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.

Information sheet
Study title: The effectiveness of intracytoplasmic sperm injection versus conventional in vitro fertilisation in couples with non-male factor infertility: a randomised controlled trial
Study intervention: ICSI, IVF
Sponsor of the study: My Duc Hospital, Ho Chi Minh City, Vietnam
Funder: MSD (Merck Sharp and Dohme (Asia) Ltd)
ICF version: V1
ICF date: ________________
Investigator: Dang Quang Vinh
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 do not hesitate to ask the trial doctor if you have any questions.

Introduction
Traditionally, for patients with non-male factor infertility, conventional in vitro fertilisation (IVF) is indicated. There is an increasing trend in using intracytoplasmic sperm injection (ICSI) for these patients with the hope to avoid total fertilisation failure (TFF) and to increase the number of embryos available, thus, increase the cumulative pregnancy rate. However, there is a lack of robust data on the effectiveness of this approach. The trial has been approved by the health authorities in Vietnam and by an ethics committee. A total of 1064 women will be included and treated in the trial. The study will be conducted from 16 March 2018 to 2 December 2020.

Purpose of this clinical research trial
The main purpose of this clinical research trial is to compare the effectiveness of one ICSI cycle and one IVF cycle in couples with non-male factor infertility. The results of this trial are anticipated to provide evidence whether ICSI, instead of conventional IVF, should be used for couples with non-male factor infertility.

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 estimated to be ~10–12 in both groups. If you take part in the trial, your participation will last for ~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: ICSI or IVF. 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
All patients undergoing IVF/ICSI will be treated with a GnRH antagonist protocol. Recombinant FSH (Puregon, Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany) will be given on Day 2 or Day 3 of menstrual cycle for 5 days. The starting dose is individualised for each patient based on the following criteria: AMH <0.7 ng/mL, dose 300 IU/day; AMH > 0.7 – 2.1 ng/mL, dose 200 IU/day; AMH > 2.1 ng/mL, dose 150 IU/day. After that, clinicians can titrate the dose based on their clinical judgement. Follicular development will be monitored by ultrasound scanning and measurement of estradiol and progesterone levels, starting on Day 5 of stimulation. Scanning and hormonal measurement will be repeated every 2–3 days, depending on the size of follicles. An antagonist is routinely used on Day 5 until the day of triggering. An antagonist (Orgalutran 0.25 mg, Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany) is routinely used on Day 5 until the day of triggering. Criteria for triggering, by human chorionic gonadotropin (hCG; Ovitrelle 250 mg, Merck Serono S.p.A., Modugno, Italy) will be the presence of at least three leading follicles of 17 mm. In women with excessive follicular response (≥15 follicles ≥12 mm), 0.2 mg Triptorelin (Diphereline, Ipsen Pharma Biotech, Signes, France) will be used when there is at least two leading follicles of 17 mm. Oocyte retrieval will be performed 36 h after triggering. On the day of oocyte pick-up, after having obtained the semen from the husband, eligible patients will be randomised to ICSI group or IVF group.

Embryology lab procedures
ICSI group
Insemination will be performed by using ICSI, 3–4 h after oocyte retrieval. Oocyte–cumulus complex (OCC) will be stripped by using hyaluronidase. Only matured oocytes will be inseminated.
Conventional IVF group
Insemination will be performed by conventional IVF. Two hours after retrieval, collected OCCs will be inseminated for another 2 h, at a concentration of 100,000 motile sperm/ml. Inseminated OCCs will be cultured overnight in culture medium. At fixed time point 66 ± 2 h after fertilisation, using the Istanbul consensus (The Istanbul consensus workshop, 2011). Embryo transfer will be performed on Day 3 under ultrasound guidance. Number of embryo transfer, from one to maximum of two embryos, will be based on patients’ preference. The remaining Grade 1 and 2 embryos will be frozen. Luteal-phase support will be done with oral estradiol valerate (Valiera®; Laboratorios Recalcine SA, Santiago, Chile) 8 mg/day and vaginal progesterone 800 mg/day (Cyclogest®; Actavis UK Ltd, North Devon, UK) until 7th week of gestation.

Frozen cycles
If there are contra-indications for fresh embryo transfer, a freeze-all strategy will be applied, using Cryotech technique. Indications for freeze-all include risk of ovarian hyperstimulation syndrome (OHSS), premature progesterone rise (>1.5 ng/ml), thin endometrium (<7 mm), fluid in cavity, enlarged ovaries, accumulation of hydrosalpinx that have not removed before oocyte retrieval. In the next cycle, the endometrium will be prepared using oral estradiol valerate (Valiera®; Laboratorios Recalcine SA, Santiago, Chile) 8 mg/day starting from the second or third day of the menstrual cycle. Endometrial thickness will be monitored from Day 6 onwards, and vaginal progesterone (Cyclogest®; Actavis UK Ltd, North Devon, UK) 800 mg/day will be started when endometrial thickness reaches 8 mm or more. A maximum of two embryos will be thawed on the day of embryo transfer, 3 days after the start of progesterone. Two hours after thawing, surviving embryos will be transferred into the uterus under ultrasound guidance. When you have more than two embryos frozen, the procedure will be repeated in subsequent cycles if the first transfer is unsuccessful.

Pregnancy monitoring
You will be monitored if you are pregnant. This includes a blood sample ~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, ~25 ml blood will be drawn each time. 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 ~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 occurs 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.

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 Puregon®. 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 Puregon® 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 if you have an excessive follicular response (≥15 follicles ≥12 mm), 0.2 mg Triptorelin (Diphereline, Ipsen Beaufour, France) will be used instead of human chorionic gonadotropin (hCG) to trigger the maturation of the eggs. 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 Puregon®.

As part of the treatment, you will receive concomitant medications, i.e. GnRH antagonist, hCG or a GnRH agonist, estradiol 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 ~0.1–0.3% of cases at our centre) or any embryos available for transfer (occurs in ~1% of cases at our centre). 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 minimised 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 are allocated in the conventional IVF group and should TFF occurs (means that there is no fertilisation occurs), you will have a subsidise in the next treatment cycle with ICSI.

Information

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

Investigator Name: Dang Quang Vinh at +84 90 8225481
Sub-Investigator Name:
  Vuong Ngoc Lan at +84 90 3008889
  Ho Manh Tuong at +84 90 3633377
  Ha Nhat Anh at +84 93 2170687
  Nguyen Ngoc Quynh +84 93 3310693
  Truong Thanh Binh at +84 98 9960903

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, 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.
The effectiveness of intracytoplasmic sperm injection versus conventional in vitro fertilisation in couples with non-male factor infertility: a randomised controlled trial

Study title: The effectiveness of intracytoplasmic sperm injection versus conventional in vitro fertilisation in couples with non-male factor infertility: a randomised controlled trial

Study intervention: ICSI, IVF

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

Funder: MSD (Merck Sharp and Dohme (Asia) Ltd)

ICF version: V1

ICF date: ________________

Investigator: Dang Quang Vinh

Patient code: ________________

We confirm the following:

We have read and understand the information sheet for the above study and have had enough time to think about taking part.

We are satisfied with the answers given to all my questions.

We 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.

We understand that we are free to withdraw from this study at any time without giving a reason and without my medical care or rights being affected.

We have received an original copy of this information sheet and consent form.

We understand that we have rights to access the data provided in information sheet by responsible people.

We agree to our samples being taken and used as described in this information sheet.

We give permission for our personal information collected as part of this clinical study to be:

- identified only with our subject ID numbers;
- reviewed, processed and transferred by and to the Sponsor and its authorised 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 our country;
- transferred if required to any country, where data protection laws may be less strict.

We understand that we may also be contacted later for our permission in connection with this or any related sub study.

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

Name (Wife): ____________________ Date (DD/MM/YYYY): _______

Signature: ____________________

Name (Husband): ____________________ Date (DD/MM/YYYY): _______

Signature: ____________________

Investigator/Authorised designee:

I have fully and carefully explained the study to the persons 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: ____________________ Date (DD/MM/YYYY): _______

Signature: ____________________

Data Safety Monitoring Committee Charter

CONFIDENTIAL

Author: Dr Vinh Q Dang

Version: Draft 2

Date: 20 October 2017

Introduction

This Charter is for the Data Safety Monitoring Committee (DSMC) for the ‘ICSI vs. IVF in couples with non-male factor infertility’ trial. The objective of this trial is to compare the effectiveness of one ICSI cycle and one conventional IVF cycle in couples with non-male factor infertility. The purpose of this document is to describe the roles and responsibilities of the DSMC, including the timing and format of meetings, methods of providing information to and from the DSMC, statistical monitoring guidelines and relationships with other committees.

Roles and Responsibilities

The aims of the DSMC 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 DSMC 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 DSMC 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 DSMC recommendations;
- monitoring TSC compliance with previous DSMC recommendations.

### Early input

All potential DSMC members will be offered access to the draft trial protocol and DSMC charter before agreeing to join the committee. If a potential DSMC 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 DSMC. All DSMC members should be independent and provide constructive criticism of the trial, but should also be supportive of the aims and methods of the trial.

DSMC 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 DSMC, the TSC will appoint a suitable replacement.

A preliminary skype or teleconference meeting will be held involving DSMC 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 DSMC charter and the open and closed reports, to be presented in the open and closed sessions of DSMC meetings.

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

### Composition

The DSMC will be an independent multidisciplinary group consisting of three individuals and will include IVF specialists and a biostatistician, one of whom will be elected to be the DSMC Chair. All DSMC members must have clinical trial experience and at least one DSMC member must have prior DSMC experience. DSMC members should be independent of the trial and should not serve on DSMCs 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 DSMC members must be approved by the TSC.

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

The DSMC IVF specialists are expected to provide clinical expertise. The DSMC Biostatistician is expected to provide independent statistical expertise and to help guide DSMC members through the open and closed reports. The DSMC Biostatistician is not expected to prepare the DSMC reports.

The DSMC will be restricted to individuals free of apparent significant conflicts of interest. Any conflicts of interest of DSMC members, both real and potential, must be declared in the conflicts of interest form (Appendix 1) to be returned to the TSC Chair prior to the initial DSMC meeting, and disclosed to all DSMC members at the initial DSMC meeting. Any changes in conflicts of interest during the trial monitoring period must be reported promptly to the TSC Chair and disclosed to all DSMC members at the next meeting, and may in some cases require resignation from the DSMC.

The members of the DSMC for the ICSI vs. IVF in couples with non-male factor infertility trial are:

| DSMC role       | Name               |
|-----------------|--------------------|
| IVF specialist  | J LH Evers         |
| IVF specialist  | S Bhattacharya     |
| Biostatistician | E Schuit           |

### Relationships

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

The TSC Chair and Trial Coordinator will attend the open sessions of DSMC meetings to help guide DSMC members through the open report and answer any questions from DSMC members about the specifics of the trial. The TSC Chair is responsible for identifying and providing to DSMC members any external evidence relevant to the trial for consideration, and for notifying the DSMC of any changes to the trial protocol or conduct or the addition of any side studies. This information will be presented to DSMC members during the open sessions of DSMC meetings.

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

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

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

| Role       | Name(s)                                           |
|------------|---------------------------------------------------|
| TSC Chair  | Ben Mol                                           |
| Other TSC  | Lan N Vuong, Vinh Q Dang, Tuong M Ho, Anh N Ha,  |
| Members    | Quynh N Nguyen, Binh T Truong, Rui Wang, Robert   |
|            | Norman                                            |
| Trial Statistician | Quan T Pham                           |
Organisation of DSMC meetings

The first DSMC meeting will not be held until ~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 DSMC meetings. Subsequent DSMC meetings will be held annually, with additional meetings or teleconferences to be scheduled according to the needs of the DSMC or the TSC. DSMC meetings will be conducted face to face or by teleconference or by skype. Other DSMC meetings may also be conducted as above, depending on the location and preferences of DSMC 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 DSMC members and others who can provide valuable insights into trial-related issues.

Open sessions will be attended by DSMC 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 DSMC, and for the DSMC to ask the TSC Chair and Trial Coordinator questions about the trial. Closed sessions will be attended by DSMC members only. These sessions will be used for discussing the closed report and forming recommendations about the trial.

Trial documentation and confidentiality

DSMC 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 DSMC will not necessarily be blinded to the identity of the treatment arms. The closed report will be labelled with Treatment A and B, or similar, with different labels for each meeting. DSMC members may be advised at their request which group is A and B. Deliberations of the DSMC, should only be available to those present in the closed DSMC sessions. DSMC members must not share confidential information with people outside the DSMC, including members of the TSC.

DSMC 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, DSMC members should destroy all interim reports. DSMC members will be required to sign a confidentiality agreement.

Decision making

DSMC recommendations will be based primarily on safety considerations. The possible recommendations of the DSMC 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 DSMC Chair is expected to summarise discussions and encourage consensus. In each area of discussion, the DSMC Chair should give their opinion last.

Every effort should be made for the DSMC to reach a consensus. If the DSMC 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 DSMC members will be required to attend all DSMC meetings, and meetings will be scheduled with this requirement in mind. If, at short notice, any DSMC member cannot attend at all then the DSMC meeting will be rescheduled.

Reporting

The DSMC Chair will report in writing to the TSC Chair on any actions recommended (including no action), within two weeks after each DSMC meeting. The TSC Chair is responsible for reporting back to the TSC on any DSMC recommendations. Where an action is being recommended, the DSMC Chair will circulate the letter to DSMC 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 DSMC Chair to a TSC Chair recommending no action is presented below.

Minutes should be taken at both the open and closed sessions of the DSMC 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 DSMC members, excluding the DSMC Chair, and should be agreed upon at the start of each meeting. If the DSMC wish to bring in an external person to take minutes (e.g. a personal assistant), approval must first be obtained from the TSC through the TSC Chair. All members of the DSMC should see and have the opportunity to comment on the closed session minutes. The DSMC Chair is responsible for signing off on all closed session minutes. Both the DSMC 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 DSMC Chair in writing how the TSC has acted upon any recommendations made by the DSMC.

If the DSMC 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 DSMC 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 DSMC Chair will provide copies of the closed reports and closed session minutes of all DSMC meetings to the TSC Chair.

The TSC are responsible for ensuring the trial results are published in a correct and timely manner. DSMC members will be named (unless...
Conflict of interest form

The avoidance of any perception that members of the ‘ICSI vs. IVF in couples with non-male factor infertility’ trial DSMC 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 DSMC 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;
- 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 DSMC 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: ‘ICSI vs IVF in couple with non-male factor infertility’ 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 ‘ICSI VS IVF IN COUPLES WITH NON-MALE FACTOR INFERTILITY’ TRIAL:

Signature
Name (printed)

Signature
Name (printed)
Suggested Letter from DSMC to TSC

[Insert date]

To: Ben Mol, Chair
ICSI vs IVF in couples with non-male factor infertility trial Steering Committee

Dear Prof Mol,
The Data Safety Monitoring Committee for the ICSI vs IVF in couples with non-male factor infertility 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 Safety 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
ICSI vs IVF in couples with non-male factor infertility trial Data Safety Monitoring Committee

On behalf of the ICSI vs IVF in couples with non-male factor infertility trial Data Safety Monitoring Committee (all members listed below):

[Insert names]