured by total number of gestational sacs seen on ultrasound scan/total number of embryos replaced into the womb taken from medical notes; Timepoint(s): Two weeks after embryo transfer
3. Successful clinical pregnancy measured by at least one intrauterine gestational sac taken from

medical notes/contacting the participant; Timepoint(s): 6-8 weeks after embryo transfer
4. Use of elective single embryo transfer (e-SET) recorded per participant, taken from medical notes; Timepoint(s): At embryo transfer

Clinical safety outcomes:
1. Multiple pregnancy measured by two or more gestational sacs seen on ultrasound scan taken from medical notes/contacting the participant; Timepoint(s): 6-8 weeks after embryo transfer
2. Miscarriage recorded for each pregnancy loss taken from medical notes/contacting the participant; Timepoint(s): Between 6 and 24 weeks gestation
3. Stillbirth recorded as pregnancy loss taken from medical notes/contacting the participant; Timepoint(s): After 24 weeks gestation
4. Incidence of major congenital abnormality at birth recorded as a Serious Adverse Event taken from medical notes/contacting the participant; Timepoint(s): Within 6 weeks of delivery

Overall study start date
01/09/2017

Completion date
30/09/2023

Eligibility

Key inclusion criteria
The inclusion criteria are broad in keeping with the latest NICE guidelines (2013) for NHS funded IVF/ICSI treatment.
Participants undergoing IVF/ICSI treatment and:
1. The woman is between 18 and 42 years of age at the time of consent
2. The male partner is at least 18 years of age at the time of consent
3. Receiving the first, second or third IVF/ICSI treatment cycle
4. Both partners give written informed consent
5. Those having at least 3 2PN embryos (showing 2 pro-nucleii which is a sign of normal fertilisation) on day of fertilization check

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 1575; UK Sample Size: 1125, CUHK Sample Size: 450

Total final enrolment
1575

Key exclusion criteria
Current exclusion criteria as of 06/04/2020:
1. Participants concomitantly participating in other interventional trials
2. IVF/ICSI treatment using donor gametes
3. Planned pre-implantation genetic diagnostics or screening (PGS/PGD)

Previous exclusion criteria:
1. Participants who have been randomised previously to this trial
2. Participants concomitantly participating in other trials
3. IVF/ICSI treatment using donor gametes
4. Planned pre-implantation genetic diagnostics or screening (PGS/PGD)

Date of first enrolment
01/05/2018

Date of final enrolment
30/09/2022

Locations

Countries of recruitment
England

Hong Kong

United Kingdom

Study participating centre
Homerton University Hospital
Homerton Row
London
United Kingdom
E9 6SR

Study participating centre
St Bartholomews Hospital
Centre for Reproductive Medicine
1st Floor, Kenton & Lucas Wing
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre

Bath Fertility Centre
Roman Way
Bath Business Park
Peasedown St John
Bath
United Kingdom
BA2 8SG

Study participating centre
Hammersmith Hospital
Du Cane Road
White City
London
United Kingdom
W12 0HS

Study participating centre
Complete Fertility Centre- Princess Anne Hospital
Mailpoint 105, Level G
Coxford Road
Southampton
United Kingdom
SO16 5YA

Study participating centre
Ocean Suite- Derriford Hospital
South West Centre for Reproductive Medicine
Ocean Suite, Level 6
Derriford Hospital
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Assisted Reproductive Technology (ART) Unit
Department of Obstetrics & Gynaecology
The Chinese University of Hong Kong
9F, Special Block EF
Prince of Wales Hospital
Shatin, N.T.
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Sponsor information

Organisation
Queen Mary University of London

Sponsor details
QMUL Joint Research Management Office
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E1 2EF
+44 (0)20 7882 7275
sponsorsrep@bartshealth.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.jrmo.org.uk/

ROR
https://ror.org/026zzn846

Organisation
Chinese University of Hong Kong

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1/F, Special Block
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Sponsor type
University/education

Website
http://www.cuhk.edu.hk/english/index.html

Funder(s)

Funder type
Charity

Funder Name
Barts and the London Charity and Related Charities; Grant Codes: MGU0374

Funder Name
Pharmasure Ltd

Results and Publications

Publication and dissemination plan
The Chief Investigator (CI) will have primary responsibility and co-ordinate dissemination of data from this trial. A core team consisting of the co-applicants will work closely with QMUL to plan and effectively disseminate the findings of the research to all stakeholders: participants, clinical community, user groups, funding bodies, NHS commissioners and the general public. The clinical trial report and the main manuscript will be reviewed by the Clinical Investigators Group and Trial Steering Committee before publication.

Dissemination to clinicians and clinical professional bodies will be through publications and presentations at major national and international conferences relevant to the speciality. The aim is to publish the findings in the highest impact peer reviewed journals and present them at the annual conferences related to the speciality. The trialists plan to publish the study protocol in an open access journal and to communicate the trial findings to the Cochrane Gynaecology and Fertility Group with a view to incorporate the results into the current Cochrane review.

Dissemination to the participants and the general public will be done through newsletters, NHS websites and through the meetings and websites of local PPI networks and Fertility Networks UK. In consultation with the investigators and appropriate journals, a press release will be issued to the media upon publication of the results.

Intention to publish date
01/02/2024

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 CI Dr Priya Bhide (p.bhide@qmul.ac.uk). There will be restrictions on the availability of raw data for this study, due to data confidentiality and patient privacy. Researchers wishing to access the TILT trial data for the purposes of replicating or verifying our analyses can apply to the CI at the BARC (Barts Research Centre for Women’s Health).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	01/07/2020	05/07/2020	Yes	No
HRA research summary			28/06/2023	No	No
Results article		20/07/2024	22/07/2024	Yes	No