PATIENT GUIDE

Study title:	"Standardization of variable conditions of embryo transfer into the uterine cavity in the procedure of medically assisted procreation in humans"
Subtitle:	EMBRYOPASS/ EMBRYOCASE A randomized, prospective, single-center, controlled, single-blind study evaluating the impact of standardization of variable conditions of embryo transfer into the uterine cavity in medically assisted procreation in humans on the effectiveness of the procedure, by using: standardization of culture conditions and selection of embryo for transfer through the use of an incubator with a time-lapse observation system and artificial intelligence (Artificial Intelligence), the EMBRYOPASS applicator - an electronically controlled device for controlled transfer, and the EMBRYOCASE case maintaining optimal environmental conditions for the embryo outside the incubator during the peri-transfer time.
Acronym:	EFECT
Attending physician:	Katarzyna Kozioł, MD, specialist in gynecology and obstetrics of the second degree, EGiR specialist, senior clinical embryologist of ESHRE, clinical embryologist of PTMRiE PWZ no. 6475994
Research Center:	nOvum Medical Clinic, 13 Bociania Street, Warsaw, Poland
	The therapeutic experiment received a positive opinion from the competent Bioethics Committee, in accordance with the requirements of national law

Dear patients,

We cordially invite you to take part in a study that aims to assess the impact of standardization of variable conditions of embryo transfer into the uterine cavity in the medically assisted procreation procedure on its effectiveness. However, before you decide to take the study, it is very important that you read the following information and understand why this study is being conducted and what it is about. We want your participation in the study to be a fully informed

decision, so we ask you to read the content of the following guide carefully. If you have any questions, doubts or want to get more information, please contact the attending physician at our center.

a. Information on the essence, nature and purpose of the study

The treatment process using advanced assisted reproduction techniques is multi-stage and complex. It usually consists of diagnostics and preparation of patients for the treatment process, controlled hormonal stimulation of the ovaries in order to obtain more eggs than in the natural cycle, acquisition and preparation of sperm, collection of eggs through ovarian puncture, in vitro fertilization, in vitro embryo culture, transfer of embryos into the uterine cavity, freezing of the remaining embryos for their use in the future. Embryo transfer (ET) is an integral, final and perhaps decisive element of the entire process of in vitro fertilization treatment. The effectiveness of infertility treatment, determined at the level of 25-35% of pregnancies obtained after embryo transfer, has long aroused the interest of researchers who are looking for additional solutions that can increase it. The main cause of failures is considered to be spontaneous genetic errors occurring both in embryonic development in nature and in vitro conditions, preventing the proper development of embryos and its final inhibition; These errors are not remediable. The lack of pregnancy, despite the proper development of embryos, can also be caused by hormonally unprepared endometrium of the uterus or lack of synchronization of embryo development with endometrial development. Individualization of transfers, diagnostics of the so-called "implantation window" or performing transfers of thawed embryos in natural cycles are procedures that can increase the chance of success of the treatment process. Numerous studies conducted over the last decade see the reasons for the limited effectiveness of infertility treatment using the assisted reproduction method, among others, in the technique of performing the transfer itself, and this stage of the procedure of infertility treatment using the assisted reproduction method has become the subject of particular interest of the nOvum Medical Clinic team. Success in the form of a pregnancy depends on the elimination of errors and the optimization of each of the stages of treatment.

Embryo transfer is a multi-step and complex procedure that can be further refined and optimized. To perform it, special catheters (catheters) tightly connected to a syringe are used.

The embryo transfer procedure can be divided into individual stages:

- preparing the patient for embryo transfer by ultrasound examination and a trial transfer procedure to verify that entry through the cervix into the uterine cavity is easy and to assess the length and direction of the cervix and uterine cavity;
- synchronization of the endometrium with the age of embryos;
- preparing the patient before the transfer, cleaning the cervical canal of cervical mucus to avoid possible blockage of the transfer catheter and preventing the delivery of embryos into the uterine cavity or the penetration of part of the cervical mucus into the cavity and disruption of the implantation process;
- proper collection of embryos into the transfer catheter by the embryologist, which is an extremely important element of the entire procedure. There are several methods of embryo acquisition. The researchers suggest that the density of the transfer medium, the choice of syringe type, the type of catheter, and the speed at which embryos are taken into the catheter may be key factors in the process of embryo uptake into the catheter;
- insertion of a leading catheter into the uterine cavity – involves inserting a transfer catheter through the internal cervical outlet into the uterine cavity just behind the internal outlet;
- visualization of the embryo transfer process using an ultrasound machine – this is not an element necessary for the proper conduct of the procedure, but it is very helpful. It allows you to visualize the uterus, allows you to assess possible anatomical obstacles, as well as the right depth to which the catheter should be inserted into the uterine cavity without causing damage to the mucous membrane or stimulating it to excessive contraction. It allows you to visualize the entire transfer process - the movement of embryos marked with air bubbles from the catheter to the inside of the uterine cavity;
- Proper embryo transfer - performed by a doctor with the assistance of an embryologist, consists in inserting a guide catheter, a catheter containing embryos suspended in the transfer medium, the so-called embryonic catheter, into the previously inserted uterine catheter. This is a key stage of the entire embryo transfer process – if done incorrectly, it can reduce the chances of success. After inserting the guide catheter, the operating doctor places the embryonic catheter in it and gently moves it inside the uterus. After making sure during the visualization in the ultrasound examination that the embryonic

catheter is located in the optimal place of the uterine cavity, the operator presses the plunger of the syringe connected to the embryonic catheter and carefully, by pressing on the plunger, initiates the movement of embryos from the catheter to the inside of the uterine cavity. Once the maximum resistance of the plunger has been reached and the last marking marker (air follicle) remains in the uterine cavity, the doctor retracts the catheters from the cavity. Retracting the embryonic catheter too abruptly or releasing pressure on the plunger can pull the embryos back into the catheter, while administering the embryos too abruptly can cause damage to the embryos.

- Checking the catheters – after the embryos are injected into the uterine cavity, the embryonic catheter is flushed using a transfer medium under a microscope to make sure that there are no embryos in it and that they remain in the uterine cavity.

The most important stages of embryo transfer that have become the subject of interest of the research team of the nOvum Clinic and improvement are the variable elements of the procedure, which may affect its success:

1. selection of embryos for transfer – the stage of the procedure depends on the experience of the embryologist, despite the introduction of embryo assessment standards, the embryo assessment by the embryologist remains subjective,
2. embryo collection into the catheter – a stage of the procedure that depends on the training and experience of the embryologist, and therefore is subject to variability,
3. transfer of embryos placed in a catheter from the laboratory to the transfer room – at this stage, the embryos are affected by changing environmental conditions, which may affect their development and implantation,
4. Administration of embryos from the catheter into the uterine cavity – another variable stage depending on the human factor, i.e. the experience and training of the doctor.

In recent years, scientific reports have been published on the conditions to which embryos in the catheter are subjected during transfer to the uterine cavity.

The above-mentioned reports and own experience confirming the unfavorable conditions that affect the embryos placed inside the catheter during the peritransfer time (the time the embryo remains in the catheter outside the incubator from being

taken into the catheter to be administered into the uterine cavity) and during their transfer to the uterine cavity, such as: a sharp drop in temperature, shear stress, speed and pressure differences, prompted our team to work on standardizing the embryo transfer procedure.

The first stage of work was a design on the design of an applicator that would allow for a controlled process of embryo acquisition into the transfer catheter, as well as the transfer of embryos into the uterine cavity at a constant, optimal speed and would eliminate the adverse conditions to which embryos are exposed during this procedure. An electronically controlled device for embryo transfer that increases the safety and repeatability of the procedure and thus can increase its effectiveness.

The next stage of work on the standardization of the embryo transfer procedure concerns the peritransfer conditions in which the embryo is located outside the incubator during the peritransfer time, i.e. between its collection into the catheter by the embryologist in the embryology laboratory and its administration into the uterine cavity performed by the doctor in the transfer office. Once the embryo is placed in the catheter, the embryologist must transfer the catheter from the laboratory to the transfer room and hand it over to the doctor. Even a short time outside the incubator causes a change in the environmental conditions in which the embryo placed in the catheter is located - a sharp drop in temperature, which has been described in the literature. With the current state of knowledge regarding the range of optimal and unfavorable temperatures for embryonic development, which has already been known, such reports indicate that the embryo in the peritransfer period may be subjected to unfavorable and stress-inducing environmental factors, which may result in impaired development - aneuploidy, moziacism and reduced embryo implantation potential.

Maintaining optimal environmental conditions in which the embryo is located outside the incubator during the peritransfer time may therefore turn out to be crucial and is the subject of the study.

Purpose of the study

PRIMARY PURPOSE

The key objective of the study is to confirm the positive impact of standardization of the parameters of the embryo transfer procedure variables on its effectiveness.

The indicators confirming the achievement of the primary goal will be:

1. Estimation of the percentage of biochemical pregnancies:

a. confirmation of the positive impact of standardization of the environmental conditions in which the embryo is located outside the incubator during the peritransfer time will be an increase in the percentage of pregnancies (βhCG result indicating pregnancy 10-15 days after embryo transfer) in the group of patients in whom ET was performed with the help of the EMBRYOCASE case by 10% compared to the control group;
b. confirmation of the effectiveness of the EMBRYOPASS applicator – achieving at least the same percentage of pregnancies (criteria as above) in the group of patients in whom ET was performed with the help of the EMBRYOPASS applicator in relation to the control group;
c. confirmation of the effectiveness of standardization of variable conditions in the ET procedure (environmental changes and human factor) will be an increase in the percentage of pregnancies (criteria as above) in the group of patients in whom ET was performed with the help of the EMBRYOCASE case in combination with the EMBRYOPASS applicator by 15% compared to the control group.

2. Estimation of the percentage of clinical pregnancies (visible pregnancy follicle in the uterine cavity 25-35 days after ET)

SECONDARY PURPOSE

The secondary objective of the study is:

1. confirmation of the beneficial impact of standardization of parameters and conditions of the ET procedure on its effectiveness achieved thanks to the use of the EMBRYOCASE case and the EMBRYOPASS applicator – an electronically controlled device for controlled embryo transfer by: obtaining an increased percentage of implantation (percentage of implanted embryos) – visible pregnancy follicle on ultrasound 25-35 days after ET in the group of patients in whom ET was performed with the help of the EMBRYOCASE case, EMBRYOPASS applicator, and the EMBRYOCASE kit in combination with EMBRYOPASS compared to the control group in which ET was performed according to the standard procedure adopted at the center (manually).

SECONDARY OBJECTIVE (AFTER COMPLETION OF THE STUDY)

1. estimating the impact of using the EMBRYOCASE case and the EMBRYOPASS applicator separately and in combination on the percentage of live births – LBR (after completion of the study).

SAFETY

1. Estimation of the safety profile of the use of the EMBRYOCASE case and the EMBRYOPASS applicator in the ET procedure (the percentage of adverse events during transfer in the study group and control groups).

USABILITY

1. Evaluation of the convenience of using the EMBRYOCASE and the EMBRYOPASS applicator by the embryologist and doctor.
2. Evaluation of the repeatability of the procedure - the time of embryo acquisition and the time of embryo administration.

b. Information about the treatment used in the clinical trial and the rules for random selection of participants

The acquired knowledge was used to develop solutions by the nOvum clinic that provide optimal conditions for the embryo in the peritransfer time and allow for the standardization of the embryo transfer procedure, eliminating the influence of the variable human factor on the success of the procedure.

The subject of the study is an electronically controlled EMBRYOPASS applicator enabling controlled embryo transfer into the uterine cavity, which is one of the most important elements of the medically assisted procreation procedure. EMBRYOPASS is the nOvum clinic's own invention, constructed by the clinic as part of the RPMA.01.02.00-14-5674/16 project. The applicator was tested on an animal model, achieving a high percentage of pregnancies and births. The final result of the project is a prototype model of the EMBRYOPASS applicator, meeting the assumed design conditions and functionalities, launched and tested in laboratory and clinical conditions (animal model). **The nOvum clinic has obtained a patent, a reservation of the industrial design of the EMBRYOPASS applicator, and a CE1434-MDD-089 certificate certifying compliance with the requirements for medical devices in accordance with the EEC/93/42 directive.**

Features of the EMBRYOPASS applicator:

- the cycle of taking the charge into the catheter, as well as its administration from the catheter into the uterine cavity, ensures repeatability of the procedure thanks to programmed constant values of volume, time, speed;
- the volume of the administered charge (i.e. the fluid with the administered embryo) is electronically controlled. After the injection of the entire volume of charge, it is impossible to retract the delivery system, which significantly increases the safety of the procedure of administering the embryo into the uterine cavity and eliminates the risk of retracting the embryo back into the catheter;
- the ability to detect the phenomenon of catheter obstruction.

The applicator for controlled embryo transfer was designed to work in the conditions prevailing in the embryology laboratory.

The subject of the test is also the EMBRYOCASE case

The nOvum team's knowledge of the environmental conditions in which the embryo is located outside the incubator will be used to develop a prototype device that minimizes environmental changes in the catheter by maintaining a constant and optimal temperature in the peritransfer time. The subject of the research – the EMBRYOCASE case, like the previously patented EMBRYOPASS applicator, is by definition a safe, easy to use, safe and reliable device. It will not have direct contact with the embryo or the woman's body. The implementation of the invention will enable the standardization of the embryo transfer procedure, increase the effectiveness of assisted reproduction (ART) treatment, and increase the quality of patient service.

Innovative protocol for standardization of the time-lapse (AI) EMBRYO TRANSFER PROCEDURE/ EMBRYOPASS/EMBRYOCASE

Combining three innovative solutions into one optimal system: it is supposed to improve the effectiveness of infertility treatment:

- Optimization of embryo selection through the use of a culture and monitoring device equipped with an embryo culture system in an incubator with continuous monitoring of embryo development using cameras (time-lapse) and artificial intelligence
- implementation of the centre's innovative, patented invention – the EMBRYOPASS applicator – into the embryo transfer procedure,

- development and implementation of a case stabilizing the conditions of the embryonic environment in the peritransfer period EMBRYOCASE.

Information on random selection of participants (Randomization)

Randomization (selection of participants for the control group and study groups) will be randomized. Patients who meet all inclusion criteria and do not meet any of the exclusion criteria may be randomised. Randomization will be based on a 1:1:1:1 basis. This means that 40 patients will be placed in the control group and each of the three groups of subjects:

TL/AI control group – CRIO-ET manual

research group 1 TL/AI – CRIO-ET manual + EMBRYOCASE

study group 2 TL/AI – CRIO-ET using EMBRYOPASS

research group 3 TL/AI – CRIO-ET using EMBRYOPASS + EMBRYOCASE

Blinding / Unblinding the Study

The study will be partially blinded. Patients will not be informed until the end of the study whether they will be placed in the control group or in one of the study groups. The staff participating in the study: doctors, embryologists and nurses, due to the specificity of performing the embryo transfer procedure to the uterus (no possibility of blinding), will know which group the patient has been assigned to, but they will undertake to maintain secrecy. Information on how to perform the transfer will be included in the study documentation. **During the transfer, the husband will not be able to be present.** Statisticians analyzing the results of the survey will be blinded. Unblinding will take place after analyzing the effectiveness of AE and SAE. The test will be unblinded after the test report has been prepared. Patients will be informed by the investigator about their membership in groups only at their explicit request.

Emergency Blinding

Premature blinding for an individual patient may occur in the event of AE or SAE, the occurrence of which in the investigator's judgment may be related to the use of EMBRYOCASE/EMBRYOPASS. If it is necessary to unblind the patient, it is not required to exclude her from the examination. Each case of unblinding must be documented by the investigator in the study documentation, along with a description of the circumstances and arguments in favor of unblinding.

c. Description of the procedures and medical studies related to participation in the clinical trial

The course of the study is illustrated in the diagram attached to the guide.

In order to improve infertility treatment methods and increase the effectiveness of embryo transfers, comparisons should be made. As part of this study, the effectiveness of the transfer performed with the use of the EMBRYOPASS applicator, the EMBRYOCASE case and the set consisting of both devices will be evaluated, and the results obtained will be compared with the results obtained in the group of patients in whom the transfer will be carried out by the manual method in accordance with the practice of the center.

Screening (screening period)

The screening period will include procedures to check if you can be eligible for the test. **Qualification for the examination must be preceded by the signing of an informed consent by the Patient and her husband/partner.** Qualification will be conducted a maximum of 60 days prior to randomization. During qualification, your doctor will collect the required information from you regarding your health condition and treatment history. The medical procedures performed during screening are:

- measurement of height, weight, BMI,
- measurement of pressure, heart rate and temperature,
- physical examination and gynecological examination,
- gynecological ultrasound examination (if the patient has not provided an examination performed in the last 3 months),
- Trial transfer to assess the length and direction of the uterine cavity and cervix, as well as to diagnose possible obstructions. The procedure will be performed only if there is no information in the medical records about how the previous transfer took place (if any).
- diagnostic tests (swabs, cultures, blood tests routinely ordered to patients at the center for the procedure of embryo transfer of a thawed embryo).

Synchronization of the endometrium with the age of the embryos will take place in the ovulatory cycle - natural or induced by letrozole. Once ovulation is confirmed in an ultrasound and/or hormonal examination, a temporarily synchronized embryo thawing will be ordered. Randomization will take place on the day of CRIO-ET, i.e. on the 5th day after ovulation, counting the day of follicle rupture as day 0, confirmation

of ovulation by the occurrence of the LH peak (LH peak day + 6 days), or by the administration of chorionic gonadotropin on the day of confirmation of the presence of the preovulatory follicle 17-22 mm, HCG drug (HCG administration day +7 days). Patients who meet all inclusion criteria and do not meet any of the exclusion criteria will be enrolled in the study (randomised).

Embryo thawing

The order for the embryos to be thawed by the doctor and the appointment of a transfer visit will take place in accordance with the routine practice adopted at the center.

The embryos will be thawed:

a. according to the highest rating indicated before freezing by Artificial Intelligence (AI):
b. on the day preceding CRIO-ET (for blastocysts with a degree of expansion rated as 3 before freezing);
c. on the day of CRIO-ET (for blastocysts with a degree of expansion rated at least 4, at least 2 hours prior to surgery).

Defrosting will be carried out in accordance with the routine procedure adopted at the nOvum Medical Clinic.

Evaluation of embryos after thawing

Evaluation of embryos after thawing will be performed by an embryologist and on its basis the embryo will be qualified for ET.

Transfer visit

On day 5 after ovulation (on day ET), after the embryo is thawed, randomization will take place. The transfer visit will be divided into two stages:

Stage I: The following procedures will be performed prior to randomization to ensure that the patient is eligible for the study:

- measurement of pressure, heart rate and temperature,
- gynecological ultrasound,
- the medications taken by the patient will be evaluated, and they will receive further recommendations on the use of the medication,
- AE/SAE will be evaluated,

- The doctor will communicate with the laboratory and confirm whether the embryo is eligible for transfer after thawing and whether the patient meets the criteria for inclusion in the study.

Stage II: after randomisation, the patient enrolled in the clinical trial will undergo embryo transfer of a thawed embryo using a method consistent with the randomisation group in which she was placed.

Soft catheters will be used to perform the embryo transfer procedure. In addition, in the test groups, the EMBRYOPASS applicator, the EMBRYOCASE case or both devices will be included in the catheter/syringe transfer set. Common to the control group and all research groups will be the cultivation of embryos in the TL (Time) system and the evaluation and selection of embryos for transfer by artificial intelligence (AI).

The embryo transfer procedure will be divided into stages:

a. Preparation of the patient before the transfer, as described above.

In all groups, the control group and the three subjects, patients will be prepared for embryo transfer in the same way.

b. The insertion of a catheter leading to the uterine cavity consists in inserting, with great delicacy, the catheter through the internal opening of the cervix into the interior of the uterine cavity just behind the internal outlet. Once the catheter is placed, the nurse assisting the doctor will inform the embryologist that they are ready for transfer. The embryologist will then begin the procedure of collecting embryos into the catheter. In all groups, this stage of the embryo transfer procedure will look the same.

c. Proper embryo acquisition into the transfer catheter. The embryos will be taken into the catheter directly from the medium (medium) intended for embryo transfer from the transfer dish, and the whole operation should not take more than 2 minutes, according to the scheme: air (marker) - medium with embryo-air (marker)-medium. This step of the procedure will vary from group to group:

in the control group (TL/AI – ET manual) and study group No. 1 (TL/AI – ET manual + EMBRYOCASE), the embryologist will collect embryos into the transfer catheter in a manual manner, in accordance with the above scheme adopted at the center. The time from the start of the 1st air bubble intake to the completion of the media intake will be measured by a stopwatch.

in study groups 2 (TL/AI – ET using EMBRYOPASS) and 3 (TL/AI – ET using EMBRYOPASS + EMBRYOCASE), the embryologist will collect embryos into the

transfer catheter with the help of the EMBRYOPASS applicator, in accordance with its instructions for use. The embryo acquisition time will be measured.

d. After collecting the embryos into the catheter, the embryologist will transfer the catheter to the transfer room without additional protection in the control group and study group 2, or after placing the catheter with the embryo in the EMBRYOCASE case (group 1 and 3).

e. Visualization of the embryo transfer process using an ultrasound machine allows you to visualize the entire process of embryo transfer from the catheter to the inside of the uterine cavity.

In all groups, transfers will take place under ultrasound control.

f. Embryo transfer - the proper administration of embryos into the uterine cavity consists in the insertion by the doctor of a guide catheter, a catheter, containing embryos suspended in the medium, the so-called embryonic catheter. This is a key stage of the entire embryo transfer process.

This step of the procedure will vary from group to group:

- **In the control group and the 1 study group,** the doctor, after inserting the guide catheter, places the embryonic catheter in it and gently moves it inside the uterus. After making sure that the embryonic catheter is in the optimal place of the uterine cavity, the operator presses the plunger of the syringe connected to the embryonic catheter with his finger and carefully causes the embryos to move from the catheter to the inside of the uterus by pressing on the plunger. Once the maximum resistance of the plunger has been reached and observing whether the last marking marker remains in the uterine cavity, the doctor retracts the catheters from the cavity. To measure the time it takes for the embryos to be placed in the uterine cavity, the doctor will inform the embryologist of the start and end of the procedure, and its duration will be measured;
- in study groups 2 and 3, the doctor will administer embryos from the transfer catheter into the uterine cavity using the EMBRYOPASS applicator. Instead of pressing the plunger of the syringe, the doctor will press the appropriate button on the EMBRYOPASS applicator, which will trigger the movement of the syringe plunger.

As the time of embryo administration with the EMBRYOPASS applicator is a constant value, there is no need to control the time at this stage. The catheter will be withdrawn from the uterine cavity immediately after the embryos are administered.

g. Once the embryos have been administered into the uterine cavity, the embryonic catheter will be flushed using a transfer medium under a microscope to make sure that the embryo remains in the uterine cavity.

h. The course of the procedure and any adverse events that will occur during the embryo transfer procedure will be recorded in the documentation.

i. Immediately after the transfer, the patient will get up from the chair and leave the office.

βhCG Visit

10-15 days after embryo transfer, the patient will perform a pregnancy test from blood serum. If the pregnancy test result is negative, the patient will end the test.

Visit – confirmation of clinical pregnancy.

Confirmation of clinical pregnancy will occur at the visit 25 – 35 days after ET. During this visit, a

- measurement of pressure, heart rate and temperature;
- physical examination;
- examination in speculums;
- ultrasound examination to assess the presence of a pregnancy follicle in the uterine cavity

The examination is completed.

It is possible for the patient to carry out the pregnancy outside the research center at the place of residence, provided that medical data on individual stages of pregnancy development (βhCG, ultrasound tests will be made available to the nOvum clinic doctor in the form of documents, e.g. scans, photocopies or consulted with the doctor through any form of consultation: televisits, video consultation).

Termination of pregnancy

Data on the termination of pregnancy (data on childbirth, miscarriage or ectopic pregnancy) will be obtained from you by means of a questionnaire developed by the researchers, the template of which is Appendix No. 4 to this guide. The patient can send the questionnaire to the center or provide the information contained in it by phone to one of the members of the research team.

At each stage of the study, the doctor will inform the patients about the schedule of taking the permitted drugs.

Permitted Medications/Therapies

- Letrozole
- Progesterone (Duphaston, Cyclogest) to supplement the luteal phase,
- Ovulation induction medications, if used,
- other medicines/supplements that the investigator considers have no effect on fertility or the outcome of the embryo transfer procedure,
- Bokmål

Prohibited Medications/Therapies

- preparations other than hCG used for the purpose of liberation, which prevent the embryo transfer procedure from being performed,
- drugs with proven harmful effects on fertility,
- drugs used in oncological therapy with a proven harmful effect on fertility,
- drugs that have a relaxing and antispasmodic effect on the uterus – atosiban, relanium, scopolan (hyoscine butylbromide) or other hyoscine derivatives,
- heparin drugs,
- acetylsalicylic acid.

d. Responsibilities of study participants

When participating in the study, it is necessary that you:

- follow the recommendations of the attending physician;
- provide all information regarding your health and medical history and answer all questions truthfully;
- reported to the center for designated visits;
- it is important that you do not use any other therapies or medications, including herbal products, without the consent of your treating physician (except as a matter of urgency);
- immediately inform the research team of any changes in the patient's health;
- have not participated in another clinical trial during the course of this study;
- provided information on the course of pregnancy, childbirth and health of the child/children after birth in accordance with the survey.

e. Information about the foreseeable risks and inconveniences to the participant in the clinical trial, to the embryo, foetus or breastfed infant

- **Blood collection**

Risks associated with taking blood from the forearm can include pain, bruising, feeling light, and in rare cases, infection.

- **Ultrasound examination**

Transvaginal ultrasound is a standard method used by a doctor to examine the uterus. Inserting an ultrasound head into the vagina does not cause pain, but you may feel a slight discomfort during the examination.

In an ultrasound examination through the abdominal membranes, a small amount of ultrasound gel is applied to the skin of the lower abdomen, and then an ultrasound head is used to examine through the gel layer and the skin. The examination is painless, although it may be accompanied by a feeling of cold on the skin.

- **Transfer zarodka**

The transfer is preceded by inserting a speculum into the patient's vagina (this does not cause pain, but you may feel slight discomfort). The entire procedure is performed under ultrasound control through the abdominal membranes. During the procedure, a guide catheter will be inserted into the patient's uterus, followed by an embryonic catheter, in which the embryo to be transferred will be placed. After the transfer and checking whether the embryo remains in the uterus, the guide and speculum will be removed. Immediately after the procedure, the patient can leave the transfer room. The embryo transfer procedure is painless for most patients and takes only a few to several minutes.

- **Risks of using the EMBRYOCASE case and the EMBRYOPASS applicator**

Both devices do not have direct contact with either the embryo or the patient's body, so their use is not associated with discomfort. The aim of the study is to demonstrate the complete safety of the use of the EMBRYOPASS electronic device for controlled embryo transfer and the case stabilizing environmental conditions during the EMBRYOCASE procedure.

f. Information about the expected benefits of the clinical trial

The benefits of using the EMBRYOPASS applicator and the EMBRYOCASE case in the embryo transfer procedure are, first of all, the possibility of standardizing the procedure, which may lead to an increase in the percentage of pregnancies and implantations obtained as a result of the assisted reproduction procedure. These benefits are possible to achieve through the use of the EMBRYOPASS applicator because:

- **The negative impact of factors affecting embryos during transfer** to the uterine cavity has been eliminated thanks to:
  a. constant, optimal rate of embryo uptake into the catheter,
  b. a constant, optimal volume of charge taken into the catheter,
  c. constant, optimal rate of embryo injection from the catheter into the uterine cavity,
  d. determining and programming the optimal duration of embryo injection from the transfer catheter into the uterine cavity,
- **the negative impact of the human factor on the quality of the embryo transfer procedure into the** uterine cavity has been eliminated by eliminating pressure spikes in the catheter (the pressure force on the plunger is constant) both during the collection of the load into the catheter and during injection into the uterine cavity,
- **The safety of the embryo transfer procedure** into the uterine cavity has been increased by:
  a. introduction of a catheter occlusion detection system,
  b. Eliminating the possibility of retracting the plunger and pulling the embryo back into the catheter, during or after its injection into the uterus.

Introduction to the Embryo Transfer procedure of the EMBRYOCASE will allow you to

- **eliminate the negative impact of environmental factors affecting the embryo** placed in the transfer catheter outside the incubator during the peritransfer time (associated with a sharp drop in temperature).

The market of products dedicated to assisted reproduction techniques lacks electronic devices to standardize the embryo transfer procedure. On the other hand, the interest in this topic indicates a high awareness of the importance of the embryo transfer procedure into the uterine cavity in the community of researchers involved in the treatment of infertility. If the effectiveness of the EMBRYOPASS, EMBRYOCASE and

TL(AI)/ EMBRYOPASS/ EMBRYOCASE protocol is supported by an increase in the rate of pregnancies during the embryo transfer procedure to the uterus, it will be a significant breakthrough in this field. The protocol for standardizing embryo transfer conditions, which the nOvum Clinic would like to implement, containing two inventions that eliminate the influence of external factors (human, environmental) on the success of the ET procedure, significantly exceeds the procedure used so far. It will improve and increase the efficiency of the embryo transfer procedure used so far in everyday practice, which will be measured by the estimated percentage of pregnancies, as well as fill the existing gap in this area. This will bring great benefits to patients, shortening the time to pregnancy and will increase the safety of the embryo transfer procedure by optimizing the conditions to which embryos are subjected during the procedure.
Both EMBRYOPASS, EMBRYOCASE and the innovative protocol for standardizing the embryo transfer procedure Time-Lapse (AI)/ EMBRYOPASS/ EMBRYOCASE are solutions that have not yet been introduced on the market in Poland and abroad. An analysis of the range of products and services offered to patients by competing centres through the presented websites indicates that there are no service providers, manufacturers or entities in the country that use such a solution in clinical practice.

g. Information on available alternative treatments and related procedures, as well as the benefits and risks of their use

An alternative method to the embryo transfer procedure using the EMBRYOPASS applicator and the EMBRYOCASE case is the manual method of performing the transfer, routinely used in the center. This method will be used to perform procedures in the control group. A detailed description of this method is given in point a.

h. Information about compensation or treatment for a clinical trial participant in the event of harm incurred in connection with participation in a clinical trial

Insurance

If the Patient suffers any damage as a result of taking part in a treatment experiment related to the procedures used during the treatment, you are entitled to compensation in accordance with the provisions of Polish law. In accordance with the Regulation of the Minister of Finance, Funds and Policy of 23 December 2020 on mandatory civil

liability insurance for medical experiments (Journal of Laws of 2020, item 2412), the study was insured by:

Sopot Insurance Companies ERGO Hestia SA

ul. Hestii 1, 81-731 Sopot, KRS: 0000024812

Policy number: 436000368342

a. Information about the payment method (if any) for the study participant

Participation in the study is free of charge for you (patients do not incur any additional costs related to participation in the study). During the examination, you will incur the standard costs associated with the preparation and commencement of the embryo transfer procedure of a thawed embryo (cryotransfer) at the nOvum Medical Clinic – including the costs of visits and ordered tests and procedures.

b. Information about the anticipated expenses that a clinical trial participant may incur in connection with participation in the study

Participation in the study does not incur any additional costs for the patient beyond those that the patient would incur if undergoing a routine embryo transfer procedure at the nOvum clinic.

c. Information on the principles of voluntary participation and the possibility of refusing and withdrawing the participant from the clinical trial at any time without harm to himself or loss of benefits to which the participant is otherwise entitled

Informed consent of patients to participate in the study

The decision to participate in the study is voluntary and belongs entirely to the Patient **and her husband/partner.** If you decide to participate in the study, you will be asked to sign an informed consent form in the presence of the investigator before proceeding with any medical procedures, after obtaining all information about the clinical trial from the investigator, both the patient and her husband/partner. Each of you will receive an original, self-signed informed consent form with the following guide: "INFORMED CONSENT FORM - PATIENT" (attachment no. 1) and "INFORMED CONSENT FORM – PATIENT" (attachment no. 2). The informed consent document will include the

patient's identification number in the clinical trial (the so-called screening number) – the next number from EEZ4412_001 to EEZ4412_200.

The "Informed Consent Form" must be signed by the Patient in duplicate. Each copy will bear the signature of the patient and the researcher, respectively. One copy of each of the consents will remain in the documentation of the examination at the nOvum Medical Clinic, the next will be handed over to the patient and her partner, respectively. From the moment of signing the informed consent until the end of the patient's participation in the clinical trial, all information about the patient covered by the subject of the study will be collected in the form of paper medical documentation, in electronic form in the electronic database of the nOvum Medical Clinic "bmedica2" and the database dedicated to clinical trials – eCRF.

Refusal to participate or withdrawal of consent to participate in the study

You may refuse to participate in the study, but once you have agreed to participate in the study, you may withdraw from the study at any time, for any reason, without any penalty or loss of other benefits to your entitlement. If you do not wish to participate in this study or withdraw from it at a later date, it will not affect your healthcare or relationship with your doctor.

The withdrawal of consent must be made in writing in the presence of the attending physician. The form of withdrawal of consent to participate in the study is attached as Appendix No. 5 to this guide. After the withdrawal of consent by the patient, no additional treatment data will be collected, but any medical data collected until the withdrawal of consent may be analysed, used for statistical purposes, scientific publications, etc.

Below you will find relevant information on:

l. **the need to give written consent to make source documents concerning the participant in the clinical trial available to entities authorized to carry out monitoring, auditing, inspection of clinical trials;**

m. **the need to consent to the investigator's access to the clinical trial participant's medical records created before the start of the clinical trial and the need to consent to the processing of the study participant's personal data related to his/her participation in the clinical trial;**

n. **maintaining the confidentiality of this part of the clinical trial documentation, and excluding personal data from the possible publication of the results of the clinical trial;**

Confidentiality, protection and authorized use of personal data

The administrator of your personal data is Przychodnia Lekarska nOvum Katarzyna Kozioł, Piotr Lewandowski sp. komandytowa, 13 Bociania Street, 02-807 Warsaw.

The Data Protection Officer at the nOvum Medical Clinic is Marzena Secomska, who you can contact by e-mail iod@novum.com.pl or by phone at: +48 22 566 80 00 ext. 129.

The processing of your personal data is carried out on the basis of Article 6(1)(a) and Article 9(2)(a) of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (GDPR) and on the basis of the provisions of applicable law.

You have the right to access the data, rectify and supplement it, request restriction of processing, object to processing, transfer – in cases specified by the provisions of the GDPR and the right to lodge a complaint with the President of the Personal Data Protection Office. Full information on data processing can be found in the Privacy Policy available at the Treatment Room, in the Clinic Registration and on the **website of the www.novum.com.pl**

The data collected about you and your child/children will be used anonymously in accordance with the purpose of this survey. The data collected and stored in a dedicated database in electronic form (eCRF) without the possibility of identification by name or date of birth. The data will be identified only by the number of the patient in the study.

Investigators will have a list assigning the patient's number in the study to your personal information. Legal authorities, study site personnel, representatives or authorized persons may have access to the registry and have access to your medical data in accordance with their authorization. This is necessary due to the control of the correctness of the survey and the accuracy of the information. Persons who have access to the data are obliged to comply with the principle of confidentiality during and after the completion of this study.

Once the test is complete, your data will be archived by the nOvum Medical Clinic, in accordance with the current rules and regulations. The medical records will remain in the archive for 90 years. The data used in the described study will be classified and it will not be possible to directly identify you. The results of the study may be presented at scientific conferences or in publications, but your identity will not be disclosed. This study will be conducted solely by collecting and using your medical information. National and international data protection regulations guarantee you the right to control how your medical information is used. Therefore, by signing the Informed Consent to Participate in the Study Form, you authorize the review, transfer, and processing of your medical information in the following ways:

- authorized persons will be able to review your medical information thanks to direct access to the documentation and databases of the nOvum Medical Clinic, this applies to the medical records of the clinical trial participant created during and before the start of the clinical trial;
- Study data, including your medical information, and information about any medical specimens may be processed, which means that it will be collected, entered, without being identified, into computer databases, verified, analyzed, printed and reported as necessary for legitimate scientific purposes.
- The survey data may be transferred to other countries for processing. This also applies to countries with a different level of legislation on the protection of personal data; However, confidentiality is guaranteed.

If you do not agree with the data processing activities, you have the right to lodge a complaint with the competent supervisory authority:

General Inspector for Personal Data Protection, 2 Stawki Street, 00-193 Warsaw.

For further information on your rights as a study participant or in the event of a study-related injury, study participants and their legal representatives can contact the Office of the **Patient Rights Ombudsman at the Ministry of Health, 46 Młynarska Street, 01-171 Warsaw** or by calling the free helpline **of the Patient Rights Ombudsman, tel. +48 800 190 590.**

o. Ensuring that any new data on the clinical trial that may affect the will to continue to participate is promptly communicated to the clinical trial participant or his/her statutory representative;

We would also like to ensure that during the course of a clinical trial, any new information that may affect your decision to continue participating, such as the emergence of relevant data regarding safety, efficacy of treatment, or other factors that may change the perception of the study, will be promptly communicated to study participants or statutory representatives.

p. Contact a person who can be contacted for additional information about the clinical trial, the rights of the participants in the clinical trial and to report any damages incurred in connection with participation in the clinical trial;

The person who can be contacted in order to obtain additional information about the clinical trial, the rights of clinical trial participants and to report any damages incurred in connection with participation in a clinical trial is the **Principal Investigator Dr Katarzyna Kozioł tel.: +48 22 566 80 00**

q. Information about the foreseeable circumstances and reasons why participation in the clinical trial could be discontinued;

Discontinuation

During the study, it may happen that for your safety and for the safety of the study, the treating physician will withdraw you from the study.

Your doctor will then present you with further options for medical care.

During the clinical trial, the patient may be excluded from participation in the study by the investigator due to:

- failure to meet the inclusion or exclusion criteria at each stage of the study;
- an adverse event AE/SAE that, in the opinion of the investigator, prevents the patient from further participation in the study,
- withdrawal of consent by one or both partners,
- a material breach of the protocol – failure to comply with the rules of the protocol, as a result of which the test results could be falsified,
- inability to contact the patient.

In addition, the entire study may be terminated at any time by the nOvum Medical Clinic, the Bioethics Committee or any other supervisory authority for safety or other reasons.

The Centre may decide to discontinue the examination in the event of:

1. Patient safety issues:
   a. the occurrence of unexpected, serious side effects that outweigh the benefit of the treatment,
   b. unacceptable risks, e.g. the discovery of new information that suggests that the risks associated with the therapy outweigh the potential benefits.
2. Lack of treatment efficacy:
   a. periodic analyses will show that the subject of the study is not effective in achieving the assumed goals,
   b. The data will indicate that the continuation of the study will not bring positive clinical results.
3. Violations of ethical principles.
4. Organizational or financial problems:
   a. lack of sufficient financial resources to continue the study,
   b. too low a level of recruitment of participants, which makes it impossible to obtain representative data.

r. Information about the time of participation of a participant in this study

The study is scheduled to start on 01.01.2025 and end on 31.12.2026. If it is necessary to extend the duration of the study, the research center will apply to the Bioethics Committee for approval.

s. Information about the expected number of participants in a clinical trial

The study will involve patients whose embryos have been created and subjected to cryopreservation at the nOvum Medical Clinic. Patients will be informed about the possibility of taking part in the study by the attending physician and, additionally, in the form of an internal announcement, leaflets, website and Social Media of the nOvum Clinic. The study population will consist of patients aged ≥18 to ≤38 years who have undergone a controlled ovarian stimulation and puncture procedure, and then the collected oocytes have been fertilized by IVF or ICSI. The embryos were cultured in a Time-Lapse incubator, the embryos were evaluated by an embryologist and an Artificial Intelligence system, and then all were cryopreserved according to the highest rating made by the AI. Patients preparing for their first cryotransfer (or the next one if the first one was successful) will be invited to participate in the study.

The total planned number of randomized patients is 160. Due to the risk of not being qualified for transfer on the 5th day after ovulation for various reasons (lack of a good quality embryo, lack of adequate endometrial width or other important causes in the investigator's assessment in all patients), it is estimated that the percentage of the so-called "screen failure", i.e. patients who do not meet the criteria for inclusion in the study on the day of randomization, will be about 20%, Therefore, the assumed number of patients who will undergo screening is 200. In addition, it is estimated that about 1% of patients will lose contact with the center, as a result of which it will not obtain complete data.

Attachments:

1. Informed consent – Patient (her)
2. Informed consent – Patient (him)
3. Study design.
4. A survey for patients on the course of pregnancy and childbirth.
5. Withdrawal of consent to participate in a clinical trial.

Thank you very much for reading the above guide.

INFORMED CONSENT FORM – PATIENT (her)

Study title:	**"Standardization of variable conditions of embryo transfer into the uterine cavity in the procedure of medically assisted procreation in humans"**
Subtitle:	EMBRYOPASS/ EMBRYOCASE A randomized, prospective, single-center, controlled, single-blind study evaluating the impact of standardization of variable conditions of embryo transfer into the uterine cavity in medically assisted procreation in humans on the effectiveness of the procedure, by using: standardization of culture conditions and selection of embryo for transfer through the use of an incubator with a time-lapse observation system and artificial intelligence (Artificial Intelligence), the Embryopass applicator - an electronically controlled device for controlled transfer, and the Embryocase case maintaining optimal environmental conditions for the embryo outside the incubator during the peritransfer time. **ACRONYM: EFECT**
Attending physician:	Katarzyna Kozioł, MD, specialist in gynecology and obstetrics of the second degree, EGiR specialist, senior clinical embryologist of ESHRE, clinical embryologist of PTMRiE PWZ no. 6475994
Research Center:	Clinic "nOvum" 13 Bociania Street, Warsaw, Poland
	The therapeutic experiment received a positive opinion from the competent Bioethics Committee, in accordance with the requirements of national law

Patient number .....

Yes, ...

(name and surname of the patient – written in capital letters)

I give my informed consent to take part in the study and declare that I have read the content of the "Patient Guide" concerning this study. I received all explanations about the nature and purpose of the study and the foreseeable effects and risk factors associated with it. I had enough time to decide and was given the opportunity to ask questions about the study and its course. I was given satisfactory answers to all my questions.
I am aware that my participation in the study is voluntary and that signing this consent is a prerequisite for taking part in the study. I also understand that I can withdraw from the study at any time, without giving reasons and without affecting the medical care provided to me.

I agree/do not agree* to be contacted by me and my husband/partner after childbirth to obtain information about the course of pregnancy, childbirth and the health condition of my child/children. At the same time, I agree to the use and sharing of child/children's documentation and information on the child/children's health in connection with the observation within this study, as specified in the "Patient Guide".

I declare that I have been clearly informed about the insurance cover and the related obligations – I have been informed that the research center is covered by mandatory civil liability insurance related to the conduct of this study. I can get the terms of insurance at any time at my request. I agree to the terms and conditions of insurance.

I hereby voluntarily agree to participate in the study.

Patient's signature ..... **Date.....**

(legible, handwritten signature) (dd/mm/yyyy)

*delete unnecessary

CONSENT TO THE PROCESSING OF PERSONAL DATA

I consent to the processing of my personal data by the nOvum Clinic for the purpose of conducting the examination, including sensitive data – pursuant to Article 6(1)(a) and Article 9(2)(a) of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (GDPR) and on the basis of the provisions of applicable law. I declare that I have been informed of all my rights, including the right to withdraw this consent.

I understand that my personal data will be processed in accordance with the provisions of the "Patient Guide". I hereby consent to access my personal and medical data generated and stored both before and during the study by authorized representatives of the research center and the competent supervisory authorities (entities authorized to monitor, audit and inspect clinical trials), obliged to maintain professional secrecy. This applies to my medical documentation to the extent necessary to verify the correctness of the examination. To this end, I exempt researchers from the obligation to maintain secrecy.

I agree/do not agree* for my primary care physician to be notified of my participation in the study.

Doctor's name: .....

(do not fill in if the Patient does not agree)

I agree / do not agree* to the collection of data on my health condition from doctors who do not work at the center conducting the study to the extent necessary for the proper course and monitoring of the study. To this end, I release these doctors from the obligation of secrecy.

Patient's signature ..... **Date.....**

(legible, handwritten signature) (dd/mm/yyyy)

The interview with the Patient was conducted by: .....

(name of the investigator/treating physician)

I, the undersigned, have provided the Patient with detailed information regarding the above study in a complete and diligent manner and confirm that, to the best of my knowledge, the Patient fully understands the nature, objectives and benefits of the study and is aware of its consequences, risks and possible inconveniences associated with participation in the study.

I handed the Patient an original copy of the "Patient Guide" and the "Informed Consent Form".

Signature of the researcher ..... Date.....

(legible, handwritten signature) (dd-mm-yyyy)

*delete unnecessary

Signed documents – "Patient Guide" and "Informed Consent Form – Patient" should be fastened. The original should be given to the patient.

INFORMED CONSENT FORM - PATIENT

Study title:	**"Standardization of variable conditions of embryo transfer into the uterine cavity in the procedure of medically assisted procreation in humans"**
Subtitle:	EMBRYOPASS/ EMBRYOCASE A randomized, prospective, single-center, controlled, single-blind study evaluating the impact of standardization of variable conditions of embryo transfer into the uterine cavity in medically assisted procreation in humans on the effectiveness of the procedure, by using: standardization of culture conditions and selection of embryo for transfer through the use of an incubator with a time-lapse observation system and artificial intelligence (Artificial Intelligence), the EMBRYOPASS applicator - an electronically controlled device for controlled transfer, and the EMBRYOCASE case maintaining optimal environmental conditions for the embryo outside the incubator during the peri-transfer time. **ACRONYM: EFECT**
Attending physician:	Katarzyna Kozioł, MD, specialist in gynecology and obstetrics of the second degree, EGiR specialist, senior clinical embryologist of ESHRE, clinical embryologist of PTMRiE PWZ no. 6475994
Research Center:	Clinic "nOvum" 13 Bociania Street, Warsaw, Poland
	The therapeutic experiment received a positive opinion from the competent Bioethics Committee, in accordance with the requirements of national law

Patient number .....

Yes, ...
(name and surname of the Patient – written in capital letters)

I give my informed consent to take part in the study and declare that I have read the content of the "Patient Guide" concerning this study. I have received all explanations regarding the nature and purpose of the study and the foreseeable effects and risk factors associated with it. I had enough time to decide and was given the opportunity to ask questions about the study and its course. I was given satisfactory answers to all my questions.
I am aware that my participation in the study is voluntary and that signing this consent is a prerequisite for taking part in the study. I also understand that I can withdraw from the study at any time, without giving reasons and without affecting the medical care provided to me.

I agree / do not agree* to be contacted by my wife/partner after childbirth to obtain information about the course of pregnancy, childbirth and the health condition of my child/children. At the same time, I agree with the use and sharing of child/children's documentation and information on the child/children's health in connection with the observation within this study, as specified in the "Patient Guide".

I declare that I have been comprehensively informed about the insurance cover and the related obligations – I have been informed that the research center is covered by mandatory civil liability insurance related to the conduct of this study. I can get the terms of insurance at any time at my request. I agree with the terms and conditions of insurance.

I hereby voluntarily agree to participate in the study.

Patient's signature ..... **Date.....**
(legible, handwritten signature) (dd/mm/yyyy)

*delete unnecessary

CONSENT TO THE PROCESSING OF PERSONAL DATA

I consent to the processing of my personal data by the nOvum Clinic for the purpose of conducting the examination, including sensitive data – pursuant to Article 6(1)(a) and Article 9(2)(a) of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (GDPR) and on the basis of the provisions of the applicable law. I declare that I have been informed of all my rights, including the right to withdraw this consent

I understand that my personal data will be processed in accordance with the provisions of the "Patient Guide". I hereby consent to access my personal and medical data generated and stored both before and during the study by authorized representatives of the research center and the competent supervisory authorities (entities authorized to monitor, audit and inspect clinical trials), obliged to maintain professional secrecy. This applies to my medical documentation to the extent necessary to verify the correctness of the examination. To this end, I exempt researchers from the obligation to maintain secrecy.

I agree/do not agree* to the collection of data on my health condition from physicians who do not work at the center conducting the study to the extent necessary for the proper conduct and monitoring of the study. To this end, I release these doctors from the obligation of secrecy.

Patient's signature ..... **Date.....**

(legible, handwritten signature) (dd/mm/yyyy)

The interview with the Patient was conducted by:

.....

(name of the investigator/treating physician)

I, the undersigned, have provided the Patient with detailed information regarding the above study in a complete and diligent manner and confirm that, to the best of my knowledge, the Patient fully understands the nature, objectives and benefits of the study and is aware of its consequences, risks and possible inconveniences associated with participation in the study.

I handed the Patient an original copy of the "Patient Guide" and the "Informed Consent Form".

Signature of the researcher ..... Date.....

(legible, handwritten signature) (dd/mm/yyyy)

**delete unnecessary*

Signed documents – "Patient Guide" and "Informed Consent Form – Patient" should be fastened. The original should be given to the patient.

Appendix No. 4

Questionnaire for patients on the course of pregnancy and childbirth.

Madam!

Please complete this survey and send it to the nOvum clinic by post or electronically. **If you have been pregnant with multiple pregnancies, you should fill out a separate questionnaire for each of the children.** We will be grateful if you attach a photocopy or scan of the necessary documents to the survey:

1. The so-called genetic ultrasound performed around the 12th week of pregnancy
2. Ultrasound from the third trimester of pregnancy
3. Results of prenatal tests, if performed
4. Hospital discharge of the baby after birth

PATIENT'S NAME		
CHILD NO. (MARK IN CASE OF MULTIPLE PREGNANCIES)	***CHILD 1*** ○	***CHILD 2*** ○
DATE OF BIRTH/MISCARRIAGE dd/mm/rrrr		
WAS THE BABY BORN ALIVE?	○ *YES* ○ *NO* ***If so, please fill in below***	○ *YES* ○ *NO* ***If so, please fill in below***
CHILDBIRTH	○ *NATURAL* ○ *USING A VACUUM (VACCUM)* ○ *FORCEPS BIRTH* ○ *CAESAREAN SECTION*	○ *NATURAL* ○ *USING A VACUUM (VACCUM)* ○ *FORCEPS BIRTH* ○ *CAESAREAN SECTION*
POSITIONING THE BABY	○ *HEADGEAR* ○ *BUTTOCKS* ○ *TRANSVERSE* ○ *OTHER(WHAT?)* ……	○ *HEADGEAR* ○ *BUTTOCKS* ○ *TRANSVERSE* *OTHER (WHAT?)* ……
GENDER	○ *BOY* ○ *GIRL*	○ *BOY* ○ *GIRL*
BABY WEIGHT		
LENGTH IN CM		
APGAR SCORING AFTER 1 MINUTE		
APGAR SCORE AT 5 MINUTES		
APGAR SCORE AT 10 MINUTES		

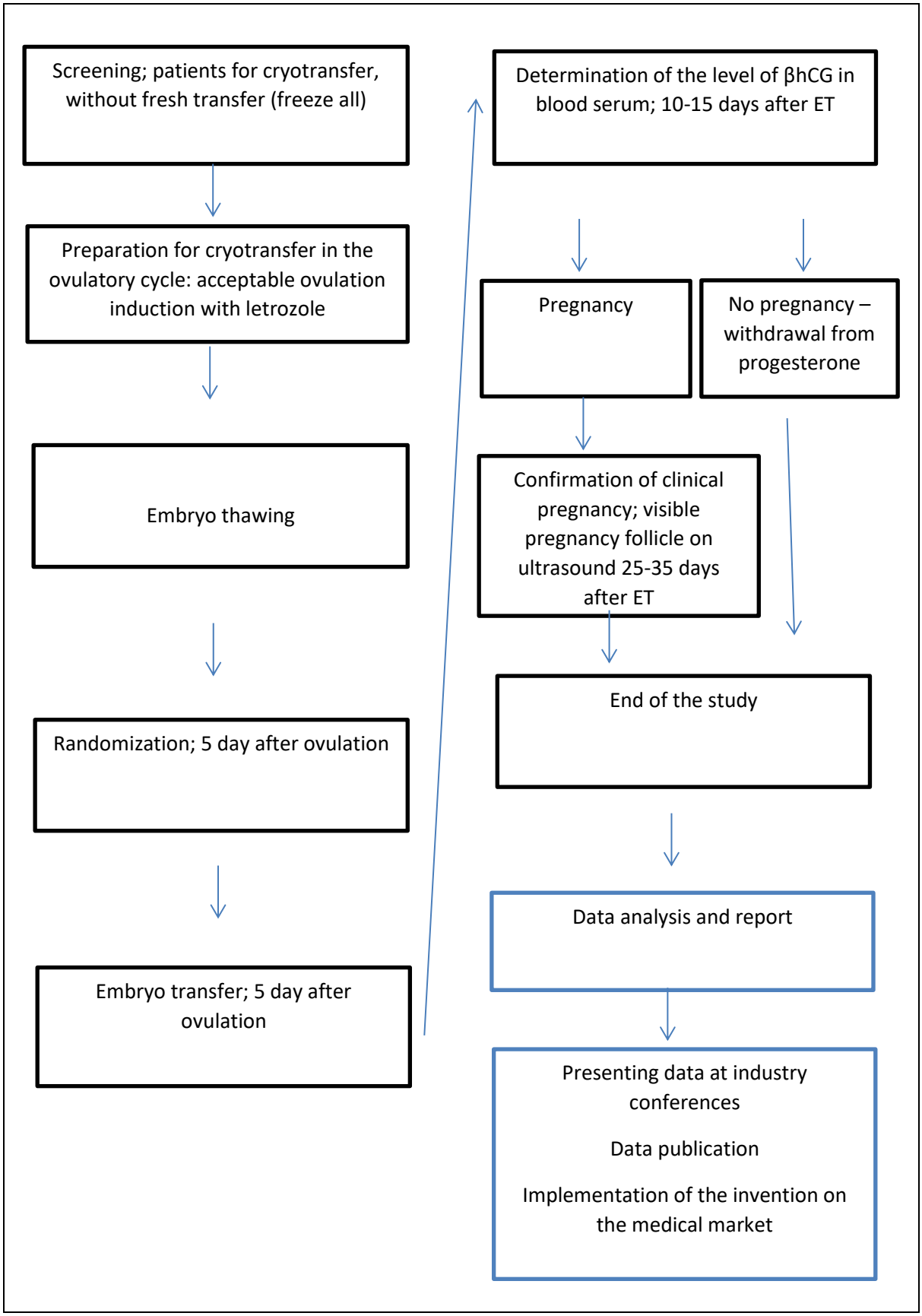
WAS THE CHILD HOSPITALIZED IN THE NEONATAL INTENSIVE CARE UNIT?	○ *YES* ○ *NO*	○ *YES* ○ *NO*
DID THE BABY DIE AT BIRTH?	○ *YES* ○ *NO* *IF SO, IS THE CAUSE KNOWN?* ○ *YES.....* ○ *NO*	○ *YES* ○ *NO* *IF SO, IS THE CAUSE KNOWN?* ○ *YES.....* ○ *NO*
DID YOU PERFORM PRENATAL TESTS DURING PREGNANCY?	○ *YES* ○ *NO* ***If so, please fill in below***	
TEST DATE		
CHORIONIC BIOPSY	○ *YES* ○ *NO* *IF SO, WHAT WAS THE RESULT? PLEASE DESCRIBE AND ATTACH DOCUMENTATION.....* *.....* *.....*	
AMNIOCENTESIS	○ *YES* ○ *NO* *IF SO, WHAT WAS THE RESULT? PLEASE DESCRIBE AND ATTACH DOCUMENTATION.....* *.....* *.....* ○	
INNE (NP. TEST PAPPA)	○ *YES* ○ *NO* *IF SO, WHAT WAS THE RESULT? PLEASE DESCRIBE AND ATTACH DOCUMENTATION.....* *.....* *.....*	
DID YOU PERFORM AN ULTRASOUND IN THE THIRD TRIMESTER OF PREGNANCY?	○ *YES* ○ *NO* ***If so, please fill in below***	
ULTRASOUND DATA FROM THE THIRD TRIMESTER		
NUMBER OF FETUSES		
NUMBER OF FETUSES WITH A HEARTBEAT		
HAVE FOETAL DEFECTS BEEN FOUND?	○ *YES.....* ○ *NO*	○ *YES.....* ○ *NO*

	IF SO, WHAT ARE THEY? PLEASE DESCRIBE AND ATTACH THE RELEVANT DOCUMENTATION *……..* *……..*	*IF SO, WHAT ARE THEY? PLEASE DESCRIBE AND ATTACH THE RELEVANT DOCUMENTATION* *……..* *……..*

IN THE CASE OF A MULTIPLE PREGNANCY, PLEASE INDICATE WHETHER IT WAS A PREGNANCY:			
MONOAMNIOTIC /MONOCHORIONIC	*BIAMNIOTIC /MONOCHORIONIC*	*BIAMNIOTIC /CHORIONIC*	*I DO NOT KNOW*

HAVE YOU PERFORMED THE SO-CALLED GENETIC ULTRASOUND?	○ YES ○ NO ***If so, please fill in below***
TEST DATE	
NUMBER OF FETUSES	
NUMBER OF FETUSES WITH A HEARTBEAT	
HAVE FOETAL DEFECTS BEEN FOUND?	○ YES ○ NO IF SO, PLEASE DESCRIBE AND ATTACH YOUR MEDICAL DOCUMENTATION…… …… ……
WERE THERE ANY COMPLICATIONS DURING PREGNANCY OR CHILDBIRTH?	○ YES ○ NO IF SO, PLEASE DESCRIBE AND ATTACH YOUR MEDICAL DOCUMENTATION…… …… ……
WERE YOU EXPOSED TO HARMFUL FACTORS THAT COULD CAUSE DEFECTS IN THE BABY DURING PREGNANCY?	○ YES ○ NO IF SO, PLEASE INFORM US WHAT THESE FACTORS WERE (E.G. X-RAYS, CHEMICAL AGENTS, SMOKING, INFECTIONS) …… ……

Appendix 3 – Study Design



Appendix No. 5

WITHDRAWAL OF CONSENT TO PARTICIPATE IN A CLINICAL TRIAL

Study title:	"Standardization of variable conditions of embryo transfer into the uterine cavity in the procedure of medically assisted procreation in humans"
Subtitle:	EMBRYO PASSPORT/ EMBRYOCASE A randomized, prospective, single-center, controlled, single-blind study to evaluate the impact of standardization of variable embryo transfer conditions in a medically assisted procreation procedure in humans on the effectiveness of the procedure, by using: standardization of culture conditions and selection of embryo for transfer through the use of an incubator with a time-lapse observation system and artificial intelligence, an Embryopass applicator - electronically controlled device for controlled transfer, and the Embryocase case maintaining optimal environmental conditions for the embryo outside the incubator during the peri-transfer time.
Principal investigator:	Katarzyna Kozioł, MD, specialist in gynecology and obstetrics of the second degree, EGiR specialist, senior clinical embryologist of ESHRE, clinical embryologist of PTMRiE PWZ no. 6475994
Research Center:	Clinic "nOvum" 13 Bociania Street, Warsaw, Poland

.....

(name and surname of the Patient – written in capital letters)

I withdraw my informed consent from (date)..... to participate in this study. At the same time, I declare that I am aware that therefore the embryo transfer procedure will be performed in accordance with the standard method used in the nOvum Medical Clinic (manually).

Signature of the patient ..... **Date.....**

(legible, handwritten signature) (dd-mm-yyyy)