**PROTOCOL**

**Study Acronym**

**3D / 4D UGET**

**Study Title**

**3D / 4D Ultrasound Guided Embryo Transfer vs. Clinical Touch Technique: a randomised controlled trial**

**Version 3.0**

**21st March 2016**

**Sponsor:** Liverpool Women’s NHS Foundation Trust

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**NRES Reference:** tbc

**Study Team**

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**Clinical Queries**

Clinical queries should be directed to Richard Russell.

**Sponsor**

For further information regarding the sponsorship conditions, please contact:

R&D Manager, Liverpool Women’s NHS Foundation Trust.

**STUDY SUMMARY**

This protocol describes the 3D / 4D ultrasound guided embryo transfer study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the Study. Problems relating to this Study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

**GLOSSARY OF ABBREVIATIONS**

|  |  |
| --- | --- |
| IVF | In vitro fertilisation |
| ICSI | Intracytoplasmic insemination |
| ET | Embryo transfer |
| OR | Oocyte retrieval |
| TVS | Transvaginal ultrasound scan |
| LBR | Live birth rate |
| HFEA | Human Fertilisation &Embryology Authority |
| βHCG | Beta Human Chorionic Gonadotrophin |

**KEYWORDS**

Embryo transfer, 3D ultrasound, 4D ultrasound, IVF, Assisted Conception, Pregnancy rate

**TITLE**

3D / 4D Ultrasound Guided Embryo Transfer vs Clinical Touch Technique; a randomised controlled trial

**DESIGN**

Single Centre Prospective randomised controlled trial

**AIMS**

To learn whether using advanced ultrasound imaging during the process of embryo transfer, improves the clinical pregnancy and live birth rate after IVF treatment.

**OUTCOME MEASURES**

Primary Outcome: Live birth

Secondary outcomes:Biochemical pregnancy (defined as positive urinary pregnancy test or serum βHCG >15 iu)

Clinical pregnancy (presence of intrauterine pregnancy with fetal heart rate >100bpm between 6-8 weeks pregnancy).

 Miscarriage

Ectopic pregnancy

Multiple pregnancy

Failed embryo transfer

Grading of ease of procedure (Easy 1 to Difficult 5)

Duration of procedure

Patient experience

**POPULATION ELIGIBILITY**

All patients attending the Hewitt Fertility Centre for embryo transfer.

**DURATION**

During embryo transfer only.

Contents

[1. INTRODUCTION 7](#_Toc443859761)

[1.1 BACKGROUND 7](#_Toc443859762)

[1.2 RATIONALE FOR CURRENT STUDY 8](#_Toc443859763)

[2. STUDY OBJECTIVES 8](#_Toc443859764)

[3. STUDY INTERVENTION 8](#_Toc443859765)

[3.1 Intervention Group 8](#_Toc443859766)

[3.2 Control Group 9](#_Toc443859767)

[4. STUDY DESIGN 9](#_Toc443859768)

[4.1 RANDOMIZATION PROCEDURES 9](#_Toc443859769)

[4.2 STUDY OUTCOME MEASURES 10](#_Toc443859770)

[5. PARTICIPANT ENTRY 10](#_Toc443859771)

[5.1 PRE‐REGISTRATION EVALUATIONS 10](#_Toc443859772)

[5.2 INCLUSION CRITERIA 10](#_Toc443859773)

[5.3 EXCLUSION CRITERIA 10](#_Toc443859774)

[5.4 WITHDRAWAL CRITERIA 11](#_Toc443859775)

[6. ADVERSE EVENTS 11](#_Toc443859776)

[6.1 DEFINITIONS 11](#_Toc443859777)

[6.2 REPORTING PROCEDURES 11](#_Toc443859778)

[6.2.1 Non serious AEs 11](#_Toc443859779)

[6.2.2 Serious AEs 11](#_Toc443859780)

[7. ASSESSMENT AND FOLLOW‐UP 12](#_Toc443859781)

[8. STATISTICS AND DATA ANALYSIS 12](#_Toc443859782)

[9. REGULATORY ISSUES 13](#_Toc443859783)

[9.1 ETHICS APPROVAL 13](#_Toc443859784)

[9.2 CONSENT 13](#_Toc443859785)

[9.3 CONFIDENTIALITY 13](#_Toc443859786)

[9.4 INDEMNITY 13](#_Toc443859787)

[9.5 SPONSOR 13](#_Toc443859788)

[9.6 FUNDING 13](#_Toc443859789)

[9.7 AUDITS 13](#_Toc443859790)

[10. STUDY MANAGEMENT 13](#_Toc443859791)

[11. END OF STUDY 14](#_Toc443859792)

[11. ARCHIVING 14](#_Toc443859793)

[12. PUBLICATION POLICY 14](#_Toc443859794)

[13. REFERENCES 14](#_Toc443859795)

# 1. INTRODUCTION

## 1.1 BACKGROUND

Since the first pregnancy using in vitro fertilisation, many aspects of the procedure, such as ovarian stimulation, oocyte recovery and the in vitro techniques of fertilisation and embryo transfer have undergone major transformation. In contrast, the technique of embryo transfer remains largely unchanged. It is estimated that up to 85% of replaced embryos fail to implant, despite apparently normal embryos for transfer (Sallam 2002). This failure may be due to lack of chromosomally normal embryos, lack of uterine receptivity or the embryo transfer technique itself.

Traditionally there have been two techniques used: a “clinical touch” method used to guide placement of the transfer catheter to within 10mm of the uterine fundus prior to injection of the embryo. This is essentially a “blind” procedure and works on tactile sensation. Similarly some clinicians transfer the embryos at a fixed distance from the external os (approximately 6cm), however this works on the assumption that the uterine dimensions including cervix are the same for all women. Assessment of these two methods has been demonstrated to be suboptimal (Woolcott 1997), with the catheter indenting or embedded in the endometrium. Inadvertent endometrial trauma or contact with the fundus induces high frequency uterine contractions which leads to lower implantation rates (Fanchin 1998).

The use of ultrasound at the time of ET was first discussed by Strickler et al. in 1995, who postulated that this would allow accurate and atraumatic positioning of the catheter tip near the uterine fundus and hence improve clinical pregnancy rates. The technique has often been described as “cleaner” with the ability to tailor the placement of the embryo to the individual (Prapas 2001).

A Cochrane review (Brown J *et* al. 2010) suggested no difference in live birth rates when comparing ultrasound guided and clinical touch techniques OR 1.14(95%CI 0.93 to 1.39), but a significant increase in clinical pregnancy rate, OR 1.38 (99%CI 1.16 to 1.64). Ultrasound guided embryo transfer is recommended by NICE and appears to be utilised in 77% of embryo transfers worldwide (Tobler 2014).

Positioning of the embryo(s) at transfer less than 10mm from the fundal endometrial surface results in a decrease in implantation and clinical pregnancy rate (Cenksoy 2014).

Traditionally, ultrasound guided embryo transfer has been performed using trans-abdominal 2D ultrasound. More recently, ultrasound technology and capabilities have advanced so that 3D and 4D imaging of the uterus can now be achieved, visualising finer detail with greater clarity, as well as enabling spatial awareness in terms of the dimensions and volume of the uterus. It is reasonable to assume that more accurate placement of the transfer catheter and replacement of the embryo(s) could result in higher ongoing pregnancy outcome. In a feasibility study, transabdominal 3D USS was employed to confirm correct placement of a trial catheter prior to embryo transfer, which was not subsequently performed under ultrasound guidance (Baba 2000). A second feasibility study also confirmed the ability to ensure correct catheter placement using 3d and 4D ultrasound using transabdominal ultrasound and reported an increase in pregnancy rate from 36.66% to 65% comparing control and intervention groups (Gergely 2005).

With the availability of the Kitazato embryo transfer catheter, the ability to perform an embryo transfer using a transvaginal 3D/4D ultrasound scan has become possible. The resolution of images obtained using transvaginal ultrasound appears superior to similar images obtained through transabdominal scanning. Is it possible that this would result in superior pregnancy rates and outcomes.

## 1.2 RATIONALE FOR CURRENT STUDY

Does the use of advanced ultrasound techniques during embryo transfer improve the pregnancy rate and outcome for patients undergoing IVF treatment?

Embryo implantation is a critical step in successful IVF treatment. Correct placement of the embryo(s) within the uterine cavity can result in improved implantation. If the uterine cavity can be assessed in greater detail, is the more accurate placement of the embryo possible and will this improve implantation and pregnancy rates?

# 2. STUDY OBJECTIVES

Does 3D / 4D embryo replacement during embryo transfer improve pregnancy rates and outcomes for patients undergoing IVF treatment?

# 3. STUDY INTERVENTION

## 3.1 Intervention Group

The Kitazato ET Catheter Inner 3Fr. 40cm Guide 30° / 20cm. Ref 223340 (CE 0086 International (Single Use) (Kitazato Medical Co. Tokyo) has been designed to allow transvaginal replacement of the embryo under transvaginal ultrasound guidance. The following steps describe the process using this catheter in the intervention group.

1. The patient should have an empty bladder at the beginning of the procedure.
2. With the patient in the lithotomy position, a transvaginal ultrasound is performed to identify the angle of the utero-cervical junction, the length of the cervix and the maximal thickness and general appearance of the endometrium.
3. The embryo transfer catheter outer sheath is altered in residual length to correspond with the length of the cervical canal (utilizing an inbuilt sliding catheter bung).
4. A speculum is inserted in the vagina to expose the external os of the cervix followed by preparation of the visual field and cervix according to routine procedures with removal of residual cervical mucus.
5. The embryo transfer sheath is inserted into the cervix to the predefined point identified on initial scan (the distal tip of the outer sheath catheter will be placed at the level of the internal os.
6. The transvaginal ultrasound probe is re-introduced into the vagina. The proximal end of the transfer catheter sits alongside the ultrasound probe and is easily accessible for insertion of the inner catheter.
7. The speculum is withdrawn from the vagina, maintaining the position of the catheter.
8. The inner catheter is loaded with the embryo(s) by the embryologist and the inner catheter inserted through the catheter sheath with further advancement of the distal end of the catheter performed under direct ultrasound guidance, utilizing 2D, 3D and live 4D views to optimize placement of the catheter tip.
9. The embryo is displaced form the catheter tip.
10. The catheter is withdrawn and embryo transfer is confirmed by the embryologist.
11. The procedure is complete.

## 3.2 Control Group

The control group will have embryo transfer according to accepted standard practice often called the “clinical touch” technique. This group pf patient will utilize the Wallace Classic Embryo Transfer Catheter (18 or 23cm) soft with centimeter graduations (Smiths Medical International Ltd, UK, CE marked). Stylets will be used according to clinical requirements.

1. The patient is advised to have a comfortably full bladder at the beginning of the procedure.
2. The patient is placed in lithotomy position.
3. A speculum is inserted in the vagina to expose the external os of the cervix followed by preparation of the visual field and cervix according to routine procedures with removal of residual cervical mucus.
4. The catheter is loaded with the embryo(s) by the embryologist and handed to the ET practitioner.
5. The embryo catheter is advanced through the external os up to the 6cm graded mark. The embryo is then replaced.
6. The catheter is removed and the replacement of the embryo confirmed by the embryologist.
7. The procedure is complete.

# 4. STUDY DESIGN

Prospective Randomised Controlled Trial (unblinded) Parallel study comparing two techniques for embryo transfer.

In a non-randomised pilot study of an unselected population (50 patients), an increase in live birth rate biochemical pregnancy rate of 15% was observed in the intervention group compared with a control group.

The sample size in this study assumes an expected response rate in the study group of 40% and in the control group of 25%. To achieve an 80% power to detect the difference, with a significance level of 5%, it is calculated that 149 subjects per group will be required. With a withdraw/non-evaluable subject rate of 5%, a total of 157 subjects per group will need to be recruited, leading to a total required sample size of 314 subjects.

## 4.1 RANDOMIZATION PROCEDURES

Patients will be randomized to the study group or control group using computer generated numbers, centrally distributed consecutively by telephone to a non-involved research nurse.

## 4.2 STUDY OUTCOME MEASURES

The study aims to confirm the superiority of one embryo transfer technique compared with another.

**Primary Outcome:** Live birth

**Secondary outcomes:** Biochemical pregnancy (defined as urinary pregnancy test positive)

Clinical pregnancy (presence of intrauterine pregnancy with fetal heart rate >100bpm between 6-8 weeks pregnancy)

 Miscarriage

Ectopic pregnancy

Multiple pregnancies

Failed embryo transfer

Grading of ease of procedure (Easy 1 to Difficult 5)

Duration of procedure

Patient experience

# 5. PARTICIPANT ENTRY

## 5.1 PRE‐REGISTRATION EVALUATIONS

No specific screening tests will be required for study consideration. However all patients will undergo a pelvic ultrasound assessment during IVF treatment.

## 5.2 INCLUSION CRITERIA

1. All women undergoing fresh or frozen embryo transfer
2. All women able to provide written informed consent

## 5.3 EXCLUSION CRITERIA

1. Known or suspected hydrosalpinx
2. Fluid within the endometrial cavity
3. Gross distortion of endometrium (e.g. fibroids etc.)
4. Previous myomectomy
5. Previous randomization
6. Significant health issues, e.g. HIV , Hepatitis C, Hepatitis B, previous trachelectomy

## 5.4 WITHDRAWAL CRITERIA

A trial subject may withdraw from the study at any time.

# 6. ADVERSE EVENTS

## 6.1 DEFINITIONS

**Adverse Event (AE):** any untoward medical occurrence in a patient or clinical study subject.

**Serious Adverse Event (SAE):** any untoward and unexpected medical occurrence or effect that:

* **Results in death**
* **Is life‐threatening** – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
* **Requires hospitalisation, or prolongation of existing inpatients’ hospitalisation**
* **Results in persistent or significant disability or incapacity**
* **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life‐threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

**Exclusion for AE / SAE**

The following will not be considered as AEs or SAEs:

Bleeding in pregnancy, negative pregnancy test, biochemical pregnancy loss, miscarriage, ectopic pregnancy, any complication of pregnancy beyond 8 weeks gestation. (While these maybe not need to be reported as AEs or SAEs if they are directly related to the mode of ET, they should still be reported.)

## 6.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

### 6.2.1 Non serious AEs

All such events, whether expected or not, should be recorded, unless excluded.

### 6.2.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, death and hospitalisations for elective treatment of a pre‐existing condition do not need reporting as SAEs.

All SAEs should be reported to the Independent Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

* ‘related’, i.e. resulted from the performance of the study intervention; and
* ‘unexpected’, i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non‐IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs:

R&D Manager

Liverpool Women’s NHS Foundation Trust Hospital

Crown Street

Tel 0151 702 4241

Fax: 0151 702 4299

# 7. ASSESSMENT AND FOLLOW‐UP

All patients report pregnancy outcome to the Hewitt Fertility Centre as standard practice. All patients with a biochemical pregnancy undergo a pregnancy viability ultrasound assessment at around 7 weeks gestation. All patients report the outcome of their pregnancy to the Hewitt Centre. All patient / IVF cycle outcome data must be reported to the HFEA (Human Fertilisation & Embryology Authority).

# 8. STATISTICS AND DATA ANALYSIS

In a non-randomised pilot study of an unselected population (50 patients), an increase in live birth rate of 15% was observed in the intervention group compared with a control group.

The sample sizing assumes that the expected percentage response in the study group is 40% and in the controls is 25%. To achieve an 80% power to detect the difference, with a significance level of 5%, it is estimated that 149 subjects per group will be required. With a withdraw/non-evaluable subject rate of 5%, a total of 157 subjects per group will be recruited, leading to a total required sample size of 314 subjects.

# 9. REGULATORY ISSUES

## 9.1 ETHICS APPROVAL

The Chief Investigator will obtain research approval from an Independent Research Ethics Committee. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

## 9.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant’s best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow‐up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

## 9.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

## 9.4 INDEMNITY

There are no requirements for arrangements for extra indemnity cover. This owes to the fact that there are no significant risks posed to any participants or researchers in this study and also that Liverpool Women’s Hospital NHS foundation Trust has agreed to act as sponsor of this project.

## 9.5 SPONSOR

The Liverpool Women’s NHS Foundation Trust will act as the Sponsor for this study.

## 9.6 FUNDING

The Hewitt Fertility Centre is funding this study and will cover costs associated with purchase of additional equipment and clinician time to complete the study.

## 9.7 AUDITS

The study may be subject to inspection and audit by the sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

# 10. STUDY MANAGEMENT

The day‐to‐day management of the study will be coordinated by Mr Richard Russell (Consultant Gynaecologist and Subspecialist in Reproductive Medicine & Chief Investigator).

# 11. END OF STUDY

The end of the study is defined as having achieved full recruitment of the desired number of study participants with full pregnancy outcome details up to and including live birth.

# 11. ARCHIVING

Data and all appropriate documentation should be stored for a minimum of 5 years after the completion of the study, including the follow‐up period, unless otherwise directed by the funder/sponsor/regulatory bodies.

# 12. PUBLICATION POLICY

Dissemination will occur through departmental meeting including research meetings. This potentially will extend to national/ international conferences and publications in the field of fertility.

# 13. REFERENCES

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