CLINICAL STUDY PROTOCOL

Multi-national, multi-center, randomized controlled trial to evaluate the clinical utility of non-invasive endometrial receptivity test (ora™) in patients with implantation failure

Name of Study Test	Non-Invasive Endometrial Receptivity Test	
Study Acronym	ORA RCT	
Sponsor	Inti Taiwan, Inc.	
Clinical Protocol	**Doc. No.**	ORA-PTL-2024-01
	Version	1.0
	Date	2024/01/10

Sponsor contact details

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Principal Investigator Signature Page

- I agree to conduct this study in accordance with the Regulations on Good Clinical Practice for Medical Devices and ISO 14155:2020, all applicable legal and regulatory requirements, and in compliance with the provisions of this Protocol.

- I am responsible for ensuring that the investigation is conducted according to this protocol and for protecting the rights, safety, and welfare of research subjects.

- I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator Name/ Title/ Site	Principal Investigator Signature	Date

List of abbreviation

AE	Adverse Event
BMI	Body Mass Index
CIOMS	Council for International Organization of Medical Sciences
CRF	Case Report Form
FBT	Frozen-thawed blastocyst transfer
FET	Frozen Embryo Transfer
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
ICSI	Intracytoplasmic Sperm Injection
IEC	Institutional Ethics Commitee
IRB	Institutional Review Board
IVF	In Vitro Fertilization
LDT	Laboratory Developed Test
MRN	Medical Record Number
NGS	Next Generation Sequencing
SAE	Serious Adverse Event
SET	Single Embryo Transfer
WOI	Window of Implantation

Table of Contents

1. Protocol Synopsis

Protocol Title: Multi-national, multi-center randomized controlled trial to evaluate the clinical utility of non-invasive endometrial receptivity test ora™ in patients with implantation failure
Sponsor: Inti Inc., Taiwan
Intended use: The ora™ test is a laboratory-developed test (LDT) designed to analyze the expression profile of miRNA isolated from plasma. It is intended to identify the optimal window of implantation (WOI) in patients undergoing in vitro fertilization (IVF).
Investigational product/ Model name： Non-invasive endometrial receptivity test / ora™
Objective: To evaluate the clinical utility of non-invasive endometrial receptivity test (ora™) in patients with implantation failure.
Population: Patients who have experienced at least one implantation failure with a euploid or low-level mosaic (< 30%) embryo transfer in the past two years.
Sample Size: The study is expected to enroll up to 800 subjects.
Study design: ■ Study type: Prospective ■ Blinding：No ■ Randomization: Yes ■ Study location: Multi-national and multi-center ■ Study Period: 6-15 months ■ This study aims to enroll subjects who have experienced at least one implantation failure with a euploid or low-level mosaic (< 30%) embryo transfer in the past two years. Subjects should have a euploid embryo, and will be randomly assigned into two groups: control and study group. The study group will undergo frozen embryo transfer based on ora™ timing, while the other group will adhere to the standard timing protocol. The subjects will provide blood samples for the ora™ test during the mock cycle for the study group or during the frozen embryo transfer cycle for the control group. The study will compare pregnancy outcomes to assess whether ora™ timing provides clinical benefits to the patients.
Endpoints (Outcome measure)： Primary endpoint: Clinical pregnancy, defined as presence of one or more intrauterine gestational sacs after 6 weeks of gestation. Secondary endpoint 1. Ongoing pregnancy, defined as presence of fetal heartbeat after 12 weeks of gestation. 2. Live birth, defined as baby survival after 20 weeks of gestation. 3. Abortion and miscarriage rates. 4. Frequency and intensity of adverse events (AEs).

Inclusion/Exclusion Criteria：

Inclusion Criteria:

1. Patients who have at least one implantation failure with a euploid or low-level mosaic (< 30%) embryo transfer in the past two years.
2. Females within 28-45 years old.
3. Those who agree to undergo one mock cycle for ora™ test and execute single frozen embryo transfer in the later cycle.
4. Those who has at least one remaining euploid or low-level mosaic (< 30%) embryo.

Exclusion Criteria:

1. Known uterine factor (such as endometriosis, uterine fibroids) impacting the endometrium.
2. Presence of any clinically relevant systemic disease (such as immune disease) that contraindicates assisted reproductive technology.
3. Body mass index (BMI) exceeds than 30 kg/m^2.

Statistical Methodology:

1. The outcome of clinical pregnancy, ongoing pregnancy and live birth rate per transfer will be compared between the study and control groups by chi-square analysis.
2. The quantitative outcomes such as gestational age and BMI, etc. will be compared between treatment groups by the Mann-Whitney U test.

2. Introduction

2.1. Background and Study Rational

The successful implantation of blastocysts is a crucial milestone in human reproduction, requiring a harmonious alignment between a viable embryo and a receptive endometrium. Next-generation Sequencing (NGS) technology allows us to explore the intricate transcriptomic details of the human endometrium throughout the menstrual cycle.[1] By analyzing the gene expression patterns in the human endometrium, we can identify distinctive gene expression patterns, particularly during the receptive phase.[2]

Endometrial receptivity testing has emerged as an evaluation tool that takes advantages of the unique gene expression signature of the endometrium during the implantation window.[3] One innovative test is the ora™, which uses blood samples to examine over 110 differentially expressed miRNAs.[4] The ora™ test categorizes the receptivity stages into three phases: pre-receptive, receptive, and post-receptive. Based on the results, patients receive recommendations for the timing of frozen embryo transfers in subsequent cycles, whether it be earlier, later, or at the same time.

The primary objective of this clinical trial is to investigate whether vitrified/thawed euploid embryo transfers result in improved pregnancy outcomes when precisely timed using the ora™ test. To achieve this, we propose implementing a randomized clinical trial. The outcomes, including clinical pregnancy rate and live birth rate, will be calculated.

2.2. Test Description

The ora™ test is a Laboratory Developed Test (LDT) performed within a single laboratory. Using NGS, the ora™ test is a miRNA-based endometrial receptivity test designed to identify the optimal window of implantation (WOI) based on miRNAs isolated from plasma processed from peripheral the whole blood samples of the patients.

The results of WOI identification for endometrial receptivity are reported in three statuses: “PRE-RECEPTIVE”, “RECEPTIVE”, and “POST-RECEPTIVE”. The pre-receptivity result, reported as “PRE”, indicates that the endometrium is not yet at peak receptivity at the time of sampling and the WOI is delayed. In the pre-receptivity status, the endometrium is not yet ready for embryo implantation, and it is recommended to delay embryo transfer from the sampling time. The receptive result, which is reported as “WOI”, indicates that the endometrium is at peak receptivity at the time of sampling and is ideal for embryo implantation. Embryo transfer is recommended at the same time of sampling. The post-receptive result, which is reported as “POST”, indicates that the endometrium has past peak receptivity at the time of sampling and the optimal time for embryo implantation has passed. Therefore, embryo transfer is recommended to take place earlier than the sampling time.

Indication For Use

The ora™ test is a Laboratory Developed Test (LDT) designed to analyze the expression profile of miRNAs isolated from plasma. It is intended to identify the optimal window of implantation (WOI) in patients undergoing in vitro fertilization (IVF).

3. Objectives and Endpoints

3.1. Description of the Study

The study is a two-arm, randomized controlled trial that aims to compare clinical pregnancy-related outcomes in different groups. Patients who have experienced at least one failed implantation with a euploid or low-level mosaic (< 30%) embryo transfer in the past two years will be recruited. They will undergo a single frozen embryo transfer, with the timing determined by either ora™ testing or a standardized approach.

3.2. Study Objectives

To evaluate the clinical utility of non-invasive endometrial receptivity test (ora™) in patients with implantation failure.

3.3. Study Endpoints

(a) Primary Endpoint

Clinical pregnancy, defined as presence of one or more intrauterine gestational sacs after 6 weeks estimated gestational age.

(b) Secondary Endpoint

1) Ongoing pregnancy, defined as presence of fetal heartbeat after 12 weeks of gestation.
2) Live birth, defined as baby survival after 20 weeks of gestation.
3) Abortion and miscarriage rates.
4) Frequency and intensity of adverse events (AEs).

4. Study Population

4.1. Number of Subjects

The study is expected to enroll up to 800 subjects.

4.2. Inclusion criteria

(a) Subjects who have at least one implantation failure with a euploid or low-level mosaic (< 30%) embryo transfer in the past two years.

(b) Females within 28-45 years old.

(c) Those who agree to undergo one mock cycle for ora™ test and execute single frozen embryo transfer in the later cycle.

(d) Those who has at least one remaining euploid or low-level mosaic (< 30%)embryo.

4.3. Exclusion Criteria

(a) Known uterine factor (such as endometriosis, uterine fibroids) impacting the endometrium.

(b) Presence of any clinically relevant systemic disease (such as immune disease) that contraindicates assisted reproductive technology.

(c) Body mass index (BMI) exceeds than 30 kg/m^2.

4.4. Withdrawal criteria

(a) During the research process of this research project, all subjects can unconditionally choose to withdraw.

5. Study Procedures

5.1. Overall Design

This study aims to enroll up to 800 subjects who have experienced at least one implantation failure with a euploid or low-level mosaic (< 30%) embryo transfer in the past two years. Subjects should have at least one euploid or low-level mosaic (< 30%) embryo for the study. Subjects will be randomly assigned to either the control or study group. In the control group, subjects will simultaneously provide blood samples for the ora™ test and undergo Hormone Replacement Therapy (HRT) frozen embryo transfer during the standard implantation window (day 5 of progesterone supplementation: P+5/120 hours). In the study group, subjects will provide blood samples for the ora™ test during a mock HRT cycle; in the subsequent cycle, the subject will undergo HRT frozen embryo transfer during the period which the implantation window is confirmed as "Receptive" by ora™'s analysis. The study aims to compare pregnancy outcomes to evaluate whether ora™ timing offers clinical advantages to the patients.

Control Group: Euploid embryo transfer at standard implantation window (day 5 of progesterone supplementation: P+5/120 hours)

Study Group: Mock cycle followed by euploid embryo transfer at implantation window confirmed as "Receptive: by ora ™'s analysis.

5.2. Subject Recruitment

Subjects with at least one implantation failure with a euploid or low-level mosaic (< 30%) embryo transfer in the past two years will be invited based on the inclusion/exclusion criteria during a private fertility consultation with their physician. Subjects will be recruited for the current study only after presenting their own volition.

5.3. Informed Consent Process and Informed Consent Text

Before each subject is selected into this study, the investigator/researcher is responsible for fully and comprehensively introducing the purpose and possible risks of this study to the subject in written form. Subjects must be informed that they have the right to withdraw from the study at any time and that their personal information will be kept confidential.

A written informed consent form (ICF) must be given to each subject prior to enrollment. It is the investigator's responsibility to obtain informed consent from each subject prior to entry into the study and to keep it in the study file.

5.4. Payment for the Participation

Subjects meeting inclusion/exclusion criteria and do not drop out of the study will be compensated for their participation in the study. The details of compensation will be provided to the subjects in the ICF. The expense for ora™ test will be covered by the Inti, Inc. Taiwan, and the expense of ultrasound, medication and bloodwork to assess the endometrial cycle will be covered by the testing sites. Subjects will be billed in the usual manner for screening, diagnostic costs, IVF/ICSI including egg retrieval and anesthesia, embryo vitrification, and FBT through the hospital or reproductive clinics (the testing sites).

Standard IVF and endometrial preparation medications will be prescribed as per standard clinical practice and covered by the subject or her medical insurance as per usual. Subjects who wish to maintain embryo in cryopreservation will have to pay a standard annual storage fee as per routine.

5.5. Data collection and protection

All data obtained in clinical trials are subject to data protection. The paper informed consent and case report form (CRF) will be stored in a locker on the test facility and/or electronically separately. Investigators/researcher shall not disclose the subject's name and other identifiable personal data (excluding year of birth/age, weight, height and medical record number (MRN)).

Any documents submitted to Inti Labs do not contain names, but only subject codes. Likewise, data for statistical evaluation can only be accessed under the subject code. Only the researcher can identify the subject's name and other personal information through the code. If the name of a subject needs to be identified for medical reasons during the research, all subjects involved are obliged to keep it confidential.

5.6. Research Process

(a) Randomization:

After signing the ICF, the investigator will assign a **subject code** to each enrolled subject. This subject code will consist of two parts: the center identification number and the subject identification number. For instance, TW01-001.

1) The center identification number is structured using the first two letters of the country name followed by a two-digit site number. Examples include TW01, TW02, SG01, JP01, etc.

2) Within each age category at each center, subjects will receive a subject identification number assigned based on their order of inclusion in the study. The first subject enrolled will be labeled as 001, followed by 002, and so forth, maintaining chronological order.

Once the subject receives the unique subject code, the subject will be randomized to one of the two study groups through a simple 1: 1 randomization program stratified by center (to avoid bias). The randomization number will be assigned to each subject included in the study, as well as their corresponding group. The randomization program will be set up by the Inti Inc., Taiwan.

For example, the randomization process for a subject attending the initial clinical site in Taiwan:

Subject code	Randomization number	Group
TW01-001	1	Control
TW01-002	2	Study
TW01-003	3	Study
TW01-004	4	Control
TW01-005	5	Control
TW01-006	6	Study

(b) Subjects will undergo the hormone replacement therapy (HRT) in a frozen embryo transfer (FET) cycle. The HRT treatment cycle will be performed following medical criteria and in accordance with the usual practice of the clinic and the doctors. Ideally, the subjects in the control and study groups should follow identical drug prescription program.

(c) Endometrial receptivity test by ora™:

1) Study group subjects will undergo blood sampling for the ora™ test on the fifth day of progesterone administration in a **mock cycle** (120 ± 3 hours after the first progesterone injection); the control group subjects will undergo blood sampling for the ora™ test and frozen embryo transfer at the standard time (120 ± 3 hours after the first progesterone injection) for data collection.

2) The collected blood samples will be processed into plasma by the researchers, and these samples will then be sent to the Inti Service Laboratory in Taiwan for an endometrial receptivity test. The results, indicating the receptivity timing as determined by ora™, will be provided 10 days later. The results include:

    a. Receptive Phase: At the time of blood draw, it is the optimal Window of Implantation (WOI) for embryo implantation. It is recommended to perform embryo implantation at the sampling time point.
    b. Pre-Receptive: At the time of blood draw, it is before the optimal Window of Implantation (WOI). The endometrium is not yet ready for embryo implantation. It is suggested to delay the embryo implantation window by 24 hours.
    c. Post-Receptive: At the time of blood draw, the endometrium has passed the optimal time for embryo implantation. It is recommended to advance the embryo transfer time by 24 hours.

3) Any subject whose blood sample does not provide adequate information to recommend timing for FET will be withdrawn from the study.

(d) Frozen embryo transfer

On the day of embryo transfer, one of the subject's vitrified, euploid blastocysts will be thawed, and the subject will undergo single embryo transfer. **The frozen embryo transfer in the study group should follow the exact same drug prescriptions and dosage without deviation from the mock cycle**.

1) If the subject is assigned to the control group, a single embryo transfer will be performed on the subsequent cycle after randomization. The transfer timing follows the standard HRT protocol at 120 ±3 hours post initiation of progesterone.

2) If the subject is assigned to the study group, a single embryo transfer will be performed on the HRT cycle after the mock cycle. The transfer timing is based on the implantation window indicated by ora™ test results.

(e) Results confirmation

1) Approximately 10 days following implantation, a serum hCG concentration will be detected.

2) Around 6 weeks after estimated gestational age, an ultrasound will be performed to assess the presence of a gestational sac, providing an estimate of clinical pregnancy.

3) Around 12 weeks after estimated gestational age, an ultrasound will be performed to assess the presence of a fetal heartbeat, providing an estimate of ongoing pregnancy.

4) Around 20 weeks after estimated gestational age, live birth will be evaluated.

5) Abortion and miscarriage rates would be calculated.

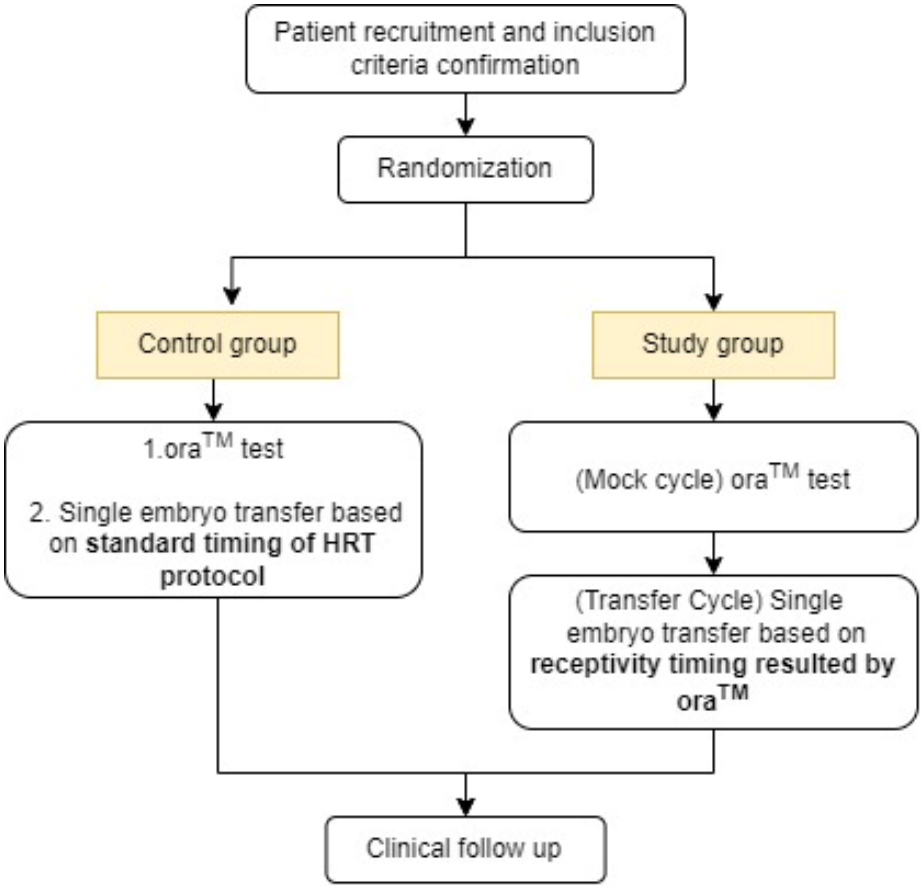

Fig. 1 Flowchart of the clinical trial

5.7. Schedule of Activities

This project is expected to be implemented for 6-15 months for individual sites depending on the allocated subject size.

6. Risk and benefit analysis

The execution process of this study follows the standard procedures of in vitro fertilization (IVF), except for the blood specimen collection for endometrial receptivity testing. Rigorous standard operating procedures have been established for the specimen collection process, specimen storage, and specimen transportation. Only relatively sensitive subjects may experience discomfort during blood specimen collection, but noticeable improvement is observed after a period of rest.

7. Statistical considerations

7.1. Sample size calculation

The sample size calculation for the two-armed endpoint suggests that obtaining data from 650 participants (325 subjects for each group). This sample size is adequate to detect a 10% difference in clinical pregnancy outcomes between groups given an alpha level of $p < 0.05$ and a power of 0.8 and using 50% anticipated LB in the control arm (based on current success rates among euploid embryo transfers conducted with standard timing protocol). Accounting for 10-20% dropout rate, the goal is to enroll 800 subjects in total.

7.2. Data Evaluation and Statistical Considerations

(a) The outcome of clinical pregnancy and live birth rate, etc. per transfer will be compared between the study and control groups by chi-square analysis.

(b) The quantitative outcomes such as gestational age and BMI, etc. will be compared between treatment groups by the Mann-Whitney U test.

7.3. Data Management

(a) Data management organization and procedures

1) Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents must be reviewed by study personnel and data entry staff, which will ensure that they are accurate and complete.

2) CRFs are provided for each subject in printed or electronic format. Source documentation must be available for the following to confirm data collected in the CRF. The sponsor will review CRFs for accuracy and completeness; any discrepancies will be resolved with the investigator or designee, as appropriate.

(b) Electronic data validation, verification, and protection procedures

After upload of the data into the study database they will be verified for accuracy and consistency with the data sources

8. Adverse events (AE), Adverse reactions and medical device deficiency

During and following a subject's participation in the study, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

In the event medical care to a subject is required, the medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, other healthcare providers.

8.1. Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury in subjects, users or other persons, that is considered a change from baseline or pre-study status, whether or not related to the investigational medical device.

Any pre-existing medical condition or symptoms present in a subject will not be considered an Adverse Event in this study, unless it worsens because of this study.

All Adverse Events (AEs) will be reported on an AE Case Report Form and will include the following: Date/time of onset, description of the event, the duration of the event, the severity of the event, assessment of the relation of the event to the study device and procedure, description of action taken (if any) and the event outcome.

8.2. Serious Adverse Events

A Serious Adverse Event (SAE) is defined as an adverse event that is anticipated or unanticipated and which reasonably suggests that one of the manufacturers' devices has or may have caused or contributed to a death or serious injury.

A Serious Adverse Event is an Adverse Event that led to: (a) death, (b) serious deterioration in the health of the subject that either resulted in a (i) life-threatening illness or injury or (ii) permanent impairment of a body structure or a body function, or (iii) in-patient or prolonged hospitalization or (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function or (c) fetal distress, fetal death or a congenital abnormality or birth defect.

These events are typically reportable to health authorities. Serious Adverse Events will be reported to the Sponsor within 24 hours of knowledge of the event.

9. Regulatory, Ethical and Study Oversight Considerations

9.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

(a) Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

(b) Applicable Good Clinical Practice (GCP) Guidelines

(c) Applicable laws and regulations

The protocol, protocol amendments, ICF, and other relevant documents must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

(a) Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.

(b) Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures; and

(c) Providing oversight of the conduct of the study at the site and adherence to requirements of ISO 14155:2020, the IRB/IEC, or all other applicable local regulations.

9.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9.3. Informed Consent Process

(a) The investigator or designee must obtain written informed consent before any clinical study related activity takes place. The investigator or designee will explain the nature of the study to the subject and answer all questions regarding the study.

(b) Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of ISO 14155:2020, local regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

(c) The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

(d) A copy of the ICF(s) must be provided to the subjects.

9.4. Data Protection

(a) Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

(b) The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the study p subject.

(c) The subject must be informed that his/her medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.5. Data Quality Assurance

(a) All subject data relating to the study will be recorded on Case Report Forms (CRFs). The Investigator/researcher is responsible for verifying that data entries are accurate and correct by physically signing the CRF.

(b) The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

(c) The Investigator must permit study-related monitoring (if applicable), audits (if applicable), IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

(d) Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

(e) The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

(f) The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

(g) Study monitors will perform ongoing source data verification to confirm that data entered the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

(h) Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period.

(i) No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

9.6. Source Documents

(a) Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

(b) Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

(c) Source documents may include original documents, data, and records e.g. hospital records, clinical/office charts, laboratory notes, etc.

(d) If study data is recorded directly on the CRFs (i.e., no prior written or electronic record of data), it is source data.

9.7. Study and Site Closure

The Sponsor and/or designee reserves the right to pause enrollment, to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

(a) Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.

(b) Inadequate recruitment of subjects by the investigator

(c) Discontinuation of further study intervention development

9.8. Insurance

This trial/study is not covered by human subject liability insurance.

10. References

1. Achache, H., & Revel, A. (2006). Endometrial receptivity markers, the journey to successful embryo implantation. Human Reproduction Update, 12(6), 731–746.

2. Ruiz-Alonso, M., Blesa, D., & Simón, C. (2012). The genomics of the human endometrium. Biochimica Et Biophysica Acta (BBA) - Molecular Basis of Disease, 1822(12), 1931–1942.

3. Doyle, N., Jahandideh, S., Hill, M. J., Widra, E., Levy, M. J., & Devine, K. (2022). Effect of Timing by Endometrial Receptivity Testing vs Standard Timing of Frozen Embryo Transfer on Live Birth in Patients Undergoing In Vitro Fertilization. JAMA, 328(21), 2117.

4. Chen, M., Hsu, A., Lin, P. C., Chen, Y., Wu, K., Chen, K., Wang, T., Yi, Y., Kung, H., Chang, J., Yang, W., Lu, F., Guu, H., Chen, Y., Chuan, S., Chen, L., Chen, C. H., Yang, P. E., & Huang, J. Y. (2023). Development of a predictive model for optimization of embryo transfer timing using Blood-Based microRNA expression profile. International Journal of Molecular Sciences, 25(1), 76.