WCMC Protocol #: 1612017837
Version Date: V2 5.17.2018
NCT Identifiers: NCT03522350

Title:
Randomized Controlled Trial Comparing EmbryoScope Time-Lapse System with the new model EmbryoScope+.

Required Summary:
The purpose of the study is to compare the current EmbryoScope Time-Lapse System being used in IVF which has become standard of care to the new model EmbryoScope+.

Performance Sites
Weill Medical College of
Cornell University
Grants & Contracts 1300 York Avenue, Box 89 New York NY -
10021 USA

Performing Organization
Weill Medical College of
Cornell University
Grants & Contracts 1300 York Avenue, Box 89 New York NY -
10021 USA

Investigators
Person Name Primary Title Directory Title Units Affiliate Training Flag
Zaninovic, Nikica
Associate Professor- Clinical Ph.D. Medicine
PI - Responsible for Entire Protocol

Co-Investigators:
Clarke, Robert N., PhD- Associate Professor- Clinical
Joseph-Sohan, Mitasha- Research Nurse Specialist
Stubbs, Rodriq E., NP- Research Practice Administrator
Witzke, Justine D., PhD- Operations Administrator
Ye, Zhen Staff Associate B.Sc.
Zhan, Qiansheng, PhD.- Assistant Professor- Research

Protocol Versions and Dates:
Original Version1 dated 6/19/2017
Continuing Review and Amendment dated 4/29/2018

Study Summary:

The purpose of the study is to compare the current EmbryoScope Time-Lapse System being used in IVF, which has become standard of care, to the new model EmbryoScope+.

Brief background/rationale for the study:

During in vitro fertilization, human embryos are evaluated to assess their speed and morphological characteristics that allow prediction of their developmental potential and probability to achieve pregnancy and implantation. The advancement of the time-lapse technology enable us to understand the embryo development in vitro. IVF practices is improved by selection of the embryos with the highest implantation potential using time-lapse technology. Automated recording of embryos provides the opportunity to determine the exact timing of embryo cleavages and accurate selection of the viable embryos for transfer. EmbryoScope time-lapse system is the most used for IVF with over 300,000 patient treatments since 2009. The new time-lapse instrument, EmbryoScope+, is the newer model that provides the same result with 3.3 times greater capacity and a more efficient workflow with the automated registration of the EmbryoSlide+ culture dishes. It has been used in Scandinavia in over 500 treatments. We aim to compare the current EmbryoScope Time-Lapse System being used in IVF, which has become standard of care, to the new model EmbryoScope+ to demonstrate that the EmbryoScope+ is as safe and reliable as the EmbryoScope.

Brief study summary including, if applicable:

- Randomization arms: Standard EmbryoScope Time-Lapse system versus EmbryoScope+ on sibling oocytes.
- Length of time on treatment, length of follow-up: 10 months

Brief Summary:

- In-vitro Fertilization (IVF) will be completed according to normal clinical procedures. Participant's oocytes will be randomly assigned to one of two groups: Standard EmbryoScope versus EmbryoScope+.
- The best quality embryos are selected for embryo transfer and the pregnancy outcome is evaluated.
- Study participants will not be compensated.

Key eligibility:

Inclusion:

40 years of age or younger (maternal)

65 years of age or younger (paternal)

Fresh or frozen (including donor) sperm can be used

Fresh or frozen oocytes (including donor), 10 or more oocytes

ICSI only

Frozen embryos from this study can be included in the outcome portion of this study.

Exclusion:

Patients with less then 10 oocytes

Co-culture patients

Study Design:

This is a randomized, controlled, single-center study in otherwise healthy infertile female subjects undergoing in vitro fertilization (IVF). The subjects recruited for this study will be among those patients who have been diagnosed with infertility and are planning to undergo IVF at the center where this study is being performed. The subjects will have undergone the usual informed consent procedure at the center.

Subjects will undergo ovarian stimulation, oocyte retrieval, IVF, and Intracytoplasmic Sperm Injection (ICSI) procedure following the center's usual procedures. At the time of retrieval, participant's oocytes will be randomly assigned to one of two groups: Standard EmbryoScope versus EmbryoScope+. The best quality embryos are selected for embryo transfer and the pregnancy outcome is evaluated.

"Best grade" embryos will be transferred regardless of EmbryoScope use. The standard EmbryoScope as well as the EmbryoScope+ monitor system as assigned during the randomization process will be used to observe the embryo development and document timing of embryo cleavages and morphology dynamics. Subjects will not be provided with the time- lapse images.

Endpoints will be Day 3 and Day 5/6 embryo development, implantation and pregnancy rate. The study is approximately 2 months, the estimated time it takes a physician to perform one IVF-ART treatment cycle. If embryos are frozen, the patient may be in the study until the time they choose to thaw the embryos or up to 1 year if they become pregnant. We aim to compare the current EmbryoScope Time-Lapse System being used in IVF which has become standard of care to the new model EmbryoScope+ to demonstrate that the EmbryoScope+ is as safe and reliable as the EmbryoScope.

Primary Objective:

Comparison of embryo development using standard assessments of morphokinetic parameters, embryo selection algorithms and standard embryo grading.

Secondary Objective:

1- Implantation and clinical pregnancy rates

2- Embryo transfer rate

3- Morphokinetic data

4- Frozen embryo transfer outcomes

Statistical Considerations:

The primary outcome of the study is the comparison of embryo development between oocytes assigned to Standard EmbryoScope versus oocytes assigned to EmbryoScope+. The proposed sample size is 100 subjects and their partner, if applicable. In order to compare embryo development (primary endpoint) and implantation rate (secondary endpoint), as well as resulting pregnancy outcome (secondary endpoint), between the two EmbryoScope devices, a sample size of 100 subjects (200 including partners) will result in approximately 1000 embryos available for randomization.

Each subject's oocytes will be randomly divided between the two study arms, resulting in at least 500 oocytes per study arm. With a sample size of 500 oocytes per study arm, a 95% confidence interval for the proportion of oocytes undergoing adequate embryo development (at day 3 and day 5/6) in each study arm can be constructed to be within ± 4.4% of the observed proportion of oocytes experiencing adequate embryo development. This calculation assumes an adequate embryo development proportion of 50% to conservatively maximize the width of the obtained confidence intervals. The chi-square test or Fisher's exact test will be used, as appropriate, to compare the adequate embryo development proportion between the Standard EmbryoScope and EmbryoScope+ study arms. Similar analyses will be performed for the secondary endpoints of implantation proportion, pregnancy proportion, embryo transfer proportion, and descriptive morphokinetic data proportions. A univariate generalized estimating equations (GEE) model will also be used to compare the adequate embryo development proportion between the two study arms, correcting for clustering by subject (i.e., multiple oocytes per subject). Lack of any observed statistically significant differences between the two study arms will not constitute evidence of equivalence or non-inferiority between the two study arms; rather, estimates of the adequate embryo development proportion in each group will serve as preliminary data for further investigation (i.e., hypothesis-generating). All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals for the adequate embryo development proportion, as well as the secondary outcome proportions of interest, will be calculated to assess the precision of the obtained estimates. All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and Stata Version 14.0 (StataCorp, College Station, TX). Note: The statistical considerations section was written in

conjunction with Dr. Paul Christos, in the Division of Biostatistics and Epidemiology, Department of Healthcare Policy & Research.

Pregnancy Rate will be defined as:

Biochemical pregnancy - positive beta hcg after embryo transfer

Clinical pregnancy - identification of fetal sac in ultra sound post embryo transfer

Ongoing pregnancy - identification of fetal heart in ultra sound post embryo transfer

Delivery rate - live birth

Miscarriage rate - positive fetal sac or fetal heart without live birth.