



Hospital Data Imprint/Stamp

Extra-Corporeal Fertilisation Treatment

(In-vitro Fertilisation, IVF;
Intracytoplasmatic Sperm Injection, ICSI)

Patient identification sticker

Dear Husband and Wife,

Our preliminary discussions and analysis of the findings have revealed that fertilisation outside of the body (**extra-corporeal fertilisation, "artificial fertilisation"**) has good prospects in your case. The purpose of this informed consent form is to help you prepare for the patient-doctor discussion. Please read it carefully before the discussion and complete the questionnaire carefully and completely.

Assumption of costs

German legislature stipulates in which cases and to which extent the public health insurance providers may assume the costs for artificial fertilisation. Your doctor will inform you about the currently applicable provisions. Please clarify the assumption of costs with your health insurance provider (Krankenkasse), submitting the treatment plan we have prepared for you, **before the start of the treatment.**

The treatment cycle

1. Stimulation of egg cell maturation

The chances to harvest several ripe egg cells are increased if the ovaries are stimulated with hormones. The hormones are injected subcutaneously (under the skin) or in the muscles; in an occasional case, they are taken orally, possibly in addition. Most women inject themselves with the hormones according to the doctor's instructions.

Usually, the stimulation stage takes 8–16 days. In the meantime, we monitor the growth of the follicles containing the egg cells, extrapolating on the maturity of the egg cells from them.

In order to prevent uncontrolled ovulation or, in an occasional case, in order to regulate the menstrual cycle, other hormones (GnRH analogues) are frequently administered in the pe-cycle or treatment cycle in addition. They are injected or administered as a nasal spray,

and in an occasional case, they are combined with hormone pills.

32 to 36 hours prior to the planned harvest of egg cells, a hormone injection triggers the last meiosis of the egg cells.

2. Harvesting of eggs

The procedure is performed under short general anaesthesia in most cases; you will be informed about the anaesthetic procedures and the risks associated with them in a separate counselling discussion. Under ultrasound visualisation, a puncture needle is inserted into the abdominal cavity through the vagina. The ovaries are punctured one after the other to suction off the fluid and the egg cells contained therein from the follicles. Only in a few special cases, laparoscopy is required instead; if this applies in your case, you will be informed about it in a separate counselling discussion.

3. Combination of egg and sperm cells

IVF (in-vitro fertilisation):

Egg cells and sperms which are usually harvested and processed on the same day are incubated in a nutrient solution at body temperature. IVF is the recommended procedure in case of disorders of fallopian tube function, endometriosis, reduced fertility of the male, certain disorders of the immune system or in certain cases of inexplicable disorders of fertility.

– ICSI (intracytoplasmic sperm injection):

Under microscopic visualisation, a single, specifically prepared sperm is injected directly into one egg cell respectively. ICSI is the recommended procedure if only few sperms are present in the semen, if the sperms are not agile enough or have a very peculiar appearance or if fertilisation had not been achieved in a previous IVF cycle. Frozen egg cells (egg cell reserve) must also be fertilised in this manner for fertilisation treatment.

On the next day, it is checked which sperms have penetrated an egg cell and whether both nuclei are preparing to merge (pronucleus stage). The merger of the two nuclei is the actual fertilisation. At the merger of the two nuclei, fertilisation is complete, and the product is now referred to as an embryo. The fertilised egg cell proliferates and is called an embryo as of that moment.

4. Transfer to the uterus

– Embryo transfer:

Generally, the embryos are transferred to the woman's uterus 2–3 days after harvesting the egg cells, using a thin catheter.

- **Blastocyte transfer:** If the embryos are allowed to grow for 5–6 days in the nutrient solution, growth can be observed. The hope is identifying those embryos developing regularly and having the best capability of implanting (blastocytes). Only those are transferred to the uterus, so the risk of multiples is not too high. However, on the other hand, there is the risk that the embryos do no longer develop properly in the culture for a longer time. Therefore, the chances of pregnancy are increased by blastocyte transfer in isolated cases only. How many egg cells should be kept in the nutrient solution to achieve the desired number of blastocytes capable of development after 5–6 days must be determined individually in consultation with you (see legal restrictions).

If several embryos are transferred, the chances of a pregnancy may increase but so is the probability of a risky multiple pregnancy, in particular if blastocytes are transplanted.

5. Monitoring of success

Approx. 14 days after the transfer, a pregnancy test is performed with a blood sample. Implanting of the embryo in the uterus is usually supported by administration of hormones (progesterone, hCG).

If pregnancy has not occurred, it depends on your wishes and your physical condition if and when a subsequent treatment cycle can be performed.

We are recommending extra-corporeal fertilisation only if other, simpler methods (e.g. exclusive stimulation of ovaries and/or insemination treatment) do not offer sufficient chances of success.

Additional measures in the laboratory

Repeated unsuccessful treatment cycles or certain genetic combinations can necessitate the following additional measures in isolated cases:

- **Assisted hatching** which involved scoring the egg cell's skin with a special laser. Assisted hatching is a procedure intended to support implanting of the embryo in the uterus after in-vitro fertilisation or ICSI.
- **Polar body diagnostics (PBD)** which can identify a number of genetic defects of the egg cells. If PBD is recommended in your case, your doctor will inform you about it in detail.

Legal restrictions

Since triple pregnancies in particular are a significant medical problem and can take a great toll on the parents, the transfer is limited to two embryos per cycle in Germany as a rule. The recommendation on the number of embryos for which cultivation is continued and which are then transferred as an exception depends on the reaction of the ovaries, the number of egg cells in the pronucleus stage, the age of the woman and the course of previous treatment cycles. Transfer of more than three embryos is prohibited.

Several egg cells in the pronucleus stage may only be continued to be cultivated with the single purpose that at the end of the cultivation, usually after 5–6 days, there is just the number of regularly developed embryos intended for embryo transfer (“German compromise”). If this is recommended due to **your individual circumstances** (e.g. age, reaction of ovaries, number of harvested and developing egg cells, course and results of previous cycles), it will be discussed with you in detail.

Creating an “embryo supply” or purposeful selection of a single embryo out of several which is to be transferred (“elective single embryo transfer”) is **prohibited** by the German law on embryo protection.

If, contrary to expectations, more cells in the pronucleus stage or embryos are present than intended for transfer (in particular in the blastocyte culture), you have to decide what should happen with the excess eggs. According to the legal provisions, they must either be destroyed immediately, or they can be deep-frozen and stored (cryopreservation) so that they can be unfrozen, cultivated further and transferred in a later cycle. You will be informed about this in a separate discussion.

Are there any risks to be expected?

Despite the greatest care taken, complications can arise, which can even become life-threatening under certain circumstances and necessitate additional treatment or further

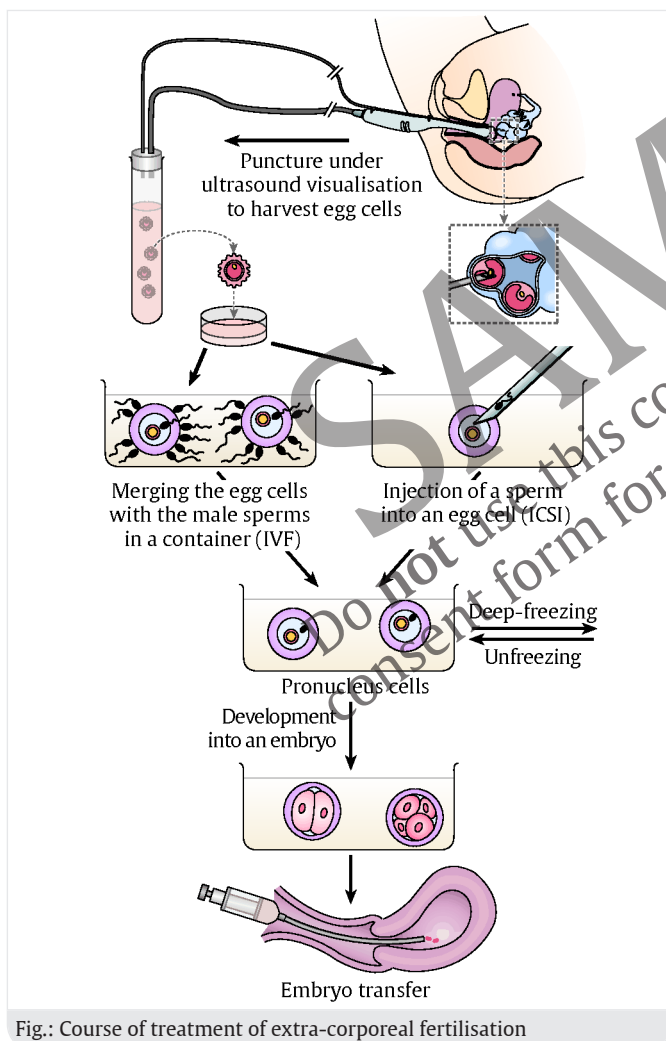


Fig.: Course of treatment of extra-corporeal fertilisation

surgery. The frequency rates are only a general estimate and are intended for weighing the risks against each other. They are not the same as the definitions of side-effects stated in the package inserts of medications. Pre-existing/Underlying diseases and individual unusual circumstances can significantly influence the rate of complications.

- In an occasional case, **indigestion, a feeling of tension in the chest, a headache, hot flashes, a painful tugging sensation in the lower abdomen, ovarian cysts or vision disorders** (e.g. blurry vision, visual snow) can be caused by the administered medications. These side-effects resolve by themselves after stopping the medication.
- **Hyperstimulation syndrome:** The treatment with **hormones stimulating the ovaries** can cause **excessive reaction of the ovaries**. This results in very many follicles maturing at once. The ovaries can **significantly increase in size, and tissue secretion can accumulate in the abdominal cavity**, in rare cases also in the **pleural gap above the lungs and/or in the pericardium**. This can cause a **sensation of being full, abdominal pain, nausea and respiratory distress (difficulty breathing)**. Discharge of fluid from the blood vessels causes the **blood to thicken**, therefore increasing the risk of formation of blood clots (**thrombosis**) which can possibly migrate into the blood stream and block a blood vessel (e.g. **pulmonary embolism, stroke, cardiac infarct, leg vein thromboses**). Such a hyperstimulation syndrome can **become life-threatening in an extreme case!** Frequently, blood-thinning medications are given as prophylaxis or if treatment is required. However, they all increase the risk of bleeding. The active substance heparin can also cause a life-threatening formation of blood clots in rare cases. In an isolated case, an ovary enlarged for this reason can turn around its anchorage (e.g. **stem rotation**). This causes severe abdominal pain. In most cases, it necessitates an emergency operation by means of laparoscopy to turn the ovary back and fixate it with sutures. If the rotation goes untreated for a longer period, the ovary can perish.
- Harvesting of egg cells can cause **infection with formation of pus in the lower abdomen, injury to the intestines and severe rebleeding** from the punctured ovary in rare cases. Antibiotics treatment and/or an abdominal operation can become necessary, with one ovary or both ovaries being removed, which is very rare, however. In very rare cases, life-threatening generalised blood poisoning (**sepsis**) can occur which necessitates intensive medical care. Rebleeding can also necessitate transfusion of blood. The risk of infection (e.g. with hepatitis, AIDS) after transfusion of foreign donor blood is extremely low.
- If pregnancy occurs due to the extra-corporeal fertilisation, the hyperstimulation syndrome is **promoted in addition** due to the hormonal changes associated with the pregnancy. Inpatient treatment – in rare cases on an intensive care unit – can become necessary to monitor and support vital organ function. Frequently, outpatient treatment is sufficient, however.
- After the puncture, **vaginal bleeding or vaginal discharge** can occur.
- **Allergy/Hypersensitivity/Incompatibility** (e.g. to latex, medications) can cause acute circulatory shock, necessitating intensive care. Severe damage (e.g. organ failure, brain damage, paralysis), which can be permanent under certain circumstances, is very rare. Mild allergic reactions may cause temporary swelling, itching, sneezing, skin rash, dizziness or vomiting.
- It is indicated that the risk of **benign or malignant tumours of the ovaries or the reproductive organs** can be permanently increased after several stimulation cycles within the course of sterility treatment. However, current research indicates that the cause for this risk could be the disorder of fertility itself and not the stimulation therapy. A final determination of the circumstances has not been achieved yet.
- In an occasional case, the embryo transfer causes **minor pain**, in particular if the cervix is severely bent. In rare cases, short general anaesthesia can therefore be necessary; we will inform you about this in due time. In rare cases, women react with temporary **abdominal cramps**.
- **Skin/Tissue/Nerve damage** due to positioning of the patient and the hormone injections (but also e.g. disinfection, laser, electric current) is rare. Side-effects/Complications that can be permanent under certain circumstances: Pain, inflammation/infection, necrosis (death) of tissue, scars and disorders of sensation or function, paralysis (e.g. of the extremities).
- In the course of “artificial fertilisation”, **tubal or abdominal pregnancy** can also occur and necessitate surgical treatment as a rule. The **rate of miscarriages** is higher than in spontaneously occurring pregnancies. In an embryo transfer, 2 embryos are transferred usually, or 3 are transferred as an exception; therefore, **multiple pregnancies** occur more frequently than in natural pregnancies.
- It cannot be excluded that the extra-corporeal fertilisation presents increased **mental stress** for the partners.
- The risk of complications of the pregnancy (e.g. premature birth, children with a very low weight at birth, toxæmia of pregnancy [gestosis]) increases if pregnancy is induced at a higher age of the woman (in particular 40 years or older).
- The risk that the child has a **congenital disease (e.g. malformation, organ defect, chromosome anomaly)** depends on the individual risk factors of the pair. In particular the age and weight of the woman, previous radiation or chemotherapy and congenital familial predisposition are of importance. In particular if the sperm is injected into the egg (ICSI), there is an indication that the risk of disorders of the child (e.g. early vascular ageing, hypertension) can be increased. In isolated cases, human genetics consultation is recommended, with prenatal examination of the child by means of ultrasound, removal of placenta tissue (chorionic villus sampling) or withdrawal of amniotic fluid or other genetic examinations if indicated.
- Scientific research of possible risks for the child after extra-corporeal fertilisation has not yet been concluded. Therefore, long-term health problems of the child possibly caused by the extra-corporeal fertilisation treatment cannot be assessed definitely.

During the patient-doctor discussion, you should ask all questions that are important to you or about anything that is still unclear!

What are the chances of success?

In isolated cases, it may become necessary to stop a treatment cycle. Possible reasons are insufficient or excessive reaction of the ovaries (hyperstimulation syndrome), ovulation occurring at an unsuitable time, semen not being avail-

able at the right time or egg cells noticeably not developing in a normal way. Egg cells already present or surplus at suspension of the treatment cycle can also be frozen.

Under ideal conditions, the probability of pregnancy occurring in the natural way is about 25 to 30 percent per cycle; in women older than 35 years, the probability is lower. The natural rates are also achieved in "artificial fertilisation" on average. However, pregnancy cannot be guaranteed, and the causes of inability to conceive, the age of the woman, smoking and obesity can worsen the chances of success significantly.

If the first treatment cycle is not successful, we will discuss the chances of success for a further treatment cycle at your request. Please inform us of any side-effects and possible complications that have occurred in previous treatment cycles. Only decide to perform another treatment cycle when possible doubts have been resolved. We will inform you of any medical circumstances that might be important for your decision not to continue the IVF/ICSI treatment. However, despite the greatest care taken, success (pregnancy) cannot be guaranteed even after several treatment cycles.

Instructions

Please list all medications that you are currently taking. In consultation with the doctor treating you, we will then decide if certain medications should be stopped or replaced by another substance. This applies in particular to anticoagulant medications (e.g. Marcumar®, Aspirin®, Plavix®, Iscover®, Pradaxa®, Xarelto®, Eliquis®, etc.).

Use the prescribed medications in the way indicated in your personal treatment plan and stop taking preparations incompatible with the treatment in consultation with the doctors treating you.

Please inform the doctors treating you immediately about any side-effects and complications (e.g. **signs of hyperstimulation such as distended abdomen, abdominal pain**) possibly associated with the treatment (e.g. **fever above 38 °C, pain, vision problems**).

Please **be sure** to come to all appointments for **check-ups and treatment** for your own safety, in particular because of the risk of hyperstimulation, and to ensure success of the treatment.

Please remember that **after the outpatient puncture**, your senses will be dulled for a certain period after receiving sedation, pain medication or an anaesthetic agent. Please arrange to have an adult pick you up and stay with you at home for 24 hours after the procedure. You **may not be actively involved in road traffic** during this time frame, nor should you engage in dangerous activities. You also should not make important decisions, nor should you drink alcohol.

In isolated cases (e.g. if vision disorders occur), stimulation treatment with medication can also impair your ability to be actively involved in road traffic and to work on running machinery. It is imperative that you refrain from doing so in this case.

After the harvesting of egg cells until the pregnancy test, you have to take it easy, in particular if signs of hyperstimulation are observed. Violent rotation and shocks should be avoided. Please make sure that you drink a sufficient amount of fluid (2.5–3 litres a day). It is recommended not to take hot baths or visit the sauna. After harvesting and due to the increased size of the ovaries, sexual intercourse can be very painful for the woman; if hormones are administered through the vagina, sexual intercourse should also be avoided.

Please note that it is possible to receive psychological consultation by the Beratungsnetzwerk Kinderwunsch Deutschland (BKID) [German consultation network for anyone wanting to have children].

If hormonal treatment is performed, in particular in association with **smoking**, there is a **significant risk** of getting a thrombosis, a cardiac infarct or a stroke which can even be fatal under certain circumstances. Smoking does also impair fertility and is harmful for a pregnancy. Therefore, it is strongly recommended that women having IVF/ICSI treatment stop smoking.

Important questions

Please answer the following questions for the female partner carefully in order to enable us to better prevent any potential risks. Please mark boxes where applicable and underline or add text where appropriate. If necessary, do not hesitate to ask for our assistance in filling out the form.

Age: _____ years • Height: _____ cm • Weight: _____ kg

Gender: _____

n = no/y = yes

1. Is the patient regularly or currently taking **medications** (e.g. anticoagulant medications [e.g. Marcumar®, aspirin®, Plavix®, Xarelto®, Pradaxa®, Eliquis®, Lixiana®, heparin], pain medications, cardiovascular medications, hormone preparations, sleep-inducing medications or sedatives, diabetes medications [in particular those containing metformin])? n y

If yes, please indicate! _____

2. Does the patient have an **allergy** such as **hay fever** or bronchial asthma or **hypersensitivity** to certain substances (e.g. medications, latex, disinfectants, sedatives, X-ray contrast media, iodine, plaster, pollen)? n y

If yes, please indicate! _____

3. Does the patient or does one of their relatives have an **increased tendency to bleed** such as e.g. frequent nosebleeds/bleeding gums, bruises, rebleeding after operations? n y

4. Does the patient have or has the patient ever had an **infectious disease** (e.g. hepatitis, tuberculosis, HIV/AIDS)? n y

If yes, please indicate! _____

5. Has the patient ever received **transfusion of blood/blood components**? n y

If yes, did any complications develop? n y

If yes, please indicate! _____

6. Has the patient ever had a vascular obstruction due to a blood clot (**thrombosis/embolism**)? n y

7. Does the patient have any known **congenital disorders of fertility** or **congenital malformations**, or do you know of any blood relatives (family of the woman or the man) having any such disorders or malformations? n y

If yes, please indicate! _____

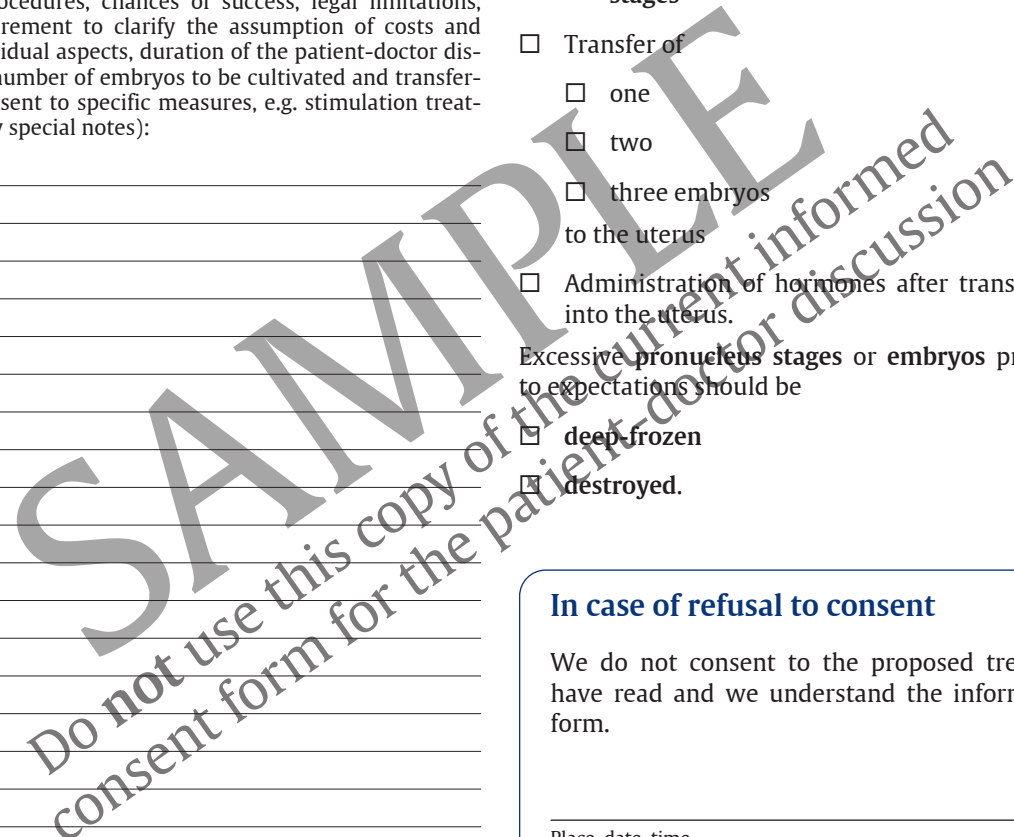
- 8. Does the patient have a **metabolic disease** n y (e.g. diabetes, gout)?
If yes, please indicate! _____
- 9. Does the patient have or has the patient ever had a **disease of the nervous system** (e.g. paralysis, seizure disorder [epilepsy], chronic pain)? n y
If yes, please indicate! _____
- 10. Does the patient have **other diseases**? n y
If yes, please indicate! _____
- 11. Does the patient use **tobacco products** regularly? n y
If yes, which type and how much? _____
- 12. Does the patient drink **alcohol** regularly? n y
If yes, which type and how much? _____

Doctor's notes on the patient-doctor discussion

The following was discussed in particular: Nature and purpose of the treatment, treatment plan, possibly required changes to the treatment plan, choice of procedure, advantages or disadvantages compared to other methods, combination with other treatments, risks, possible complications and side-effects, individual circumstances increasing the risk, risks for the child, possible subsequent and additional procedures, chances of success, legal limitations, instructions, requirement to clarify the assumption of costs and (please fill in individual aspects, duration of the patient-doctor discussion here, e.g. number of embryos to be cultivated and transferred; refusal to consent to specific measures, e.g. stimulation treatment; and possibly special notes):

The following measures are planned:

- Administration of hormones for **stimulation** of egg cell maturation
- Harvesting of egg cells by puncture** of the ovaries
- In-vitro fertilisation (**IVF**)
- Intracytoplasmic sperm injection (**ICSI**)
- Performance of **blastocyte culture** with a maximum of _____ of fertilised eggs
 - due to **age**
 - due to the **expected number** of harvested egg cells
 - due to the course of the **previous cycle**
 - due to the **number and shape of the pronucleus stages**
- Transfer of
 - one
 - two
 - three embryos to the uterus
- Administration of hormones after transfer of embryos into the uterus.
 - Excessive **pronucleus stages** or **embryos** present contrary to expectations should be
 - ~~deep-frozen~~
 - ~~destroyed~~.



In case of refusal to consent

We do not consent to the proposed treatment. We have read and we understand the informed consent form.

Place, date, time

Patient

Patient

Witness (if applicable)

Doctor

Patient's Statement of Consent

The above-named treatment, alternative treatments, their advantages and disadvantages, various risks, stresses and chances of success, the nature and significance of the procedures, risks and possible associated complications, chances of success, additional/subsequent procedures/treatment that may be needed (e.g. necessity of further treatment cycles) and possible additions to or changes of the procedure (e.g. stop of the stimulation treatment, harvesting of eggs by laparoscopy) have been fully explained to us in a patient-doctor discussion with doctor _____.

We were afforded the opportunity to ask any questions that we considered important.

We have **no further questions** and feel that **the counselling was satisfactory**; we have considered the arguments for and against artificial fertilisation for a long time and **desire merging of egg and sperms with the procedure suggested above** to help us conceive. We also consent to any unforeseen additional or subsequent treatment which may become necessary for medical reasons.

We have received **instructions and recommendations for follow-up care** after an outpatient procedure.

We were informed that

- this statement of consent to the treatment only applies for the respective treatment cycle itself,
- we can always cancel the statement of consent, also during the ongoing treatment, respectively on our own or jointly.
- anonymised data about the treatment cycle are reported to the respective state authority and the central IVF register by the centre. Anonymised data can also be used for scientific examinations.

Only for customers of public health insurance:
With our signature, we confirm that so far or since the last birth, _____ IVF and/or IC-SI treatments in total have been performed without achieving pregnancy. We have been informed that false information can cause the public health insurance provider to demand compensation of costs incurred for medical treatment and medications.

We want to have this treatment regardless of a possible claim for compensation towards the public health insurance providers, private health insurances and/or government aid offices or other organisations responsible for assumption of costs. We are willing to bear the treatment costs ourselves regardless of assumption/compensation by the above aforementioned benefactors to their full extent.

Place, date, time

Patient

Patient

Doctor

2nd treatment cycle

We wish to have a second treatment cycle and consent to all associated treatment measures which have already been explained to us.

- Performance of blastocyte culture with a maximum of _____ of fertilised egg cells or embryos
number
- due to age
- due to the expected number of harvested egg cells
- due to the course of the previous cycle

Transfer of

- one
 - two
 - three embryos
- to the uterus

Place, date, time

Patient

Patient

Doctor

3rd treatment cycle

We wish to have a third treatment cycle and consent to all associated treatment measures which have already been explained to us.

- Performance of blastocyte culture with a maximum of _____ of fertilised egg cells or embryos
number
- due to age
- due to the expected number of harvested egg cells
- due to the course of the previous cycle

Transfer of

- one
 - two
 - three embryos
- to the uterus

Place, date, time

Patient

Patient

Doctor