APPENDIX

The effectiveness and safety of in vitro maturation of oocytes versus in vitro fertilisation in women with high antral follicle count: study protocol for a randomised controlled trial

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Plan for cost-effectiveness analysis (CEA)

CEA will be performed using decision tree modelling, in which the cost component will be based on a micro-costing approach to estimate the average cost per patient following different pathways of interventions and intervention effectiveness based on the live birth rate. The decision tree model will comprise two interventions (IVF and IVM) and detail the four phases of treatment that participants go through from randomization to final outcome. Cost per participant will be assigned to different categories. Direct costs will include examinations, stimulation drugs, freezing, thawing, complications, drugs and tests during pregnancy, and delivery. Indirect costs will include travelling, lost income, and accommodation. Details of how cost components will be determined and calculated are shown in the table below:

Category	**Unit**	**Cost per unit (€)**	**Valuation method**
Direct costs			
Examination			Average market price*
Visit	Time		
Ultrasound	Procedure		
Screening test	Time		
Stimulation drug	IU		
IVF lab	Time		
Luteal support drugs			Average market price*
Progesterone 400 mg	Tablet		
Estradiol valerate 2 mg	Tablet		
Amoxicillin/clavulanic acid 1 g	Tablet		
Dicycloverine 40 mg	Tablet		
Crocin 200 mg	Tablet		
Diclofenac 25 mg	Tablet		
Embryo freezing	Time		Average market price*
Embryo thawing	Time		Average market price*
Complications			Participants' recall after treatment

Drugs during pregnancy			Average market price*
Iron + vitamins + minerals	Capsule		
Multivitamins with ginseng	Ampoule		
Ascorbic acid	Tablet		
Folic acid	Tablet		
Vitamin/folic acid	Tablet		
Test during pregnancy			Average market price*
First trimester			
Second trimester			
Third trimester			
Delivery			Average market price*
Vaginal	Procedure		
Caesarean section	Procedure		
Indirect costs			
Travel		Stratified by distance, visit, transportation type	Average market price*
Loss of income		Stratified by couple's income and visit	Participants' recall
Accommodation		Stratified by accommodation types (e.g hotel, house for rent) and treatment duration	Average market price*

*Mean unit cost for private hospitals.

The incremental cost-effectiveness ratio (ICER) will be calculated as the incremental cost per patient (IC) and the incremental effectiveness in term of live birth rate (IE), and presented as the cost per patient for IVF to achieve a 1% increase in live birth compared with IVM.

Macros in Microsoft Excel 2016 will be used to perform one-way sensitivity analysis and probabilistic sensitivity analysis. The macro program is written to make a loop of calculation from input data, in which the parameters are set up with their base-case values

and parameters of the distribution, to output data including IC, IE, ICER in each trial, with the value of each parameter ranged as described below.

One-way sensitivity analyses will be performed to examine a change of 10% in the base-case ICER when each parameter individually changed, and probabilistic sensitivity analyses to examine the change of ICER in a thousand trials, in which all parameters contemporaneously changed. The change of each parameter in one-way sensitivity analysis will be examined at 10% of its original value resulted from the studied sample. One-way sensitivity analysis results will be presented in tornado diagrams to show the change in % of ICER. In probabilistic sensitivity analysis, the change of each parameter will be examined as randomly ranging following the type of data distribution, e.g. β distribution for probabilities, and γ distribution for costs, with the relative distribution parameters, e.g. α and β, based on the original values and standard error (SE) from the studied sample. Probabilistic sensitivity analysis results will be presented as scatter plots of IC and IE in each trial.

The cost-effectiveness acceptability curve (CEAC) will also be determined. The CEAC is applied to the probabilistic sensitivity analysis result, basing on willingness to pay (WTP). This technique assesses the probability of IVF being cost-effective compared with IVM, with respect to the WTP. WTP will be assumed to be a range with a cut-off interval. Each WTP cut-off value will be applied to the trials in the probabilistic sensitivity analysis to calculate the Net Marginal Benefit (NMB). A positive NMB indicates that IVF would be more cost-effective than IVM. The probability of IVF being more cost-effective than IVM will be determined by the percentage of the trials with positive NMB.

Telephone questionnaire to collect indirect cost data

1. Has your husband accompanied you during the treatment cycle?
    a. Yes
    b. No

    If No, on what percentage of the visits did he attend appointments with you? ….%
2. What mode of transport do you usually use to attend clinic visits?
    a. Motorbike
    b. Taxi
    c. Bus
    d. Other
3. Where did you live during the treatment cycle?
    a. Hotel
    b. House for rent
    c. Relatives' house
    d. Other
4. What was the income loss per day when visiting your doctor?
    a. Husband:……..
    b. Wife:…….

Telephone questionnaire to collect direct cost data

1. Did you have any complications/treatment within your pregnancy?
    a. Yes
    b. No

If Yes, what were they? ……

2. How much did it cost for that complication/treatment?.....

Patient documents

Documents were provided to patients in Vietnamese. English translations are provided here. All patients were given the main study information sheet and consent form, while those who achieved pregnancy after IVM or ICSI were also given the genetic analysis information sheet and consent form.

Information sheet and consent form – main study

Study title: **The effectiveness and safety of in vitro maturation of oocytes versus in vitro fertilisation in women with high antral follicle count**
Study intervention: IVF, IVM
Sponsor of the study: My Duc Hospital, Ho Chi Minh City, Vietnam
Funder: Ferring Private Limited Singapore
ICF version: V1
ICF date: 31 Dec 2017
Investigator: Vuong Ngoc Lan
Patient code: _____

You are being invited to take part in a clinical research trial. Before you decide whether you want to participate, it is important that you understand why the trial is conducted and what is expected from you, as well as the associated benefits, risks and inconveniences. Take your time reading the information and don't hesitate to ask the trial doctor if you have any questions.

Introduction

In vitro maturation (IVM) is a potential alternative to conventional in vitro fertilization (IVF) to avoid ovarian hyperstimulation syndrome (OHSS). This has is particularly relevant in women with high antral follicle count (AFC), who are at increased risk for OHSS. The trial has been approved by the health authorities in Vietnam and by an ethics committee. A total of 546 women will be included and treated in the trial. The study will

be conducted from 2018 to 2020.

Purpose of this Clinical Research Trial

The main purpose of this clinical research trial is to compare the effectiveness and safety of one IVM cycle and one IVF cycle in women with high AFC-related subfertility. The results of the trial are anticipated to provide evidence for the use of IVM in women with high AFC having indications for assisted reproductive techniques (ART) in clinical practice.

Trial Procedures

Before agreeing to participate in this trial it is important that you fully understand, and are willing to comply with, all procedures including taking the medication and attending scheduled visits. The actual number of visits to the clinic will depend on your method of treatment and whether you succeed in achieving a pregnancy. The average number of visits is 5 in the IVM group and estimated to be around 10-12 in the IVF group. If you take part in the trial, your participation will last for approximately 13 months. From the time you have signed the papers for participation in this trial you will be asked to provide information regarding any treatment you have taken.

Screening

Before entering the trial, you will be asked about any medical condition you have or have had, and to provide information about aspects related to your infertility and obstetric history, and previous infertility treatments. Blood samples will be taken to assess hormone levels and a basic panel of laboratory tests to assess your general health.

Randomisation and Allocation to Treatment Group

If you are found to be eligible for the trial and meet all requirements for participation (these requirements will be fully explained to you by your trial doctor), you will be randomly assigned to one of the two treatment groups: IVF or IVM. You have an equal chance of being randomised to each of the groups, meaning the likelihood of being allocated to each treatment is 50%.

Treatment procedure

- If you are assigned to IVM and have normal cycle length (≤35 days), you will receive two injected doses of menotropins (Menopur®) 150 IU/ day; starting on day two or three of your menstrual cycle. If you do not have a normal cycle length (>35 days; 4–9 menstrual cycles in a year or amenorrhea), you will take oral contraceptive pills for 2 weeks, then receive two doses of Menopur® 150 IU/day for 2 days starting 5 days after stopping the pills. You will have the ultrasound on the second day of injection and egg retrieval is scheduled at 42 hours after the last Menopur® injection. After egg retrieval, all oocytes will be matured by placing in pre-maturation medium (CAPA pre-maturation in Medicult IVM medium; Origio, Denmark) for 24 hours, then transferred to maturation culture (Medicult IVM system with phenol red; Origio, Denmark) for 30 hours.
- If you are assigned to IVF, you will receive daily subcutaneous injections of Menopur® 150–225 IU/day, depending on age and body mass index. On stimulation day 5 you will start taking an additional hormone (gonadotropin-releasing hormone [GnRH] antagonist) to prevent you from ovulating too early. This hormone is also subcutaneously administered throughout the rest of the stimulation period. During stimulation, you will have frequent visits to the clinic to monitor your response to treatment. This includes transvaginal ultrasound examinations allowing the doctor to count and measure the size of the developing follicles in the ovaries, and the thickness of your womb lining. In addition, blood samples will be taken to evaluate estradiol and progesterone levels. At the end of stimulation, when the follicles are at the appropriate size, you will receive a final injection (a GnRH agonist) for final maturation of the eggs. Approximately 36 hours after administration of the GnRH agonist, you will undergo egg retrieval. You will not have embryo transfer in the ongoing cycle, instead, your embryos will be frozen, and can be used in subsequent cycles.

Embryology lab procedures

Mature eggs will be fertilized using ICSI (intracytoplasmic sperm injection), where a single sperm from your husband will be directly injected into a mature egg until all eggs have been fertilised. The fertilised eggs will be cultured in the laboratory for 3 days.

Pregnancy monitoring

You will be monitored if you are pregnant. This includes a blood sample approximately 2 weeks after embryo transfer, a transvaginal ultrasound examination at 5-6 weeks after transfer, and a transvaginal or abdominal ultrasound examination at 10-11 weeks after embryo transfer and until the time of delivery.

Blood sampling during the trial

Blood sampling will be done at most visits during the trial for various purposes. In total, approximately 25 mL blood will be drawn. Blood will be analysed to determine hormone levels and a basic panel of laboratory tests will be performed to assess your general health.

Pregnancy follow-up

If you become pregnant during the trial (i.e. there is a viable fetus at the ultrasound examination done around 10-11 weeks after embryo transfer), the trial doctor will collect data on the course of your pregnancy, such as complications during pregnancy, potential pregnancy loss and the health of the fetus, and data related to the delivery (e.g. whether it occurrs by vaginal delivery or Caesarean section). Finally, the trial doctor will collect data on the newborn, including date of birth, gender, weight, height and health at delivery. In case of birth defects or hospitalisation (e.g. if the child is born too early), these data will also be collected. The trial doctor may also follow up for more than 4 weeks after delivery if it is required to collect safety data from the newborn. These follow-up activities do not require any interventions, just collection of data as part of the safety evaluations performed in this clinical research trial.

Frozen cycles

All embryos will be frozen on day 3. Frozen transfer of a maximum of 2 embryos will be

performed in a subsequent cycle. The lining within the womb (endometrium) will be prepared using oral estradiol valerate (Valiera®; Laboratories Recalcine) 8 mg/day starting from the second or third day of the menstrual cycle. Endometrial thickness will be monitored from day six onwards, and vaginal progesterone (Cyclogest®; Actavis) 800 mg/day will be started when endometrial thickness reaches 8 mm or more. A maximum of 2 embryos will be thawed on the day of embryo transfer, three days after the start of progesterone. Two hours after thawing, surviving embryos will be transferred into your womb under the guidance of ultrasound. When you have more than two embryos frozen, the procedure will be repeated in subsequent cycles if the first transfer is unsuccessful.

Cost-effectiveness analysis

We will collect information relating to costs of IVM or IVF to allow a cost-effectiveness analysis to be performed. At the time of the pregnancy test, you will be asked about costs relating to your treatment, including direct non-medical costs (e.g. cost of transport to the clinic). If you have any complications related to treatment, data on the costs of these complications treatment will be collected at the time you are discharged from hospital.

Voluntary Participation

Your participation in the trial is voluntary and you can withdraw from the trial at any time without giving any reason and without penalty or loss of benefits. Such a decision will not influence your current or future treatment. If you choose to withdraw from the trial, you must notify the staff at the clinic. Information collected up to withdrawal will remain in the database, but no further information will be collected. You should be aware that samples and data obtained before your withdrawal may be analysed. You can request destruction of collected samples that would otherwise remain in storage.

Potential Risks / Discomfort

The risks associated with infertility treatment, including the risk of controlled ovarian stimulation and clinical and laboratory procedures, will be explained to you as part of the counselling prior to starting treatment.

- Controlled ovarian stimulation will be performed with Menopur®. The doses in the

present trial are based on your age, ovarian reserve tests and your history of ovarian response, and they are of within the dose range according to our hospital standard operating procedure. The most common adverse events in relation to use of Menopur® are headache and injection site reactions (all reported to occur in more than 10% of patients), abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting and diarrhoea, and mild or moderate OHSS including associated symptoms (all reported to occur in 1-10% of patients). Several, but rare, complications may appear during stimulation with hormone preparations, such as OHSS. This is usually associated with symptoms of lower abdominal pain plus nausea, vomiting and weight gain that, in rare cases, can become more serious with enlarged ovaries, accumulation of fluid in the abdomen and chest, and potential risk of blood clots that may block a blood vessel. You will be closely monitored throughout the trial and precautionary measures have been taken to reduce the risk of developing OHSS. In this trial, this risk is minimised because human chorionic gonadotropin (hCG) will not be injected after using Menopur® to trigger the maturation of the eggs. Instead, triptorelin, a GnRH agonist will be used to trigger the endogenous luteinizing hormone (LH) surge. In addition, fresh embryo transfer is not performed because all embryos are frozen for later transfer. All these interventions will minimise the risk of OHSS associated with use of Menopur®.

- As part of the treatment, you will receive concomitant medications, i.e. GnRH antagonist, hCG (or a GnRH agonist) and progesterone. The medications are commercially available products and are considered generally well tolerated. The most frequent adverse events with these medications are similar to those for follicle-stimulating hormone (FSH) preparations, including headache, injection site reactions, pelvic pain, abdominal pain, abdominal distension and allergic reactions, plus vaginal symptoms such as discharge and dryness and minor contractions of the womb known to occur with vaginal progesterone (at a frequency of 1-2%). You will receive a leaflet with detailed information about each of the medications.
- Allergic reactions to the hormone preparations may occur, but are very rarely of a serious nature.

- With respect to the procedures, you may experience discomfort during retrieval of the eggs and, very rarely, infections and bleeding. You may also experience mild discomfort and, very rarely, infections and spotting / bleeding when a thin catheter is passed into the womb to transfer the embryos. The transvaginal ultrasound examinations may be associated with mild discomfort and a very rare risk of infection. Finally, vein punctures to obtain blood samples may be associated with mild discomfort, bruising and a very rare risk of infection.
- It is possible that you do not have any eggs collected (occurs in about 0.1-0.3% of cases for both IVM and IVF at our center) or any embryos available for transfer (occurs in about 1% of cases for both IVM and IVF at our center). If either of these cases arise, your trial doctor will be consulted for an alternative in the next cycle.
- A serious concern associated with ovarian stimulation cycles is the frequency of multiple pregnancies / births and associated health problems for newborns. This risk is minimized in the trial because a maximum of two embryos are transferred at any one time.
- The incidence of miscarriage is higher in women undergoing controlled ovarian stimulation than in those conceiving spontaneously. In addition, there is a risk for pregnancy outside the womb (ectopic pregnancy) in women undergoing controlled ovarian stimulation but this primarily occurs in women with a history of tubal blockage.
- It is possible that you will not achieve a pregnancy during the trial.

Potential Benefits

Participation in this trial may benefit you personally by assisting you in achieving a pregnancy. Furthermore, the information obtained from assessments performed during the trial will help your doctors in establishing the optimal approach for you as an individual, which could be used in later treatment cycles, if required.

Alternative Options

Alternative treatment options than those used in this trial are available. Your trial doctor

will discuss with you these alternative therapies and protocols for infertility treatment.

Confidentiality and Data Protection

All information given by you will be treated as confidential. Your identity and your name will not be passed on to others, it will only be known by the personnel who treat you at the clinic. An identification system consisting of your anonymous trial participation number will be used on any recorded information and on collected samples. The trial doctor at the clinic is responsible for keeping the identification code list linking your name and your trial participation numbers. You have the right to see any personal data about you and ask to have any data errors corrected. Personal information given by you will be seen and reproduced by authorised persons from either the relevant health authority or ethics committee when reviewing the trial. This information will be treated as strictly confidential. The results of this trial may be presented at meetings or in publications, but your identity will not be disclosed in those presentations. By signing the informed consent form, you accept that ethics committee personnel and personnel from regulatory authorities (foreign or domestic) may get direct access to your original medical records for the purpose of verifying trial data. The information will be treated strictly confidential and appropriately coded. My Duc Hospital is responsible for keeping all collected data and the results of the trial. A description of this clinical trial will be publicly available on <http://www.clinicaltrials.gov/> a US clinical trials registration website. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. Trial registration may also occur in other registries in accordance with local regulatory requirements. A summary of the trial results will be made publicly available in accordance with applicable regulatory requirements.

Retention of Samples

The blood or urine samples collected prior to treatment, during treatment, 2 weeks after embryo transfer and during pregnancy (if any) will be analysed at the hospital laboratory immediately after collection. When the result is available, all blood and urine samples will be destroyed, apart from the blood sample collected prior to treatment. This will be stored

for any additional analysis, if needed. The blood sample is labelled with a code, and you remain anonymous. If analysis of additional parameters is planned you will be asked in advance if you accept the proposed analyses. You have the right to refuse such new analyses. Otherwise, destruction of the sample will take place within 1 year after reporting of the trial or when methods/results have been adequately validated.

Compensation

There will be no payment for any procedures for this trial. If you do not have any eggs collected or any embryos available for transfer, the hospital fee for egg retrieval or embryo culture will be refunded.

Information

If you want more information and/or in case of injury, you should contact the hospital staff. Please feel free to contact one of the following:

Investigator Name: Vuong Ngoc Lan at +84 90 3008889

Sub-Investigator Name:

- Ho Manh Tuong at +84 90 3633377
- Dang Quang Vinh at +84 90 8225481
- Ho Ngoc Anh Vu at +84 93 5843336
- Phung Huy Tuan at +84 90 3665992
- Giang Huynh Nhu at +84 121 3231721

If you have any complaints or questions about your rights as a research volunteer, you may contact the Research Ethics Committee:

- Name: My Duc Hospital
- Address: 4 Nui Thanh, Ward 13, District Tan Binh, Ho Chi Minh City
- Phone: +84 028 38121705

Your participation in the trial may be terminated at the discretion of the trial doctor. In that case, the reasons will be explained to you. You will be informed in a timely manner if new information becomes available that may affect your willingness to participate in this trial.

Sponsor: My Duc Hospital
4 Nui Thanh Street, District Tan Binh, Ho Chi Minh City, Vietnam
Dang Quang Vinh – Email: bsvinh.dq@myduchospital.vn

Funder: Ferring Private Limited Singapore
Address: 168 Robinson Road, #13-01 Capital Tower, Singapore 068912
Contact person: Au Thi Kim Loan – Email: loan.au@ferring.com

The sponsor and funder have no roles in study design; collection, management, analysis, and interpretation of data.

Thank you for reading this and considering whether you can take part in this study.

Consent Form

Study title: **The effectiveness and safety of in vitro maturation of oocytes versus in vitro fertilisation in women with high antral follicle count**

Study intervention: IVF, IVM

Sponsor of the study: My Duc Hospital, Ho Chi Minh City, Vietnam

Funder: Ferring Private Limited Singapore

ICF version: V1

ICF date: 31 Dec 2017

Investigator: Vuong Ngoc Lan

Patient code: _____

I confirm the following:

- I have read and understand the information sheet for the above study and have had enough time to think about taking part.
- I am satisfied with the answers given to all of my questions.
- I voluntarily agree to be part of this research study, to follow the study procedures and to provide the information the study doctor, nurses or other staff members ask from me.
- I understand that I am free to withdraw from this study at any time without giving a reason and without my medical care or rights being affected.
- I have received an original copy of this information sheet and consent form to keep for myself.
- I understood that I have rights to access the data provided in information sheet by responsible people.
- I agree to my samples being taken and used as described in this information sheet.
- I give permission for my personal information collected as part of this clinical study to be:
    - identified only with my subject ID number;
    - reviewed, processed and transferred by and to the Sponsor and its authorized representatives for the purposes described in the study protocol;

- reviewed or audited by the ethic committees;
- published and sent to regulatory authorities or health insurers in my country
- transferred if required to any country, where data protection laws may be less strict.
- I understand I may also be contacted at a later date(s) for my permission in connection with this or any related sub study.

By signing this document I give agree to take part in this study, as set out in the information sheet and consent form.

Name:_____

Signature:_____Date (DD/MM/YYYY):_____

Investigator/Authorised designee:

- I have fully and carefully explained the study to the person named above and confirm that, to the best of my knowledge, they clearly understand the nature, risks and benefits of taking part in this study.
- I confirm that I gave them an opportunity to ask questions about the study, and that I answered all the questions they asked correctly and to the best of my ability.
- I confirm that they have not been forced into giving consent, and that they have given their consent freely and voluntarily.
- I confirm they have been given an original copy of this information sheet and consent form.

Name:_____

Signature:_____Date (DD/MM/YYYY):_____

Information sheet and consent form – genetic analysis

Study title: **Investigation of genetics and epigenetics of newborn born from IVM or ICSI** ***(Part of the trial on "The effectiveness and safety of in vitro maturation of oocytes versus in vitro fertilisation in women with high antral follicle count")***
Study intervention: Genetics and Epigenetics of newborn from IVM or ICSI
Sponsor of the study: My Duc Hospital, Ho Chi Minh City, Vietnam
ICF version: V1
ICF date: 26 March 2018
Investigator: Vuong Ngoc Lan
Patient code: _____

You are being invited to take part in a clinical research trial. Before you decide whether you want to participate, it is important that you understand why the trial is conducted and what is expected from you, as well as the associated benefits, risks and inconveniences. Take your time reading the information and don't hesitate to ask the trial doctor if you have any questions.

Introduction

Recent studies have reported that there is no increase in health risks for babies born from assisted reproductive techniques (ART). The risk of congenital anomalies in babies born from ART is similar to that in babies born after spontaneous conception. However, there are limited data on genetics of babies born from ART.

Epigenetics is the study of heritable phenotype changes that do not involve alterations in the DNA sequence. Epigenetic changes may occur during the formation of gametes and the development of embryos. ART involves the manipulation of gametes and embryos outside a woman's body. Therefore, it is necessary to study the epigenetic changes of babies born as a result of using these techniques.

Purpose of this Clinical Research Trial

The main purpose of this clinical research trial is to investigate the genetics and epigenetics of newborns born after IVM or ICSI.

Trial Procedures

Before agreeing to participate in this trial It is important that you fully understand, and are willing to comply with, all procedures. The genetics and epigenetics of babies born from IVM and ICSI will be investigated as a supplementary analysis and reported separately from the main study comparing IVM and IVF.

- Prior to initiation of IVM or ICSI, 2.5mL of maternal whole blood will be collected and stored at –80ºC. This will serve as a control for the genomic variants between mother and foetus.
- At the time of delivery, materials including cord blood, neonatal buccal smear and placental tissue will be collected to study DNA methylation patterns and gene expression. A total of 11 mL of cord blood will be collected and stored at –80ºC.
- A buccal smear will be collected by placing a sponge into the neonatal cheek pouch immediately after delivery, then the sponge will be gently moved along the gums and inner cheeks for 30 seconds to soak up as much saliva as possible. Saliva samples will be stored at room temperature.
- The placenta will be weighed before collection of placental tissues. Three pieces on the maternal side and three pieces on the foetal side will be cut from areas without large blood vessels or fibrous tissue. All tissue samples will be stored in fixative solution in a container within 30 minutes after the start of tissue collection. All tissue containers will be stored at –80ºC.
- All samples will be sent to UZ Brussels, FOBI laboratory for analysis. (Professor Johan Smitz, UZ Brussels, FOBI Laboratory, route 718, Laarbeeklaan 101, B-1090, Brussels, Belgium. Tel: +32 24775050.
- Next generation sequencing (NGS) will be used to analyse genetic and epigenetic variants.

Voluntary Participation

Your participation in the trial is voluntary and you can withdraw from the trial at any time without giving any reason and without penalty or loss of benefits. Such a decision will not influence your current or future treatment. If you choose to withdraw from the trial, you must notify the staff at the clinic. Information collected up to withdrawal will remain in the database, but no further information will be collected. You should be aware that samples and data obtained before your withdrawal may be analysed. You can request destruction of collected samples that would otherwise remain in storage.

Potential Risks

There are no potential risks for mother and newborn.

Potential Benefits

Collection, storage, transportation and analysis of genetic materials will be provided free of charge.

Confidentiality and Data Protection

All information given by you will be treated as confidential. Your identity and your name will not be passed on to others, it will only be known by the personnel who treat you at the clinic. An identification system consisting of your anonymous trial participation number will be used on any recorded information and on collected samples. The trial doctor at the clinic is responsible for keeping the identification code list linking your name and your trial participation numbers. You have the right to see any personal data about you and ask to have any data errors corrected. Personal information given by you will be seen and reproduced by authorised persons from either the relevant health authority or ethics committee when reviewing the trial. This information will be treated as strictly confidential. The results of this trial may be presented at meetings or in publications, but your identity will not be disclosed in those presentations. By signing the informed consent form, you accept that ethics committee personnel and personnel from regulatory authorities (foreign or domestic) may get direct access to your original medical records for the purpose of verifying trial data. The information will be treated strictly confidential and

appropriately coded. My Duc Hospital is responsible for keeping all collected data and the results of the trial. A description of this clinical trial will be publicly available on <http://www.clinicaltrials.gov/> a US clinical trials registration website. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. Trial registration may also occur in other registries in accordance with local regulatory requirements. A summary of the trial results will be made publicly available in accordance with applicable regulatory requirements. The results of genetic and epigenetic analyses will not be provided to you unless there is a known inherited disease reported.

Retention of Samples

The samples will be labelled with a code, and you remain anonymous. Destruction of samples will take place within 2 years after reporting of the trial or when methods/results have been adequately validated.

Compensation

There will be no payment for participating in this investigation. Collection, storage, transportation and analysis of genetic materials will be provided free of charge.

Information

If you want more information and/or in case of injury, you should contact the hospital staff. Please feel free to contact one of the followings:

Investigator Name: Vuong Ngoc Lan at +84 90 3008889

Sub-Investigator Name:

- Ho Manh Tuong at +84 90 3633377
- Dang Quang Vinh at +84 90 8225481
- Ho Ngoc Anh Vu at +84 93 5843336
- Phung Huy Tuan at +84 90 3665992
- Giang Huynh Nhu at +84 121 3231721

If you have any complaints or questions about your rights as a research volunteer, you may contact Research Ethics Committee:

- Name: My Duc Hospital
- Address: 4 Nui Thanh, Ward 13, District Tan Binh, Ho Chi Minh City
- Phone: +84 028 38121705

Your participation in the trial may be terminated at the discretion of the trial doctor. In that case, the reasons will be explained to you. You will be informed in a timely manner if new information becomes available that may affect your willingness to participate in this trial.

Sponsor: My Duc Hospital
4 Nui Thanh Street, District Tan Binh, Ho Chi Minh City, Vietnam
Dang Quang Vinh – Email: bsvinh.dq@myduchospital.vn

The sponsor has no roles in study design; collection, management, analysis, and interpretation of data.

Thank you for reading this and considering whether you can take part in this study.

Consent Form

Study title: **Investigation of genetics and epigenetics of newborn born from IVM or ICSI** ***(Part of the trial on "The effectiveness and safety of in vitro maturation of oocytes versus in vitro fertilisation in women with high antral follicle count")***

Study intervention: Genetics and Epigenetics of newborns from IVM or ICSI

Sponsor of the study: My Duc Hospital, Ho Chi Minh City, Vietnam

ICF version: V1

ICF date: 26 March 2018

Investigator: Vuong Ngoc Lan

Patient code: _____

I confirm the following:

- I have read and understand the information sheet for the above study, and have had enough time to think about taking part.
- I am satisfied with the answers given to all of my questions.
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- I understand that I am free to withdraw from this study at any time without giving a reason and without my medical care or rights being affected.
- I have received an original copy of this information sheet and consent form to keep for myself.
- I understood that I have rights to access the data provided in information sheet by responsible people.
- I agree to my samples being taken and used as described in this information sheet.
- I give permission for my personal information collected as part of this clinical study to be:
    - identified only with my subject ID number;
    - reviewed, processed and transferred by and to the Sponsor and its authorized representatives for the purposes described in the study protocol;
    - reviewed or audited by the ethic committees;
    - published and sent to regulatory authorities or health insurers in my country
    - transferred if required to any country, where data protection laws may be less strict.
    - I understand I may also be contacted at a later date(s) for my permission in connection with this or any related sub study.

By signing this document I give agree to take part in this study, as set out in the information sheet and consent form.

Name:_____

Signature:_____Date (DD/MM/YYYY):_____

Investigator/ Authorided designee:

- I have fully and carefully explained the study to the person named above and confirm that, to the best of my knowledge, they clearly understand the nature, risks and benefits of taking part in this study.
- I confirm that I gave them an opportunity to ask questions about the study, and that I answered all the questions they asked correctly and to the best of my ability.
- I confirm that they have not been forced into giving consent, and that they have given their consent freely and voluntarily.
- I confirm they have been given an original copy of this information sheet and consent form.

Name:_____

Signature:_____Date (DD/MM/YYYY):_____

Data Safety Monitoring Board Charter

Author: Dr Lan N Vuong

Version: Draft 2

Date: 20 October 2017

Introduction

This Charter is for the Data Monitoring Committee (DMC) for the IVM vs IVF in high AFC women trial. The objective of this trial is to compare the effectiveness and safety of one IVM cycle and one IVF cycle in women with high AFC related subfertility.
The purpose of this document is to describe the roles and responsibilities of the DMC, including the timing and format of meetings, methods of providing information to and from the DMC, statistical monitoring guidelines and relationships with other committees.

Roles and Responsibilities

The aims of the DMC are: to safeguard the interests of the trial's participants, potential participants, investigators and sponsor; to assess the safety and efficacy of the trial's intervention; to monitor the trial's overall conduct; and to protect the validity and credibility of the trial. The DMC will review the progress and accruing data of the trial, and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).
The role of the DMC is to undertake interim reviews of the trial's progress by:

- monitoring recruitment figures and losses to follow-up
- monitoring compliance with the protocol by participants and investigators by reviewing the monitors reports
- monitoring evidence for treatment differences in key safety outcomes
- recommending any major protocol modifications
- advising on any major protocol modifications suggested by investigators
- assessing the impact and relevance of any external evidence provided
- considering the ethical implications of any DMC recommendations
- monitoring TSC compliance with previous DMC recommendations

Early Input

All potential DMC members will be offered access to the draft trial protocol and DMC charter before agreeing to join the committee. If a potential DMC member has major reservations about the trial, they should report these to the TSC Chair and may decide not to accept the invitation to join the DMC. All DMC members should be independent and provide constructive criticism of the trial, but should also be supportive of the aims and methods of the trial.

DMC members should advise the TSC Chair in writing of their agreement to join the committee for the duration of the trial. If a member must leave the DMC, the TSC will appoint a suitable replacement.

A preliminary skype or teleconference meeting will be held involving DMC members, TSC members, around the time the trial commences. The meeting will be used for introductions, to review the trial protocol, and to discuss drafts of the DMC charter and the open and closed reports, to be presented in the open and closed sessions of DMC meetings.

All DMC members must approve the final DMC charter and the content of the open and closed reports prior to the first DMC meeting. Subsequent changes to the DMC charter will be documented as an amendment that needs to be approved by the DMC and TSC. Changes to the open and closed reports will be made during the monitoring period as required, following requests from the DMC. Any DMC requests for changes to the DMC charter and/or open and closed reports are to be made in writing to the TSC Chair by the DMC Chair.

Composition

The DMC will be an independent multidisciplinary group consisting of 3 individuals and will include IVF specialists and a biostatistician, one of whom will be elected to be the DMC Chair. All DMC members must have clinical trials experience and at least one DMC member must have prior DMC experience. DMC members should be independent of the trial and should not serve on DMCs of similar, concurrently active trials, as this could compromise the independence of the trial and possibly the confidentiality of the results of the individual trials. All DMC members must be approved by the TSC.

The DMC Chair should be experienced in chairing meetings. The DMC Chair is expected to facilitate and summarise DMC discussions. They may also be required to communicate with individuals outside the DMC and TSC as appropriate, such as funding bodies or DMCs of related trials.

The DMC IVF specialists are expected to provide clinical expertise.

The DMC Biostatistician is expected to provide independent statistical expertise and to help guide DMC members through the open and closed reports. The DMC Biostatistician is not expected to prepare the DMC reports.

The DMC will be restricted to individuals free of apparent significant conflicts of interest. Any conflicts of interest of DMC members, both real and potential, must be declared in the conflicts of interest form to be returned to the TSC Chair prior to the initial DMC meeting, and disclosed to all DMC members at the initial DMC meeting. Any changes in conflicts of interest during the trial monitoring period must be reported promptly to the TSC Chair and disclosed to all DMC members at the next meeting, and may in some cases require resignation from the DMC.

The members of the DMC for the IVM vs IVF in high AFC women trial are:

DMC Role	**Name**
IVF specialist	JLH Evers
IVF specialist	S Bhattycharea
Biostatistician	E Schuit

Relationships

The DMC are advisory to the TSC. The DMC Chair will notify the TSC Chair in writing of any DMC recommendations, or the absence of any recommendations, following each DMC meeting. The TSC will promptly review the DMC recommendations and decide on the appropriate course of action. The TSC Chair will notify the DMC Chair in writing of the TSC decisions.

The TSC Chair and Trial Coordinator will attend the open sessions of DMC meetings to help guide DMC members through the open report and answer any questions from DMC members about the specifics of the trial. The TSC Chair is responsible for identifying and providing to DMC members any external evidence relevant to the trial for consideration,

and for notifying the DMC of any changes to the trial protocol or conduct or the addition of any side studies. This information will be presented to DMC members during the open sessions of DMC meetings.

The Principal Investigator will be responsible for the production of the open report and will attend the open sessions of DMC meetings. Other TSC members are able but not expected to attend the open sessions of DMC meetings. All TSC members will have input into the format of the open and closed reports.

DMC members will not receive payment for their involvement but will have reasonable travel costs covered for face to face DMC meetings.

The names of the individuals fulfilling each of the roles described above are given below:

Role	**Name(s)**
TSC Chair	Ben W Mol
Other TSC Members	Lan N Vuong, Vinh Q Dang, Tuong M Ho, Vu NA Ho, Tuan H Phung, Nhu H Giang, Anh H Le, Rui Wang, Robert J Norman, Johan Smitz, Robert Gilchrist
Trial Statistician	Toan D Pham

Organisation of DMC Meetings

The first DMC meeting will not be held until approximately 6 months after the first participant is recruited. This meeting will provide a test run for the production and usefulness of the open and closed reports, as well as the format of DMC meetings. Subsequent DMC meetings will be held annually, with additional meetings or teleconferences to be scheduled according to the needs of the DMC or the TSC.

DMC meetings will be conducted face to face or by teleconference or by skype. Other DMC meetings may also be conducted as above, depending on the location and preferences of DMC members. Meetings will consist of an open session followed by a closed session. The purpose of holding meetings in this format is to preserve the confidentiality of the unblinded data while providing an opportunity for interaction between DMC members and others who can provide valuable insights into trial related issues.

Open sessions will be attended by DMC members, the Trial Coordinators, the TSC Chair and possibly other members of the TSC. These sessions will be used for discussing the open report, for the TSC Chair to present external evidence relevant to the trial or to raise specific trial issues with the DMC, and for the DMC to ask the TSC Chair and Trial Coordinator questions about the trial.
Closed sessions will be attended by DMC members only. These sessions will be used for discussing the closed report and forming recommendations about the trial.

Trial Documentation and Confidentiality

DMC members will receive copies of the agenda at least one week prior to the meeting. The agenda will be sent by the Trial Coordinators. The DMC will not necessarily be blinded to the identity of the treatment arms. The closed report will be labeled with treatment A and B, or similar, with different labels for each meeting. DMC members may be advised at their request which group is A and B.
Deliberations of the DMC, should only be available to those present in the closed DMC sessions. DMC members must not share confidential information with people outside the DMC, including members of the TSC.
DMC members should keep the closed reports out of view during the open sessions, and store both the open and closed reports securely after each meeting so that they may check them against subsequent reports. After the trial results are published, DMC members should destroy all interim reports.
DMC members will be required to sign a confidential disclosure agreement.

Decision Making

DMC recommendations will be based primarily on safety considerations. The possible recommendations of the DMC are numerous and could include:

- No action needed, trial to continue as planned
- Early stopping due to safety concerns, slow recruitment or new external evidence
- Advising on or proposing protocol changes

The DMC Chair is expected to summarise discussions and encourage consensus. In each area of discussion, the DMC Chair should give their opinion last.

Every effort should be made for the DMC to reach a consensus. If the DMC cannot achieve a consensus, a vote should be taken. Details of the vote should not be included in the report to the TSC, as it may inappropriately convey information about the state of the trial data.

All DMC members will be required to attend all DMC meetings, and meetings will be scheduled with this requirement in mind. If, at short notice, any DMC member cannot attend at all then the DMC meeting will be rescheduled.

Reporting

The DMC Chair will report in writing to the TSC Chair on any actions recommended (including no action), within two weeks after each DMC meeting. The TSC Chair is responsible for reporting back to the TSC on any DMC recommendations. Where an action is being recommended, the DMC Chair will circulate the letter to DMC members for comment before sending it to the TSC Chair. The letter to the TSC Chair should not usually reveal any confidential information. An example letter from a DMC Chair to a TSC Chair recommending no action is presented below.

Minutes should be taken at both the open and closed sessions of the DMC meeting. The minutes need not be detailed. A summary of the main points discussed with a list of clearly marked action points should be sufficient. Separate minutes are required for the open and closed sessions. The minute taker for the open sessions will be the Trial Coordinator. The minutes will be circulated to all those who attended, as well as any other interested parties (e.g. members of the TSC not in attendance).

The minute taker for the closed sessions may be rotated amongst DMC members, excluding the DMC Chair, and should be agreed upon at the start of each meeting. If the DMC wish to bring in an external person to take minutes (for example, a personal assistant), approval must first be obtained from the TSC through the TSC Chair. All members of the DMC should see and have the opportunity to comment on the closed session minutes. The DMC Chair is responsible for signing off on all closed session minutes. Both the DMC Chair and the Independent Statistician are responsible for retaining a copy of the closed session minutes.

The TSC has ultimate responsibility for the trial and assumes primacy. However, the TSC Chair will report to the DMC Chair in writing how the TSC has acted upon any recommendations made by the DMC.
If the DMC has serious problems or concerns with the TSC decision, a meeting of these groups will be held. The information to be shown will depend upon the action proposed and the DMC concerns. The meeting will be chaired by an external expert who is not directly involved with the trial. Depending on the reason for the disagreement, confidential data may have to be revealed to all those attending such a meeting.

End of Trial Procedures

Once the trial is complete and the blinding is broken, the DMC Chair will provide copies of the closed reports and closed session minutes of all DMC meetings to the TSC Chair. The TSC are responsible for ensuring the trial results are published in a correct and timely manner. DMC members will be named (unless they specifically ask not to be) in the acknowledgements section of the primary paper but will not be offered authorship. DMC members should not discuss confidential issues arising from their involvement in the trial until 12 months after the primary trial results have been published, unless permission is granted to do otherwise by the TSC. DMC members should not trade in stock of companies affected by the trial until the results are public knowledge.

Conflict of Interest Form

The avoidance of any perception that members of the IVM vs IVF in women with high AFC trial Data Monitoring Committee (DMC) may be biased is important for the credibility of decisions made by the committee and for the integrity of the trial. Any real or potential conflicts of interest of DMC members, including but not limited to those listed below, must be declared.

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the sponsor
- Frequent speaking engagements on behalf of the intervention

- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict, e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the trial publication

Having read the above: (please check the appropriate answer)

- ❑ I have no conflict of interest to declare.
- ❑ I have provided details of any real or potential conflicts of interest below:

_____

_____

_____

_____

I, _____, hereby agree to notify the Trial Steering Committee Chair promptly, and members of the DMC at the next meeting, if any change occurs in my real or potential conflicts of interest during the tenure of my responsibilities.

Signed: _____ Date: _ _ / _ _ / _ _ _ _

Confidential DISCLOSURE Agreement

This agreement is made on the …….. Day of …….(Month) of …… (Year) by
……..……
In relation to: The IVM vs IVF in women with high AFC trial.

The above party has certain information concerning the matter specified above (the Information). In order to protect certain confidential information relating to inventions, potential and/or present patent rights, research, development, ideas, techniques and other technology which may be disclosed, the Party, intending to be legally bound, agrees to keep secret and confidential the Information disclosed subject to the terms of this agreement.

DEFINITIONS
'Confidential Information' means and includes any documentation or information marked as confidential and supplied by either Party, all scientific technical, manufacturing, performance, sales, financial, commercial, contractual or marketing information which has not been previously published or otherwise available to the general public.

'Information' means and includes information of any nature, technology, ideas, scientific data, technical data, concepts, techniques, processes, formulas, expertise, computer programs, trade secrets, inventions, discoveries, designs, methods, know-how and data, whether recorded or not.
AGREEMENT
The above Party agrees:

- to keep the Information secret and strictly confidential;
- not to disclose or divulge the Information to any third party, without prior written consent;
- the Information remains the absolute and exclusive property of the disclosing party;

- the Information will not be used other than for the purpose agreed, without prior written consent.

The obligations do not apply to information which:

- was previously known or subsequently independently developed;
- is acquired from a third party without a breach of confidence;
- is in or enters the public domain otherwise than by breach of this agreement.

The above Party agree to return all information, including materials, documents or records at the request of either party.

This Agreement will expire five (5) years from the date of execution.

FOR THE PARTY:	FOR THE IVM vs IVF in women with high AFC TRIAL:
Signature	Signature
Name (printed)	Name (printed)

Suggested Letter from DMC to TSC

[*Insert date*]

To: Ben Mol, Chair
IVM vs IVF in Women with high AFC Trial Steering Committee

Dear Prof Mol,

The Data Monitoring Committee for the IVM vs IVF in women with high AFC trial met on [*insert meeting date*] to review its progress and interim data. [*List members*] attended the meeting and reviewed the open and closed reports.

The trial question remains important and, on the basis of the data reviewed at this stage, the Data Monitoring Committee recommend continuation of the trial according to the current version of the protocol [*specify protocol version and date*] with no changes.

We shall next review the progress and data [*provide approximate timing*].

Yours sincerely,

[*Insert name*], Chair
IVM vs IVF in women with high AFC Data Monitoring Committee

On behalf of the IVM vs IVF in women with high AFC Data Monitoring Committee (all members listed below): [*Insert names*]