# Quality of Life, Decision-making, Resilience, Satisfaction and Success rate of different IVF treatment strategies: an international prospective cohort study

| | |
|---|---|
| Research legislation: | Ordinance on human research with the exception of Clinical trials (HRO) [1]. |
| Type of Research Project: | Research project involving human subjects |
| Risk Categorisation: | Risk category A (observational study) |
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# PROTOCOL SIGNATURE FORM

Study Title: **Quality of Life, Decision-making, Resilience, Satisfaction and Success rate of different IVF treatment strategies: an international prospective cohort study**

The project leader at the main coordinating center and the project leader at the local center/site have approved the protocol version ***01.20 (dated 08.12.2025)*** and confirm hereby to conduct the project according to the protocol, the Swiss legal requirements [1,2], the current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

The project leader at main center has received the ICF and consider it appropriate for use.

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## GLOSSARY OF ABBREVATIONS

| | |
|---|---|
| *AF* | *Antral follicle* |
| *AI* | *Aromatase inhibitors* |
| *AMH* | *Anti Müllerian hormone* |
| *ART* | *Assisted Reproductive Medicine* |
| *ASRM* | *American Society of Reproductive Medicine* |
| *BASEC* | *Business Administration System for Ethical Committees* |
| *BMI* | *Body Mass Index* |
| *CC* | *Clomiphene citrate* |
| *CES-D* | *Center for Epidemiologic Studies Depression Scale* |
| *CI* | *Confidence Interval* |
| *cIVF* | *Conventional In-vitro-fertilisation* |
| *COS* | *Controlled ovarian stimulation* |
| *CRF* | *Case report form* |
| *CTU* | *Clinical Trial Unit* |
| *DCR* | *Department Clinical Research* |
| *DOR* | *Diminished ovarian reserve* |
| *EDC* | *Electronic Data Capturing* |
| *ET* | *Embryo transfer* |
| *FertiQoL* | *Fertility Quality of Life* |
| *FET* | *Frozen embryo transfer* |
| *FSH* | *Follicle stimulating hormone* |
| *GnRH* | *Gonadotropin releasing hormone* |
| *hCG* | *Human chorionic gonadotropin* |
| *HFV* | *Human Forschungsverordnung* |
| *HFG* | *Human Forschungsgesetzt* |
| *hMG* | *Human menopausal gonadotropins* |
| *HRA* | *Human Research Act* |
| *HRO* | *Ordinance on Human* |
| *ICSI* | *Intracytoplasmic Sperm Injection* |
| *IVF* | *In-vitro-fertilisation* |
| *LH* | *Luteinizing hormone* |
| *Min stim-IVF* | *Minimal stimulation In-vitro-fertilisation* |

| | |
|---|---|
| *NC-IVF* | *Natural cycle In-vitro-fertilisation* |
| *NSAID* | *Non-steroidal anti-inflammatory drugs* |
| *OHSS* | *Ovarian Hyperstimulation Syndrom* |
| *OPU* | *Oocyte pick-up* |
| *PGT* | *Preimplantation Genetic Testing* |
| *SD* | *Standard Deviation* |

# 1 BACKGROUND AND PROJECT RATIONALE

Conventional *in-vitro-fertilisation* (cIVF) consists of full ovarian stimulation in order to maximize the number of oocytes to be retrieved and to carry out IVF/ICSI (Intracytoplasmic Sperm Injection). Nowadays, ovarian stimulation with gonadotropins has become a key component of assisted reproductive technologies (ART). Although cIVF protocols are associated with good clinical outcomes, they are also associated with some patient discomfort, stress, intensive monitoring, anaesthesia, high cost and higher risk of complications (ovarian hyperstimulation syndrome, OHSS) [4–7].

In contrast, Natural Cycle IVF (NC-IVF) uses the one follicle that spontaneously develops to dominance for IVF/ICSI. Minimal stimulation-IVF (Min stim-IVF) is based on NC-IVF but involves low doses of oral compounds (clomiphene citrate (CC), aromatase inhibitors (AI)), combined or not with ≤100 IU of human menopausal gonadotropins (hMG) or recombinant human follicle stimulating hormone (FSH), to induce the growth of some follicles. In both IVF treatment options, a gonadotropin-releasing hormone (GnRH) antagonist is only used in the late follicular phase to prevent untimely luteinizing hormone (LH) surges and consequent oocyte retrieval failure. Both IVF treatment options are patient-friendly treatment, as medication is not or only administered for a few days, causing few side effects, and the duration of a treatment cycle is considerably shorter than cIVF with controlled ovarian stimulation (COS). As only one or a few follicles are aspirated, the oocyte retrieval process is simple, quick and can be carried out without anaesthesia or pain relief [4]. Treatment is easily repeated in consecutive cycles and no resting cycle is necessary in between. NC-IVF and Min stim-IVF aims to achieve a more physiological response to ovarian stimulation. It has been shown to improve fertilization rate and cleavage-stage embryo morphology [8,9] . Both IVF treatments are also quite an effective treatment option in patients with a good prognosis [10].

**In summary, there are the following IVF treatment strategies available which will be also considered in our study:**

1. **cIVF,**
2. **NC-IVF/Min Stim-IVF (also known as "IVF-Naturelle")**

   In case, the woman changes the treatment:
3. **Mixed treatment**

Due to the disadvantages of cIVF and due to the desire of many women to undergo NC-IVF or Min stim-IVF, IVF treatments without any or with low-dose stimulation have experienced a revival in recent years. NC-IVF and Min stim-IVF are therefore an attractive alternative to conventional IVF with COS, which is the main form of IVF today. Obviously, a higher number of NC-IVF and/or Min stim-IVF cycles are required to obtain pregnancy rates and live birth rates comparable to those obtained with conventional IVF.

The "IVF Naturelle" network has centres in Switzerland and Germany. The network aims to offer all three types of IVF treatment, providing patients with a broader choice and more tailored treatment while bearing in mind the respective advantages and disadvantages.

The aim of our study is to assess and understand the quality of life, including psychological health experienced by patients undergoing different IVF treatments. This is important because it may affect decisions about which treatment to perform initially and whether to change treatment over time. However, the real patterns influencing

patients' decisions, as well as their satisfaction and adherence to their chosen treatment over time, remain unknown.

Therefore, firstly, this study aims to assess the **quality of life** and **mental health** of patients suffering from infertility. Secondly, this study aims to discover the true **reasons for choosing** a certain IVF treatment (whether quality of life related or otherwise) and the extent to which defined factors (e.g. cost, doctor recommendations, stress levels and effectiveness) influence this choice. Thirdly, the study aims to examine psychological **resilience** in adhering to a treatment choice and the **reasons for changing** treatment. Finally, we will evaluate the **cumulative live birth rate** over a planned timeframe, including that experienced with IVF Naturelle, as these are currently unknown. The cumulative live birth rate is also a key factor in analysing patients' choices and understanding their resilience in continuing a treatment and their satisfaction at the end of a predefined period. It is therefore mandatory. Furthermore, we will record all the main results of the IVF treatment cycles in order to adjust for biological factors related to the cycle that influence choices.

**With the Swiss government about to discuss the initiative to cover IVF treatments (NC-, Min stim- and cIVF), it is important to understand what drives patients to choose one treatment over another, their quality of life as well as the success rates.**

# 2 PROJECT OBJECTIVES AND DESIGN

## 2.1 Objectives and study questions

**Primary objective and study question**

To study the difference in Quality of Life of patients who decide to undergo NC-/Min stim-IVF versus cIVF. The validated questionnaire "**FertiQoL" (Q1.0)** will be used.

- Is the Quality of Life different in the NC-/Min stim-IVF versus cIVF?

**Key secondary objective**

To study the difference in mental/psychological health of patients who decide to undergo NC-/Min stim-IVF versus cIVF. The validated questionnaire "**CES-D**" **(Q2.0)** will be used.

**Secondary objectives and study questions**

1. To investigate Quality of Life and mental health:
    - Have the Quality of Life and the mental/psychological health of patients changed after a 6 months of IVF treatments (using the above mentioned questionnaires **Q1.0, Q2.0**)?
2. To investigate Patients' decision-making:
    - Given a certain situation and a certain recommendation from a physician based on biological/clinical criteria what factors characterize patients' decision-making processes when choosing which type of IVF treatment to undergo (NC-/Min stim-IVF versus cIVF)? (using a third questionnaire, **Q3.0**)
3. To investigate which factors characterize the decision to change treatment in a certain period of time (study period 6 months) (biological/cycle-related and non-biological factors):
    - Which factors characterize the decision to change treatment? (e.g. switching from NC-/Min stim-IVF to cIVF, or vice versa)? (questionnaire number 4, **Q4.0**)
4. To investigate the satisfaction rate with the initial choice of IVF treatment and investigate how the fact that the Swiss compulsory insurance does not cover IVF treatments affects the decision about which treatments to undergo:
    - "If you had to decide again on IVF treatment, would you make a different choice?"
    - Would the fact that IVF is not yet covered by Swiss compulsory insurance affect patient's first decision to undergo treatment? (questionnaire number 5, **Q5.0**)
5. To investigate the live birth rate of cIVF and NC-/Min stim-IVF treatment strategies after up to 6 months of treatment:
    - What is the live birth rate after up to 6 months for cIVF and NC-/Min stim-IVF and mixed IVF strategy?
    - To compare the live birth rate of cIVF and NC-/Min stim-IVF and mixed IVF treatment strategy with intended fresh/frozen transfers within 6 months.
6. To study the discontinuation/change rate of IVF treatment strategies after up to 6 months of treatment.

- What is the discontinuation/change rate of one specific IVF treatment strategy (NC-/Min stim-IVF and cIVF)?

7. To study the risks per IVF treatment strategy.
    - Is one of the IVF treatment strategy (cIVF and NC/Min stim-IVF) less risky regarding the risk of bleedings and infections?
8. To study the costs per treatment strategy in relation to overall success rate.
    - Is one of the IVF treatment strategy less expensive per achieved pregnancy?

## 2.2 Primary and secondary endpoints

**Primary endpoint:**

Quality of life related to infertility will be analysed using the FertiQoL questionnaire.

**Key secondary endpoint:**

Mental health related to infertility will be analysed using the CES-D questionnaire.

Both questionnaires have already been used by the infertility center in Berne and have revealed differences in the comparison of NC-IVF and cIVF treatment cycles [11].

**FertiQol questionnaire**

FertiQol is an internationally validated instrument for measuring quality of life in individuals experiencing fertility problems.

The questionnaire consists of 36 items scored according to 5 response categories. The response scale has a range of 0 to 4. Higher scores mean higher quality of life. Items A and B are additional items that capture on overall evaluation of physical health and satisfaction with quality of life and are not used in FertiQoL scoring. The FertiQoL questionnaire consist of Core FertiQoL and Treatment FertiQoL. The Total FertiQoL score is the average quality of life for all core and treatment domains.

Participants will complete the questionnaire before and at the end of the six-month treatment period. At the end of the study period, only questions T1–T10 will need to be completed (Treatment FertiQoL).

**Questionnaire Q1.0: Core FertiQoL and Treatment FertiQoL**

**Core FertiQoL**

| | | Very poor | Poor | Neither good nor poor | Good | Very good |
|---|---|---|---|---|---|---|
| **A** | How would you rate your health? | 0 | 1 | 2 | 3 | 4 |

**Core FertiQoL**

| | | Very dissatisfied | Dissatisfied | Neither dissatisfied or satisfied | Satisfied | Very satisfied |
|---|---|---|---|---|---|---|
| **B** | Are you satisfied with your quality of life? | 0 | 1 | 2 | 3 | 4 |

**Core FertiQoL, Category: Capacity (Scoring 0-4)**

| | | Comple-tely | A great deal | Modera-tely | Not much | Not At all |
|---|---|---|---|---|---|---|
| **Q1.1** | Are your attention and concentration impaired by thoughts of infertility? | 0 | 1 | 2 | 3 | 4 |
| **Q1.2** | Do you think you cannot move ahead with other life goals and plans because of fertility problems? | 0 | 1 | 2 | 3 | 4 |
| **Q1.3** | Do you feel drained or worn out because of fertility problems? | 0 | 1 | 2 | 3 | 4 |
| **Q1.4** | Do you feel able to cope with your fertility problems? | 4 | 3 | 2 | 1 | 0 |

**Core FertiQoL, Category: Satisfaction (Scoring 0-4)**

| | | Very dissatisfied | Dissatisfied | Neither dissatisfied or satisfied | Satisfied | Very satisfied |
|---|---|---|---|---|---|---|
| **Q1.5** | Are you satisfied with the support you receive from friends with regard to your fertility problems? | 0 | 1 | 2 | 3 | 4 |
| **Q1.6** | Are you satisfied with your sexual relationship even though you have fertility problems? | 0 | 1 | 2 | 3 | 4 |

**Core FertiQoL, Category: Frequency (Scoring 0-4)**

| | | Always | Very often | Quite often | Seldom | Never |
|---|---|---|---|---|---|---|
| **Q1.7** | Do your fertility problems cause feelings of jealousy and resentment? | 0 | 1 | 2 | 3 | 4 |
| **Q1.8** | Do you experience grief and/or feelings of loss about not being able to have a child (or more children)? | 0 | 1 | 2 | 3 | 4 |
| **Q1.9** | Do you fluctuate between hope and despair because of fertility problems? | 0 | 1 | 2 | 3 | 4 |
| **Q1.10** | Are you socially isolated because of fertility problems? | 0 | 1 | 2 | 3 | 4 |
| **Q1.11** | Are you and your partner affectionate with each other even though you have fertility problems? | 4 | 3 | 2 | 1 | 0 |
| **Q1.12** | Do your fertility problems interfere with your day-to-day work or obligations? | 0 | 1 | 2 | 3 | 4 |
| **Q1.13** | Do you feel uncomfortable attending social situations like holidays and celebrations because of your fertility problems? | 0 | 1 | 2 | 3 | 4 |
| **Q1.14** | Do you feel your family can understand what you are going through? | 4 | 3 | 2 | 1 | 0 |

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**Core FertiQoL, Category: Intensity (Scoring 0-4)**

| | | An extreme amount | Very much | A moderate amount | A little | Not at all |
|---|---|---|---|---|---|---|
| **Q1.15** | Have fertility problems strengthened your commitment to your partner? | 4 | 3 | 2 | 1 | 0 |
| **Q1.16** | Do you feel sad and depressed about your fertility problems? | 0 | 1 | 2 | 3 | 4 |
| **Q1.17** | Do your fertility problems make you inferior to people with children? | 0 | 1 | 2 | 3 | 4 |
| **Q1.18** | Are you bothered by fatigue because of fertility problems? | 0 | 1 | 2 | 3 | 4 |
| **Q1.19** | Have fertility problems had a negative impact on your relationship with your partner? | 0 | 1 | 2 | 3 | 4 |
| **Q1.20** | Do you find it difficult to talk to your partner about your feelings related to infertility? | 0 | 1 | 2 | 3 | 4 |
| **Q1.21** | Are you content with your relationship even though you have fertility problems? | 4 | 3 | 2 | 1 | 0 |
| **Q1.22** | Do you feel social pressure on you to have (or have more) children? | 0 | 1 | 2 | 3 | 4 |
| **Q1.23** | Do your fertility problems make you angry? | 0 | 1 | 2 | 3 | 4 |
| **Q1.24** | Do you feel pain and physical discomfort because of your fertility problems? | 0 | 1 | 2 | 3 | 4 |

**Treatment FertiQoL, Environment and Treatment Tolerability (Score 0-4)**

| | | Always | Very often | Quite often | Seldom | Never |
|---|---|---|---|---|---|---|
| **T1** | Does infertility treatment negatively affect your mood? | 0 | 1 | 2 | 3 | 4 |
| **T2** | Are the fertility medical services you would like available to you? | 4 | 3 | 2 | 1 | 0 |

**Treatment FertiQoL, Environment and Treatment Tolerability (Score 0-4)**

| | | An extreme amount | Very much | A moderate amount | A little | Not at all |
|---|---|---|---|---|---|---|
| **T3** | How complicated is dealing with the procedure and/ or administration of medication for your infertility treatment(s)? | 0 | 1 | 2 | 3 | 4 |
| **T4** | Are you bothered by the effect of treatment on your daily or work? | 0 | 1 | 2 | 3 | 4 |
| **T5** | Do you feel the fertility staff understand what you are going through? | 4 | 3 | 2 | 1 | 0 |
| **T6** | Are you bothered by the physical side effects of fertility medications and treatment? | 0 | 1 | 2 | 3 | 4 |

| | | Very dissatisfied | Dissatisfied | Neither dissatisfied or satisfied | Satisfied | Very satisfied |
|---|---|---|---|---|---|---|
| **T7** | Are you satisfied with the quality of services available to you to address your emotional needs? | 0 | 1 | 2 | 3 | 4 |
| **T8** | How would you rate the surgery and/or medical treatment(s) you have received? | 0 | 1 | 2 | 3 | 4 |
| **T9** | How would you rate the quality of information you received about medication, surgery and/or medical treatment? | 0 | 1 | 2 | 3 | 4 |
| **T10** | Are you satisfied with your interactions with fertility medical staff? | 0 | 1 | 2 | 3 | 4 |

**Questionnaire Q2.0 : Center for Epidemiologic studies Depression Scale (CES-D)**

Mental health will be analysed using the Depression scale questionnaire, an internationally validated instrument for measuring depression scale. Possible range of scores is 0 to 60, with the higher scores indicating the presence of more symptomatology. A score of 16 or higher is often considered to indicate the presence of depressive symptoms that put an individual at risk for depression.

Participants will complete the questionnaire before and at the end of the six-month treatment period.

**CES-D**

| | | **During the past weeks** | | | |
|---|---|---|---|---|---|
| | | Rarely or none of the time (less than 1 day) | Some or a little of the time (1-2 days) | Occasionally or a moderate amount of time (3-4 days) | Most or all the time (5-7 days) |
| **Q2.1** | I was bothered by things that usually don't bother me | 0 | 1 | 2 | 3 |
| **Q2.2** | I didn't not feel like eating, my appetite was poor | 0 | 1 | 2 | 3 |
| **Q2.3** | I felt I couldn't shake off the blues even with help from my family or friends | 0 | 1 | 2 | 3 |
| **Q2.4** | I felt I was just as good as other people | 3 | 2 | 1 | 0 |
| **Q2.5** | I had trouble keeping my mind on what I was doing | 0 | 1 | 2 | 3 |
| **Q2.6** | I felt depressed | 0 | 1 | 2 | 3 |
| **Q2.7** | I felt that everything I did was an effort | 0 | 1 | 2 | 3 |
| **Q2.8** | I felt hopeful about the future | 3 | 2 | 1 | 0 |
| **Q2.9** | I thought my life had been a failure | 0 | 1 | 2 | 3 |
| **Q2.10** | I felt fearful | 0 | 1 | 2 | 3 |

| | | | | | |
|---|---|---|---|---|---|
| **Q2.11** | My sleep was restless | 0 | 1 | 2 | 3 |
| **Q2.12** | I was happy | 3 | 2 | 1 | 0 |
| **Q2.13** | I talked less than usual | 0 | 1 | 2 | 3 |
| **Q2.14** | I felt lonely | 0 | 1 | 2 | 3 |
| **Q2.15** | People were unfriendly | 0 | 1 | 2 | 3 |
| **Q2.16** | I enjoyed life | 3 | 2 | 1 | 0 |
| **Q2.17** | I had crying spells | 0 | 1 | 2 | 3 |
| **Q2.18** | I felt sad | 0 | 1 | 2 | 3 |
| **Q2.19** | I felt that people dislike me | 0 | 1 | 2 | 3 |
| **Q2.20** | I could not get "going" | 0 | 1 | 2 | 3 |

Other secondary endpoints:

**Questionnaire Q3.0:**

Question: Which factors have affected your **first choice** of IVF treatment strategy? (Multiple answers possible)

| | **Yes/No** | **Questions** |
|---|---|---|
| **Q3.1** | Yes/No | Recommendation by a physician |
| **Q3.2** | Yes/No | Information pack/flow chart provided by the clinic |
| **Q3.3** | Yes/No | Recommendation by a friend or family |
| **Q3.4** | Yes/No | Wish to avoid/reduce number of injections |
| **Q3.5** | Yes/No | Wish to have full hormonal stimulation |
| **Q3.6** | Yes/No | Desire to utilize one's own hormone system during treatment |
| **Q3.7** | Yes/No | Wish to have less costs per treatment cycle |
| **Q3.8** | Yes/No | Wish to avoid anesthesia |
| **Q3.9** | Yes/No | Wish to have anesthesia |
| **Q3.10** | Yes/No | Afraid of ovarian hyperstimulation syndrome |
| **Q3.11** | Yes/No | Wish to avoid/reduce side effects of the ovarian stimulation |
| **Q3.12** | Yes/No | Desire for therapy that can be timed as well as possible |
| **Q3.13** | Yes/No | Hope of reducing treatment-related stress |
| **Q3.14** | Yes/No | Desire for a more natural and physically gentle approach |
| **Q3.15** | Yes/No | Wish to avoid multiple pregnancies |
| **Q3.16** | Yes/No | Wish to have preimplantation genetic testing |
| **Q3.17** | Yes/No | Wish to maximize chances per cycle |
| **Q3.18** | Yes/No | Wish to freeze as many fertilized oocytes/embryos as possible |
| **Q3.19** | Yes/No | Desire to possibly create a fertilized oocyte/embryo bank for further children |
| **Q3.20** | Yes/No | Ethical reasons |
| **Q3.21** | Yes/No | Successful previous pregnancy achieved using a specific IVF treatment strategy |

**Questionnaire Q4.0** in case of changing or discontinuing IVF treatment strategy (NC/Min stim-IVF ↔ cIVF ↔ mixed).

Question: What are the reasons for **changing or discontinuing** the initially chosen IVF treatment strategy? (Multiple answers possible)

| | **Yes/No** | **Questions** |
|---|---|---|
| **Q4.1** | Yes/No | Lack of success |
| **Q4.2** | Yes/No | Treatment stress |
| **Q4.3** | Yes/No | Costs |
| **Q4.4** | Yes/No | Psychological factor/burden |
| **Q4.5** | Yes/No | Physician's advice |
| **Q4.6** | Yes/No | Age |
| **Q4.7** | Yes/No | Poor response |
| **Q4.8** | Yes/No | Change of centre/Continuation of treatments abroad |
| **Q4.9** | Yes/No | Spontaneous pregnancy |
| **Q4.10** | Yes/No | Postponement of IVF treatment for a certain reason |
| **Q4.11** | Yes/No | Others (describe): |

**Questionnaire Q5.0: Satisfaction** with the initial choice and influence of the insurance system

| | **Yes/No** | **Questions** |
|---|---|---|
| **Q5.1** | Yes/Maybe/No | If you had to decide again on IVF treatment, would you make a different choice? |
| **Q5.2** | Yes/Maybe/ Partially/No | Are the costs of treatment covered by insurance? |
| **Q5.3** | Yes/Maybe/ Partially/No | Did the costs you will face influence your decision regarding which IVF treatment strategy to pursue? |

The following treatment related and success related parameters will be collected to evaluate **secondary** endpoints

- Number of pregnancies (clinical/ongoing)
- Any live birth (defined as at least one delivery of a live infant resulting from all NC/Min stim-IVF, cIVF or mixed treatment cycles, inclusive frozen embryo transfer (FET) cycles until pregnancy occurred or until 6 months were over).
- Type of IVF (in each cycle): NC-, Min stim- and cIVF
- Number of miscarriages
- Number of ectopic pregnancies, others outcome of pregnancy
- Number of women who discontinue IVF treatment
- Premature ovulation: yes/no
- Number of oocytes, zygotes, embryos and frozen embryos (inclusive day of freezing)
- Preimplantation Genetic Testing (PGT) (yes or no)
- Technology of fertilization (IVF or ICSI or both)

- Day of embryo transfer (2, 3 or 5)
- Number of transferred embryos
- Number of frozen embryos remaining at the end of the six-month observation period (inclusive day of freezing)

The following basic parameters will also be collected:

- Age of the woman
- Body mass index (BMI) (weight and height)
- Smoking status (yes/no)
- Cause of infertility (female, male, idiopathic or mixed)
- Duration of infertility (years)
- Number of previous pregnancies with live birth (≥0) and art of the pregnancies (spontaneous or ART)
- Anti Müllerian hormone (AMH) level at the beginning of IVF treatment
- IVF cycles related complication: OHSS, miscarriage, bleeding
- Number of consultations
- Domicile (Switzerland or Germany)
- Educational level: primary education (obligatory); secondary education, non-university; university

## 2.3 Project design

International prospective, multi-centre, observational cohort study without direct treatment intervention.

# 3 PROJECT POPULATION AND STUDY PROCEDURES

## 3.1 Project population, inclusion and exclusion criteria

The project population consists IVF patients who are willing to participate in this study. Patients should not have had an IVF treatment before or, if a clinical pregnancy had been achieved by IVF, a new IVF therapy should not have started since then.

After receiving advice on the advantages and disadvantages of each type of in vitro fertilisation treatment (NC/ Min-stim IVF and cIVF strategy), couples will be free to decide which IVF treatment strategy they wish to follow. Couple are also free to change treatment strategy during the 6 month treatment phase.

The following NC-/Min stim-IVF treatments ("IVF Naturelle") are applied (subdivided in protocols 1, 2 and 3):

**Protocol 1: Natural Cycle IVF (NC-IVF):**

The principle of NC-IVF is based on the concept of natural follicle recruitment and selection and an unsupported luteal phase. This means that gonadotropin injections and luteal phase support is not applied, but if necessary treatment is modified with medications to avoid premature ovulation (non-steroidal anti-inflammatory drugs (NSAIDs) and/or single injections of GnRH antagonist) are given. Today the administration of hCG (human chorionic gonadotropin) trigger to induce the ovulation in NC-IVF is standard. "Natural" is only related to the menstrual cycle, IVF/ICSI still takes place in the IVF laboratory.

A typical cycle: 1st consultation on cycle day 11 ± 1 (for 28 day cycles) to monitor follicle growth by ultrasound and also based on blood samples measuring oestrogen and LH. The goal is to schedule the day of the aspiration. The triggering of the ovulation is performed with 5000 E hCG (Choriomon®) and the aspiration of the oocyte takes place 36 hours afterwards.

In our clinics such kind of IVF corresponds to "**Protocol 1**".

**Minimal Stimulation IVF:**

This treatment is defined as IVF with low doses of HMG or FSH alone, or with Letrozol®. HCG injection to induce the ovulation and luteal support are also usually administered. The aim is to collect 1 to 3 oocytes. We defined these kind of protocols:

- "**Protocol 2**": minimal stimulation with the oral compounds such as aromatase inhibitors (Letrozol®) à 5 mg starting from day 2 to 4 of cycle for 5-6 days.
- "**Protocol 3**": minimal stimulation with oral compounds such as aromatase inhibitors (Letrozol®) à 5 mg starting from day 2 to 4 of cycle for 5-6 days plus 75-100 IU of gonadotropin (HMG/FSH) injections.

NC-IVF and Min stim-IVF are analysed together as one therapy group, regardless of whether the patient undergoes only NC-IVF, only Min stim-IVF, or a combination of both.

**Conventional IVF (cIVF), Antagonist protocols ("Protocol 4"):**

This treatment is defined as IVF with higher dose of HMG/FSH, 150-300 IE HMG or FSH daily, to collect many oocytes and GnRH antagonist to block premature ovulation. Triggering of the ovulation still happens with hCG and follicle aspiration is usually done with anaesthesia in the operation theatre because of the many follicles. Luteal support is mandatory in conventional IVF. Acquiring several oocytes enables long-term embryo culture up to 5 to 6 days, including selecting the best blastocysts for transfer and eliminating those of low quality. Any additional high-quality embryos are usually frozen.

**Key inclusion criteria**

- Female patient age ≥ 18 till 44
- Indication for IVF/ICSI
- First IVF treatment or first IVF treatment after a clinical pregnancy (spontaneous conception or pregnancy achieved by IVF)
- Cycles with intended fresh and/or frozen ETs within 6 months (= study period)
- In case of NC-IVF: regular menstrual cycle (Eumenorrhae = 24-38 day of cycle)

**Key exclusion criteria**

- IVF cycle with PGT for monogenetic diseases
- cIVF cycles with PGT for aneuploidy without the intention to have an embryo transfer within 6 months
- Social freezing cycles
- Medical freezing cycles

## 3.2 Recruitment, screening and informed consent procedure

Women, according to the key inclusion criteria described above, will be asked to consent to participate in the trial using a dedicated study specific subject information and consent form. The Swiss centers will use the consent prepared for this application.

The project leader and their collaborators explain the nature of the research project, its purpose, the procedures involved, its expected duration and any potential risks or discomfort it may entail, to each participant. Each participant is informed that the participation in the research project is voluntary and that she may withdraw from the research project at any time and that withdrawal of consent will not affect her subsequent medical assistance and treatment. The participants are informed that she can ask any question. Enough time is given to the participant. In any case, sufficient time must legally pass between receiving information about IVF and starting treatment.

All participants are given an information document and a consent form describing the research project. The formal consent of a participant, using the approved consent form, is obtained before the participant is enrolled in the research project.

The participant should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the participant and the project leader (or her designee). The signed consent form is retained as part of the investigation records.

**Screening and recruitment, study centres:**

This study is set out as a multi-centered study involving 2 other centers in Switzerland:

- Infertility clinic YUNA Kinderwunschzentrum of St. Gallen,
- Infertility clinic Kinderwunschzentrum Baden in Baden-Dättwil, additional to
- Kinderwunschzentrum Frauenklinik Inselspital Bern

as well as 5 others centers in Germany

- Kinderwunsch im Zentrum München,
- Kinderwunschzentrum Bonner Bogen, Bonn,
- Kinderwunschzentrum Villa Kinderwunsch, Ulm,
- Kinderwunschzentrum Frauenärzte, Neckarsulm,
- Kinderwunschpraxis an der Promenade, Münster.

All centers perform the same kind of IVF therapies. All the measurements described in point 2.2 are part of routine assessment during IVF-therapies.

### 3.3 Study procedures and time line

**New patients** with an indication for IVF and who are willing to undergo IVF treatment are invited to participate. The choice of IVF treatment protocol (**NC-IVF and/or Min stim-IVF** and **cIVF**) will depend on the couple's medical characteristics but at the end also on personal wishes. None of the patients will be obliged to undergo a specific IVF treatment as they will be free to change the method during the 6 month observation period.

Physicians categorise patients as having a good or low prognosis based on biological reliable objective parameters, such as age, AMH levels and/or number of antral follicle (AF) and the cause of infertility.

Patients with a good prognosis are usually young (aged ≤35 years), have an AMH level of at least 1.2 ng/ml, and/or have idiopathic infertility or mild male factor infertility. Patients with a low prognosis might be older than 35 years, have a low AMH level (less than 1.2 ng/ml, diminished ovarian reserve (DOR) [12]) and/or suffer from endometriosis or severe male factor.

Furthermore, despite significant advances in reproductive medicine, 9 to 24% of women undergoing IVF show a poor ovarian response to stimulation [13].

According to the literature, NC- and/or Min stim-IVF could be a valuable alternative to cIVF for expected poor responders and/or low prognosis patients [14]. Retrospective analyses and randomized controlled trials published in the last decade have provided strong evidence against the use of increased dose of gonadotropins, once the results did not differ from low-dose protocol [15]. Finally, the American Society for Reproductive Medicine (ASRM) guideline states that Min stim-IVF should be considered for patients who are poor responders [16].

In an ongoing debate about which ovarian stimulation therapy is most suitable for patients, physicians belonging to the IVF Naturelle network offer both treatment options: NC- and/or Min stim-IVF and cIVF.

**The patients decision and the physician's recommendation will be documented.**

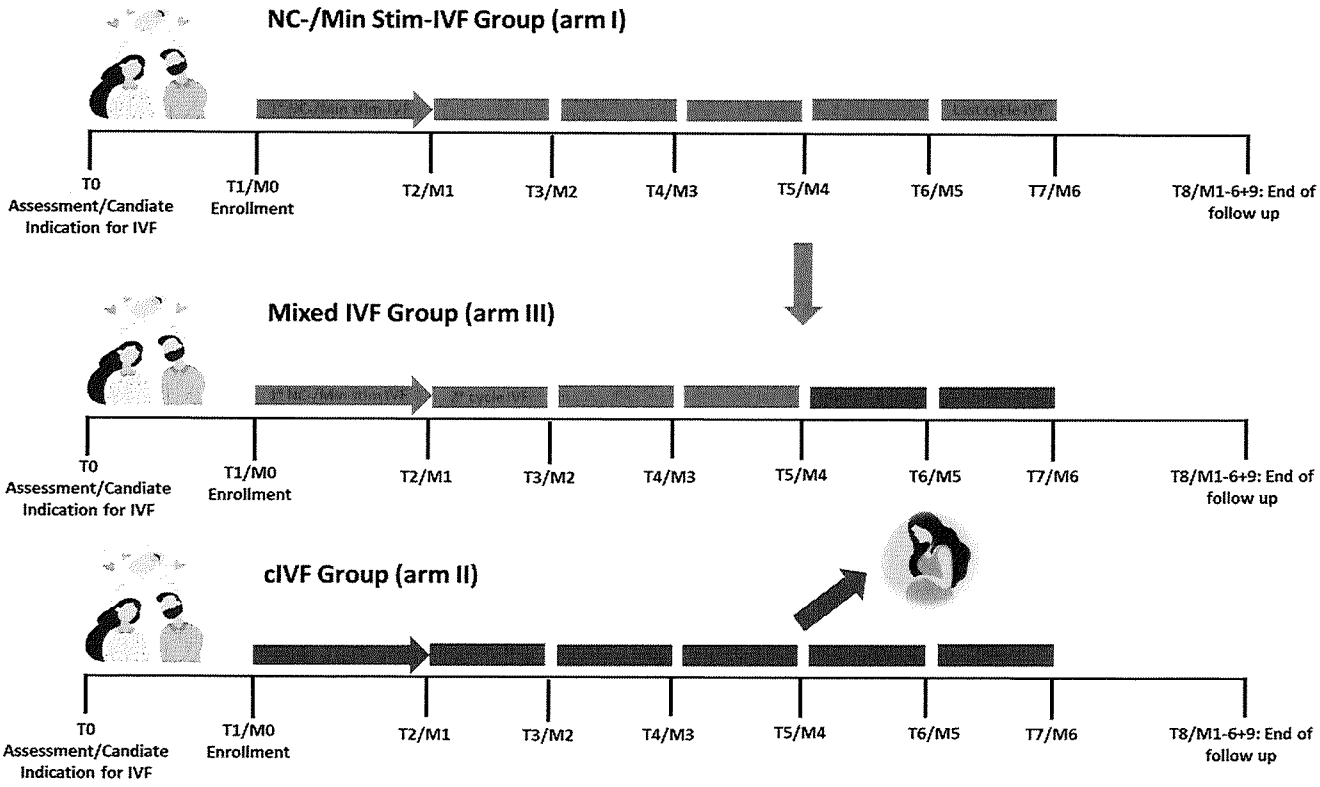
The following simplified **flowchart** will be used to counsel patients by all the involved physicians:

**Characteristics of the IVF treatment strategies - Patient centered decision making**

| | Natural Cycle und Minimal stimulation IVF («IVF-Naturelle») | Conventional, full stimulated IVF |
|---|---|---|
| **Characteristics of the treatment strategies** | **Overall aspects**<br>o Natural/low dose hormonal stimulation<br>o More natural and gentle approach<br>o Focus on oocyte quality<br>o Several stimulation cycles required<br>o Apparently lower treatment related stress<br>o Lower costs per cycle (average costs per achieved pregnancy probably similar)<br>o Probably no surplus fertilized oocytes/embryos to be frozen and used later<br>o No risk of ovarian hyperstimulation syndrome<br>**Technical aspects**<br>o Few injections per cycle<br>o More flexibility for monitoring consultations required<br>o No anaesthesia for oocyte retrieval required<br>**Further aspects**<br>o Very low risk for multiple pregnancies<br>o Does probably not affect endometrial function | **Overall aspects**<br>o High dose hormonal stimulation<br>o More artificial and intensive approach<br>o Focus on oocyte quantity<br>o Fewer stimulation cycles required<br>o Apparently higher treatment related stress<br>o Higher costs per cycle (average costs per achieved pregnancy probably similar)<br>o Possibly freezing of surplus fertilized oocytes/embryos to be used later<br>o Low risk of ovarian hyperstimulation syndrome<br>**Technical aspects**<br>o Many injections per cycle<br>o Less flexibility for monitoring consultations required<br>o Anaesthesia for oocyte retrieval required<br>**Further aspects**<br>o Low risk of multiple pregnancies<br>o Might negatively affect endometrial function |
| **Ideal biological circumstances** | Any ovarian reserve including very low ovarian reserve | Normal and high ovarian reserve |

Only patient data on the results of IVF cycles during the **first six months** will be recorded (**study period**). In case of pregnancy, patients will be followed till the end of pregnancy, in order to calculate the cumulative live birth rate. There will be a group of patients who will undergo NC/Min stim-IVF ("IVF-Naturelle", green, **Group 1**) and a group of patients who will undergo cIVF (red, **Group 2**), and there will also be a group of patients who will undergo a mix of IVF treatments due to a change of treatments during the 6 month study period (Mixed IVF Group, green and red, **Group 3**).

**Therapy thread**




**Monitoring of cycles**: IVF cycles will be monitored by ultrasound and serum E2 and LH measurements. GnRH antagonist will be started regularly in cIVF and NC- and/or Min stim-IVF depending on follicle size and hormonal results. Oocyte retrieval (oocyte pick-up, OPU) is performed 36 hours after ovulation induction. For oocyte retrieval in NC- and/or Min stim-IVF, aspiration is performed without anaesthesia/analgesia and, if necessary, the follicle is flushed. In case of premature ovulation, the cycle is cancelled. OPU in cIVF with COS is performed according to standard procedures. IVF or ICSI will be used as the fertilisation technique.
Embryo transfer is usually performed on the 5th day, otherwise on the 2nd or 3rd day after aspiration.
During the study period, frozen embryos of previously generated embryos are also transferred to assess the pregnancy rate over time and cycles.

**The following questionnaires will be given to the patients:**

**T1/M0:** Before 1st IVF cycle:

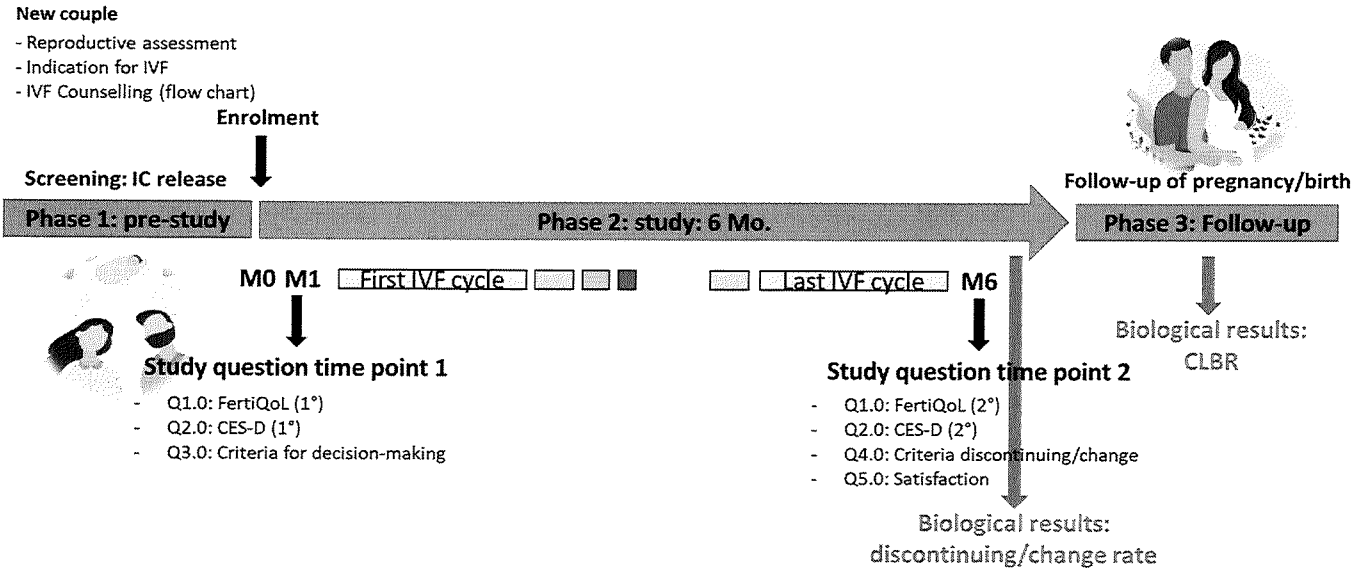
- **Q1.0** FertiQoL Questionnaire (1st time)
- **Q2.0** CES-D Questionnaire (1st time)
- **Q3.0:** Which factors have affected your first choice of IVF treatment?

**T7/M6:** At the end of the 6-month study period:

- **Q1.0** FertiQoL Questionnaire (2nd time, only the questions related to the treatment: T1-T10)
- **Q2.0** CES-D Questionnaire (2nd time)
- **Q4.0:** Reasons for changing or discontinuing IVF treatment (in case of changing treatment)
- **Q5.0:** Satisfaction with the first choice and influence of the insurance system

Surveys will be sent out to women who will not return for further treatment within 6 months following a failed attempt (including frozen embryo transfers). Patients will be asked whether they intend to return for further treatment and if not what their primary reason for stopping is. Some couples will receive medical advice to discontinue treatment because of a poor ovarian response or poor embryo quality. However, this advice will never be binding.

**Study flow chart**




## Time line:

- The recruitment period will last for 12 months,
- followed by 6 months for the study period of the last recruited patients and
- 9 months follow up to collect data on pregnancy outcome.

Accordingly, in total the study will last for 2 years and 3 months.

## 3.4 Withdrawal and discontinuation, definitions

Once participants have been enrolled, there are mainly three possible scenarios that could happen:

1. Withdrawal: Women undergoing NC-IVF/Min stim-IVF or cIVF may decide to stop treatment after a few cycles, but before the end of the 6-month study period. These women will not be excluded.
2. Discontinuation: It is possible that women undergoing Min stim-IVF or cIVF may decide to interrupt treatment for a certain amount of time after a few cycles, but before the end of the study. These women will not be excluded.
3. Change: Women undergoing NC/Min stim-IVF or cIVF may decide to change their treatment method: From NC/Min stim-IVF to cIVF, or from cIVF to NC/Min stim-IVF. According to the study, the group of women who change the main treatment modality during the study period (i.e. undergoing both Min stim-IVF and cIVF) will not be excluded.

# 4 STATISTICS AND METHODOLOGY

## 4.1. Statistical analysis plan

Statistics will be performed by the Clinical Trials Unit (CTU) of the Department of Clinical Research (DCR) of the University of Bern. For this purpose, data collected in Germany is transferred to Switzerland.

**Number of participants**

Our focus is on the mechanisms behind the IVF treatment decision (i.e. c-IVF or NC-IVF), twith pre-choice stress being considered the primary outcome. A precision-based sample size is appropriate for our observational study. Seven centres will participate in the study during a 12-month recruitment phase, with a minimum potential enrolment of 300 participants. If fewer than 300 participants have been recruited within 12 months, the recruitment period may be extended by up to 6 months.

An effect size estimation was computed based on a potential total sample size of 300 participants. It is reasonable to assume that half of the participants will chose c-IVF and the other half NC-IVF, i.e. 150 participants in each of the group. Hence, an effect size of 0.33 can be detected using a two-sided type I error of 5% and a power of 80%. Using standard deviations (SDs) derived from a study performed previously by us to compare NC-IVF and cIVF [11], an effect size of 0.33 represents the following effect measure. For the primary outcome, level of FertiQuol score at the timing of the treatment choice, assuming a score SD of 12, an effect size of 0.33 represents a mean difference of 4.0 points score. For CES-D score, the key secondary outcome, assuming a score SD of 7, an effect size of 0.33 represents a mean difference of 2.3 points score.

**Statistical analysis**

Participants' characteristics will be summarized in a table, overall and by treatment choice. Descriptive statistics will include frequencies and proportions for categorical variables and median (interquartile range) or means (standard deviations) for continuous variables depending on their distribution. Outcomes will be presented in a table for the different time points and the mean differences and their 95% Confidence Interval (CI) will be computed between the two treatment decision groups at baseline. Outcomes' change in time will be also presented by group with their 95% CI.

Secondary outcomes as criteria for the treatment choice of the participants and pregnancy outcome will be presented through frequencies and proportions, overall and by treatment's choice group.

Time to pregnancy will be present through a Kaplan-Meier curves for each of the initial treatment decision.

Time to treatment change will also be presented descriptively and through Kaplan-Meier curves for each of the initial treatment decision.

All the analysis will be done using R (version 4.5.1 or later) or Stata (version 18 or later).

## 4.2. Handling of missing data

All variables with missing data will be reported descriptively. Primary analyses will be conducted using complete case data. If necessary, additional analyses using appropriate statistical methods such as multiple imputation may be performed to assess the sensitivity of the results.

# 5 REGULATORY ASPECTS AND SAFETY

## 5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the Human Research Act (HRA) [2] and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The project leader and the Sponsor acknowledge their responsibilities.

## 5.2 Notification of safety and protective measures (HRA Art. 15, HRO Art. 20)

If, during the research project, circumstances arise which could jeopardise the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the benefits, all the measures required to ensure protection will be taken without delay.

The project leader and the Sponsor are promptly notified (within 24 hours) if immediate safety and protective measures must be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

## 5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1]

The project leader reports to the ethics committee on the connection between the event and the collection of health-related personal data. At the same time, the project leader submits proposals concerning the next steps to be taken.

Any new relevant information and the outcome to the original Serious Event is reported to the ethics committee via BASEC.

## 5.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

### 5.5 End of project

The completion of the research project is defined by the last collection of health-related personal data. Upon project completion or discontinuation, the Ethics Committee is notified within 90 days.

After the termination of the project, the coded health-related data will be stored in a specific platform (REDCap®).

### 5.6 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO).

# 6 FURTHER ASPECTS

## 6.1 Overall ethical considerations

This project will be conducted according to the requirements by HFG, especially HFV. Prerequisite of conduction of this project is the vote of the ethics committee.

As the study design is observational, there are practically no burden for the patients, who are free to choose their IVF treatment and the number of cycles, and can also change their treatment (from NC-IVF or Min stim-IVF to cIVF or conversely). During the study, we will only collect the necessary data to calculate the outcomes, according to the list of endpoints. All the endpoints are part of routine IVF treatment. We do not expect any "surplus information" or "incidental findings". We also don't collect genetic data.

## 6.2 Risk-Benefit Assessment

Similar research projects do not exist in the literature, so the results will be both new and unique. The additional scientific and social value is significant, as the live birth rate in NC- and Min stim-IVF is currently unknown.

As we are collecting data that would be collected anyway during normal IVF treatment (study design observational), and there are no additional visits or blood examinations, we don't expect any risks for the participants. Indirectly, participants are affected by the risks connected with the data storage (the risk of unauthorized data access through third parties or unwanted identification of participants). The details of the data protection concept will be explained in the next subchapter.

Participants will also not have any benefits from the study. However, the investigation is warrant and relevant for future patients, as the live birth rate in NC-/Min stim-IVF is currently unknown.

# 7 QUALITY CONTROL AND DATA PROTECTION

## 7.1 Quality measures

All team members of the department are trained on all important study related aspects and had performed a Good-Clinical-Practice (GCP) course.

The project leader has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 4 HRO).

For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

## 7.2 Data recording and source data

The project is recorded with an electronic Case Report Form (eCRF) called Redcap. The project data is stored by the Department of clinical research (DCR) of the University of Bern. No data is transferred from Switzerland to Germany. The following source data is used in the study: Study Case Report Form (RedCap®), general consent for further use of health-related data and samples for research purposes, request to participate in medical research, standardised questionnaires on stress level.

Only routinely collected data is part of participant file but it may be transferred to the participant's CRF under the condition that, in this case, the CRF will no longer be considered as source data.

## 7.3 Confidentiality and coding

**Project data** (trial and participant data) will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other project specific documents, participants are only identified by a unique participant number. Coding is done using a method based on the current state of the art that (Art. 26 HRO).

In practice, all co-workers of the Division are allowed to handle the data as far the treatment of the patients is concerned. The project specific collection and handling of the data will be limited to those who are involved in the project. Only the study team will have access to the uncoded data and samples. The study team consists of:

- Michael von Wolff, Professor, MD, Chief Physician, Gynaecological Endocrinology and Reproductive Medicine, University Women's Hospital, Insel Gruppe AG und University of Bern
- Isotta Martha Magaton, MD, Gynaecological Endocrinology and Reproductive Medicine, University Women's Hospital, Insel Gruppe AG und University of Bern

Storage of data

We will install a REDCap file (https://redcap.ctu.unibe.ch,) and all participating centers will have password secured access. The electronic data capturing (EDC) system is activated for the trial only after successfully passing a formal test procedure. All data entered, are stored on a Linux server in a dedicated MySQL database. Responsibility for hosting the EDC system and the database lies with CTU (DCR) Bern. The server hosting the EDC system and the

database is kept in a locked server-room. Only the system administrators have direct access to the server and back-up tapes. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires. All data entered into the file are transferred to the database using the Transport Layer Security (TLS) encrypton. Each data point has attributes attached to identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail). A multilevel back-up system is implemented. Back-ups of the whole system including the database are run internally several times per day and on external tapes once a day. The back-up tapes are stored in a secure place in a different building. At interim and final analyses, data files will be extracted from the database into statistical packages to be analyzed. After database lock, the status of the database is recorded in special achieved tables. The sponsor will keep the Trial Master File, the extracted data, the meta data and interim/final report for at least 10 years. Data is checked by the EDC system for completeness and plausibility. In addition, central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data. Before database lock the project leader will validate the collected data with his signature.

Project data will be handles with uttermost discretion and is only accessible to authorized people who require the data to fulfill their duties within the scope of the research project. On project specific documents, only a unique participant number will identify the participants. Coded data is used. All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage with limited access. Clinical information will not be released without the written permission of the participant, except, if necessary, for monitoring and auditing by the Sponsor, its designee and Regulatory Authorities. The investigators and study site staff involved with this study may not disclose, record or use data for any purpose other than performance of the study. The same applies for other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsors or its designee must be obtained for the disclosure of any said confidential information to other parties. All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

### 7.4 Retention and destruction of project data and biological material

The project leader retains all the research project data for a period of at least ten years after the completion or early termination of the research project.

## 8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The project is funded by the Division of Gynaecologic Endocrinology and Reproductive Medicine at the Inselspital, Bern University hospital.

There are no secondary interests of the involved principal investigators. See the clinical study agreement for more information.

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**Appendix 1: Schedule of assessments <u>per IVF cycle</u>** (these appointments are necessary for people undergoing IVF, there are no additional appointments for the study. The listed procedures, e.g. OPU and ET, are part of the IVF cycle, they should not be understood as study-related interventions).

| Time (day) | > -1 | + 1month | Follicle phase | Ovulation phase | Luteal phase | 13 days after OPU |
|---|---|---|---|---|---|---|
| | | | 1 IVF cycle/1 menstrual cycle | | | |
| **Visit** | Indication for IVF | Enrollment | 1st Visit | 2nd Visit | 3th Visit | Evtl. 4th Visit |
| **Oral + written patient information** | + | | | | | |
| **Written consent (signed)** | | + | | | | |
| **In-/Exclusion criteria** | + | + | | | | |
| **Procedures*** | | | + | + | + | + |
| **Intervention*** | | | US/blood test | OPU | ET | HCG |
| **Standardised Questionnaire** | | + | | | | |

Abbreviations: ET, embryo transfer; HCG, human chorionic gonadotropin; IVF, in-vitro-fertilisation; OPU, oocyte pick-up; US, ultrasound.
*To specify: procedures and interventions are not specific for the study, but part of a normal IVF cycle. We don't test any interventions/procedures.

**Appendix 2: Schedule of assessments <u>over the study period of 6 months independent of pregnancy status</u> (these appointments are necessary for people undergoing IVF. There are no additional appointments for the study).**

| Time (day) | + 5month | Follicle phase | Ovulation phase | Luteal phase | 13 days after OPU | 6month |
|---|---|---|---|---|---|---|
| | | Last IVF cycle/1 menstrual cycle | | | | |
| **Visit** | | 1st Visit | 2nd Visit | 3th Visit | Evtl. 4th Visit | |
| **Oral + written patient information** | | | | | | |
| **Written consent (signed)** | | | | | | |
| **In-/Exclusion criteria** | | | | | | |
| **Procedures** | | + | + | + | + | |
| **Intervention** | | US/blood test | OPU | ET | HCG | |
| **Standardised Questionnaire*** | | | | | | + |

Abbreviations: ET, embryo transfer; HCG, human chorionic gonadotropin; IVF, in-vitro-fertilisation; OPU, oocyte pick-up; US, ultrasound.