Patient MPI #_____

STATE OF NORTH CAROLINA

COUNTY OF MECKLENBURG

CONSENT AND AGREEMENT FOR OVARIAN HYPERSTIMULATION, SURGICAL OOCYTE (EGG) RETRIEVAL, CRYOPRESERVATION BY VITRIFICATION, AND STORAGE

THIS AGREEMENT is made this, the _____ day of _____, 20___, for good and valuable consideration, by and between **REPRODUCTIVE ENDOCRINE ASSOCIATES OF CHARLOTTE, P.C.** (hereinafter referred to as "REACH") and

_____

(Print full name as seen on driver's license)

Introduction

This consent discusses the retrieval (collection), cryopreservation (freezing), and storage of oocytes (eggs) and also addresses the subsequent disposition of the cryopreserved eggs collected for the purpose of fertility preservation. Please read this document carefully and address any questions with your physician and healthcare team so that all your questions can be answered to your satisfaction.

Ovarian Stimulation. To increase the likelihood of multiple viable eggs to be cryopreserved, you will undergo a cycle of medication-induced ovarian stimulation prior to your egg retrieval. It is hoped and intended that several eggs can be cryopreserved to increase your chances that some of these eggs may be viable, and thus improving the chance to create viable embryos once such eggs are later fertilized with sperm. Each woman receives hormonal medications tailored to her age, history and ovarian functional status, to attempt stimulating the growth of multiple eggs in one cycle, rather than the usual one egg per cycle.

Medications are given by subcutaneous (SQ) or intramuscular (IM) injection one or more times per day. Only some or some combination of the medications below are utilized in each cycle. Their risks may include, but are not limited to, the following:

1. Gonadotropins, or injectable "fertility drugs" (Follistim®, Gonal-F®, Bravelle®, Menopur®): These hormones stimulate the ovary and are given over the span of 8 or more days. All injectable fertility drugs have FSH (follicle stimulating hormone), a hormone that will stimulate the growth of your ovarian follicles (which contain the eggs). Some medications also contain LH (luteinizing hormone) or LH-like activity. LH is a hormone that may work with FSH to increase the production of estrogen and growth of the follicles. Proper dosage of these drugs and the timing of egg recovery require frequent monitoring of the ovarian response, usually by way of blood tests and vaginal ultrasound examinations during the ovarian stimulation.

These medications are given by SQ injection. As with all injectable medications, bruising, redness, swelling, or discomfort can occur at the injection site. Rarely, there can be an allergic reaction to these drugs. Other risks and side effects of gonadotropins include, but are not limited to, fatigue, headaches, weight gain, mood swings, nausea, and clots in

blood vessels.

The intent of giving these medications is to mature multiple follicles, and many women experience some cyst formation, bloating, and minor discomfort as the follicles grow and the ovaries become temporarily enlarged. Up to 2.0% of women will develop Ovarian Hyperstimulation Syndrome (OHSS). OHSS symptoms can include increased ovarian size, nausea and vomiting, accumulation of fluid in the abdomen, breathing difficulties, an increased concentration of red blood cells, or blood clotting. Extremely rare manifestations may be kidney and liver problems, and in the most severe cases kidney failure, or death. The severe cases affect only a very small percentage of women who undergo *in vitro* fertilization and embryo transfer —0.2 percent or less of all treatment cycles—and the very severe are an even smaller percentage. Only about 1.4 in 100,000 cycles has led to kidney failure, for example. The stimulation may result in very few follicles developing. The end result may be few or no eggs obtained at egg retrieval or even cancellation of the treatment cycle prior to egg retrieval.

2. GnRH-agonists (Leuprolide acetate) (Lupron®): This medication is taken by SQ injection. GnRH-agonists initially cause a release of FSH and LH from the pituitary, and they can be used to start the growth of the follicles and/or initiate the final stages of egg maturation. Though leuprolide acetate is an FDA (Federal Drug Administration) approved medication, it has not been approved for use in IVF, although it has routinely been used in this way for more than 20 years. Potential side effects usually experienced with long-term use include, but are not limited to, hot flashes, vaginal dryness, bone loss, nausea, vomiting, skin reactions at the injection site, fluid retention, muscle aches, headaches, and depression. No long term or serious side effects are known.

3. GnRH-antagonists (Ganirelix Acetate or Cetrorelix Acetate) (Cetrotide®): These medications are used to prevent premature ovulation, and are taken as SQ injections. They are used for short periods of time in the late stages of ovarian stimulation. The potential side effects include, but are not limited to, abdominal pain, headaches, skin reaction at the injection site, and nausea.

4. Human chorionic gonadotropin (hCG) (Novarel®, Pregnyl®): hCG is a natural hormone used in many IVF cycles to induce the eggs to become mature and fertilizable. If used, potential side effects include, but are not limited to breast tenderness, bloating, and pelvic discomfort. This medication is given by SQ injection.

5. Oral contraceptive pills*:* Many ovarian stimulation protocols include oral contraceptive pills to be taken for 2 to 4 weeks before gonadotropin injections are started in order to suppress hormone production or to schedule a cycle. If utilized, side effects include unscheduled bleeding, headache, breast tenderness, nausea, swelling, and the risk of blood clots or stroke.

6. Other medications*:* Antibiotics may be given for a short time during the treatment cycle to reduce the risk of infection associated with egg retrieval. Antibiotic use may be associated with causing a yeast infection, nausea, vomiting, diarrhea, rashes, sensitivity to the sun, and allergic reactions.

For patients preserving their eggs in the face of a cancer diagnosis, it is important to understand that while the studies to date are reassuring, the effects of ovarian stimulation on cancer have not been extensively studied. Therefore, it is possible that ovarian stimulation could influence cancer cells and interfere with the outcome for cancer treatment leading to reduced longevity or cancer recurrence.
There is limited good quality information on the possibility that fertility medications may increase the risk of developing **breast disease, ovarian disease, or cancer.** There have been a very few studies which claim to have found an association between long use of fertility medications and breast / ovarian disease. These studies are typically flawed (the results can not be relied upon as truth) for two reasons: (1) These studies fail to account for the fact that women who never deliver a baby in their lifetime are at definite

increased risk for breast /ovarian tumors / cancer, so it may not be that fertility drugs are responsible for causing breast / ovarian tumors / cancer, but rather it may be that lifelong infertility is in itself a risk for breast / ovarian tumors / cancer. (2) The studies which have alleged an association between fertility medications and breast / ovarian disease have typically studied women who have used many cycles of fertility medication without becoming pregnant. This issue of risk association between the 'dose effect' of fertility medications and breast / ovarian tumors / cancer will likely be clarified with better designed research studies in the future. It is reassuring at the current time that the ***majority*** of studies which have evaluated this issue have found no significant direct correlation between fertility medications and breast or ovarian disease. Furthermore it is important to note that having a full term pregnancy seems to have a *protective effect (actually may decrease your chance)* against both breast and ovarian cancer. It is therefore our goal to treat you as efficiently as possible with a reasonable number of appropriately selected fertility treatment cycles as long as these treatments are giving you a reasonable chance of pregnancy, hopefully within the shortest timeframe possible.

Oocyte (egg) Retrieval

Oocyte retrieval is the removal of eggs from the ovaries. A transvaginal ultrasound probe is used to visualize the ovaries and the egg-containing follicles within the ovaries. A long thin needle, which can be seen on ultrasound, is guided into each follicle and the contents aspirated. The aspirated material includes follicular fluid, oocytes (eggs), and granulosa (egg-supporting) cells. Rarely the ovaries are not accessible by the transvaginal route and laparoscopy or transabdominal retrieval may be considered. These procedures and risks will be discussed with you by your doctor if applicable. Anesthesia is used to reduce if not eliminate discomfort. Complications of egg retrieval are not frequent but include:

1. ***Infection****:* Bacteria normally present in the vagina may be inadvertently transferred into the abdominal cavity by the needle. These bacteria may cause an infection of the uterus, fallopian tubes, ovaries, or other intra-abdominal organs. The estimated incidence of infection after egg retrieval is less than 0.5%. Treatment of infections could require the use of oral or intravenous antibiotics. Severe infections occasionally require surgery to remove infected tissue. Infections can have a negative impact on future fertility. Prophylactic antibiotics are sometimes used before the egg retrieval procedure to reduce the risk of pelvic or abdominal infection. Despite the use of antibiotics, there is no way to eliminate this risk completely.
2. ***Bleeding****:* The needle passes through the vaginal wall and into the ovary to obtain the eggs. Both of these structures contain blood vessels. In addition, there are other blood vessels nearby. A small amount of blood loss is common during egg retrievals. The incidence of major bleeding problems has been estimated to be less than 0.1%. Major bleeding will frequently require surgical repair and possibly loss of the ovary. The need for blood transfusion is rare. Although very rare, review of the world experience with IVF indicates that unrecognized bleeding has led to death.
3. ***Trauma:*** Despite the use of ultrasound guidance, it is possible to damage other intra-abdominal organs during the egg retrieval. Previous reports in the medical literature have noted damage to the bowel, appendix, bladder, ureters, and ovary. Damage to internal organs may result in the need for additional treatment such as surgery for repair or removal of the damaged organ. However, the risk of such trauma is low.
4. ***Unintended Pregnancy:*** All eggs may not be retrieved during egg retrieval and if ovulation occurs there is a <u>risk of unintended pregnancy</u> through intercourse. Appropriate <u>barrier contraception and/or abstinence should be used from before till well after egg retrieval</u>.
5. ***Anesthesia****:* The use of anesthesia using a single or combination of drugs (Propofol, Versed) for intravenous sedation during the egg retrieval can produce unintended complications such as an allergic reaction, low blood pressure, nausea or vomiting,

aspiration into the lungs, subsequent infection and/or hospitalization, and in rare cases, death. Obesity may increase the likelihood of difficult anesthesia administration and / or difficult maintenance of a functional airway, which may then result in ventilation / oxygen perfusion difficulty for the patient. At the discretion of the Anesthetist / Anesthesiology staff, and / or the REACH medical staff, it may be required that your egg retrieval be performed in a hospital main operating room for more advanced anesthesiology requirements.

6. ***Failure of Egg Retrieval*:** It is possible that the aspiration will fail to obtain any eggs or the eggs may be abnormal or of poor quality and fail to produce any viable eggs.

Cryopreservation

Because ice crystals can form within the eggs and damage them, the embryologist places the eggs in special solutions to remove the water from the eggs and then bathes them in protectant solutions during the 'flash' freezing process known as vitrification. Eggs may not survive the freezing process or technical or mechanical or power failures may occur causing loss of some or all of the eggs. This may or may not affect the cryopreserved egg's capacity for fertilization or implantation.

Storage

Cryopreserved / vitrified eggs are stored in liquid nitrogen storage containers until they are removed for warming**.** Technical, mechanical or power failures can occur at any point in the freezing process or anytime during the storage which could result in the loss of the future viability of the eggs. Likewise, once the eggs are in storage, technical problems, terrorism, fire, and certain acts of nature (earthquake, prolonged loss of power, etc) could result in the loss of some or all of the frozen eggs.

Summary of future procedures for subsequent attempts at egg fertilization, embryo growth *in vitro,* and embryo transfer using the cryopreserved eggs from this cycle (<u>those later procedures requiring subsequent separate informed consent and agreement documents</u>) :

At a time when you wish to attempt to conceive, you will be given medication to regulate your cycle to coincide with the time of egg warming. For the eggs that survive the warming process (if any), trained laboratory personnel will perform **Intra-Cytoplasmic Sperm Injection (ICSI)**, a procedure where one sperm is directly injected into each mature egg using a very fine glass needle to achieve fertilization. The risks of ICSI include damage to either the egg or sperm resulting in either lack of fertilization or death of the egg or sperm. In some instances, the damage is more subtle and the embryo produced will not be normal and will have to be discarded. Successful fertilization rates with ICSI are similar or superior to routine in-vitro fertilization in the hands of experienced qualified embryologists. As with all laboratory procedures, there is a risk of damage to the egg and/or sperm during handling.

There is no guarantee of how many or that any of the frozen eggs will survive the warming process or how many or if any of them will successfully fertilize and mature into an embryo. There is similarly no guarantee that any embryo resulting from a cryopreserved egg will result in a pregnancy or delivery, or development to a healthy normal infant.

The rate of successful births following fertilization of previously frozen eggs has been reported to be lower than a comparable age population that used fresh eggs for in-vitro fertilization, but more recent literature suggests improvement using newer cryopreservation techniques (vitrification). The successful pregnancy rate from previously frozen eggs depends on a number of variables, including the age of the woman when the eggs were retrieved, the initial quality and maturity of the retrieved eggs, the condition of the egg after warming, the quality of sperm used for fertilization, the quality of the embryos produced with the warmed eggs, and other factors such as laboratory conditions and experience level of embryology staff which may influence the process of in-vitro fertilization. At this current time there is limited information on

whether or not conception following egg cryopreservation carries genetic, congenital, or other risks to a resulting infant, however initial reports indicate that children born by this treatment do not have significantly higher outcomes of congenital anomalies as compared to children conceived by natural means in the general population. Until a very large number of children are born following the freezing and thawing of eggs, it will not be possible to be sure that the rate of abnormalities is unchanged from the normal rate.

If pregnancy occurs following the use of a cryopreserved egg, it is recommended that pre-natal screening by maternal peripheral blood screening, amniocentesis or chorionic villus sampling (CVS) be performed. Such testing should be discussed with and arranged by your obstetrician in charge of your pregnancy care. In any case, if a pregnancy occurs from fertilization of a cryopreserved egg, delivery of a child may not occur due to miscarriage, ectopic pregnancy, or other complications of pregnancy or delivery.

Storage Fees, Logistics, and Disposition

Eggs which are surgically retrieved and cryopreserved at the REACH program will be stored in the REACH cryopreservation facility. Your cryopreserved eggs are considered your property and no disposition of such eggs will take place without your formal instruction. It may be necessary at some unknown point in the future, for presently unknown reason that cryopreserved eggs at the REACH facility may need to be transferred to an offsite alternative long term cryopreservation facility. If such event were to be necessary REACH will make effort to contact you using such contact information that you have provided us. You are solely responsible for providing REACH updated contact information such as phone number and mailing address, as well as any change in your personal identification information such as a change in your name. At REACH there is a yearly storage fee. There are additional charges to thaw the cryopreserved eggs, inseminate the thawed eggs using intracytoplasmic sperm injection (ICSI), grow the fertilized eggs in culture, and to perform uterine transfer with the resulting embryo(s), along with other laboratory and facility fees. Information about such costs is available to you along with the opportunity to discuss this option with your physician and healthcare team. REACH reserves the right to change charges for any or all of their procedures at its sole discretion.

You have the option to move / store your cryopreserved eggs to a separate fertility center or long-term storage facility. While we do not endorse any one facility, we can provide you with a list of long-term storage facilities. You are responsible for contacting such facilities to discuss their programs and costs. If your cryopreserved eggs are moved out of the REACH cryopreservation facility to another facility, then it may not be permissible for your cryopreserved eggs to be moved back to the REACH facility at a later date.

Storage / Proprietary Contingency Status of Cryopreserved Eggs:

Once your eggs are cryopreserved at the REACH facility you will be financially responsible for all costs associated with cryopreservation and storage of eggs and you agree to notify REACH of any change in your address or change in your personal identification – such as a change in your name.

In the event of your death, or cognitive incapacitation, or in any such case that you are unable to continue sole proprietary disposition of your cryopreserved eggs and without any other legally recognized transfer of proprietary rights to such eggs, then you authorize REACH to perform the following disposition for your cryopreserved eggs:

(Please initial your choice)

a._____ Discard all my cryopreserved eggs according to acceptable laboratory practices.

b._____ Donate all my cryopreserved eggs to research, which will ultimately result in

destruction (no clinical viability) of any biological result of such research.

Any requests for transfer of ownership or contingency ownership of your stored eggs at REACH must be formally submitted to REACH so that any such documentation can become part of your medical record. You are responsible for any such documentation being legally appropriate and interpretable. In any case REACH will not recognize any such alternative proprietary disposition requests unless and until such alternative party has also formally acknowledged acceptance of such responsibilities for cryopreserved egg storage, including accepting responsibility for storage fees.

If storage fees are unpaid despite a reminder notice in writing to your mailing address of record, and / or if disposition for your cryopreserved eggs is necessary and REACH is unable to contact you at your contact information of record, then a limited number of formalized repeat attempts at contacting you will be made according to recommended standards by fertility practice / cryopreservation facility authorities. If such recommended standards are followed and completed without any response on your part, then REACH has the authority to discard your cryopreserved eggs according to acceptable laboratory practices.

Acknowledgements

I acknowledge that while the process of stimulation and retrieval of eggs will be performed there is no guarantee as to the number of eggs that will be produced or removed, whether the eggs will be normal, or whether the eggs will be mature.

I acknowledge that there are risks to the ovarian stimulation and egg retrieval process, known and unknown, and include but are not limited to ovarian overstimulation, cyst formation, internal bleeding and/or excess fluid accumulation including the need for blood transfusion and/or fluid removal by aspiration, infection with treatment with or without hospitalization.

I acknowledge that an egg or eggs remaining in my ovaries after my egg retrieval may spontaneously release from my ovaries and may become fertilized through intercourse and thus result in pregnancy, and that this eventuality can be minimized by use of contraception and/or abstinence during the cycle of treatment.

I acknowledge that no guarantees can be made as to the survivability of the eggs during freezing or during the thawing process, that the eggs can be used for fertilization, or to the outcome of the fertilization or implantation processes.

I acknowledge that no guarantees can be made that the eggs will be able to establish a pregnancy resulting in the delivery of a baby, or healthy or normal baby.

With respect to future potential clinical disposition of my eggs, I acknowledge that:

- Some or all of the eggs:
  - May not survive the warming process
  - May not fertilize
  - May not fertilize normally

- Some or all of the resulting embryos (fertilized eggs):
  - May not grow and/or divide
  - May not grow normally
  - May not be suitable for transfer to the uterus
  - May not implant if transferred to the uterus
  - May not continue to grow after implantation

- May not develop into a normal pregnancy or normal child

- The effect of cryopreservation on short term and long term normality and health of egg and/or embryo and children born following transfer is unknown at this time with any degree of certainty.

I acknowledge that no guarantees can be made as to the future health of an offspring born from these assisted reproductive processes. At this point in time, risks of the procedure may be unknown and, therefore, no representation is made as to its effectiveness. I understand that the techniques used to cryopreserve / vitrify eggs with later thawing / warming of eggs may reduce the chances for a clinical pregnancy or live birth, as compared to current literature describing such chances in the context of more standard in vitro fertilization with fresh eggs and fresh sperm.

I acknowledge that I might later conceive by natural means and if so, such event does not change the content or intent of this document, nor the responsibilities to me described herein.

I acknowledge that I have considered and herein chosen a plan for disposition of my cryopreserved eggs (as indicated above) in the case of my death or cognitive incapacitation without other documentation designating an alternative responsible party who has provided REACH with appropriate documentation confirming transfer of proprietary rights and responsibilities .

I acknowledge financial responsibility for all costs associated with cryopreservation and storage of eggs and agree to notify REACH regarding any change in my address or contact information, as well as any change in my personal identification such as a name change.

I acknowledge that if I fail to maintain financial responsibility for cryo storage of my eggs, and REACH has made appropriate yet unsuccessful attempt at contacting me per recommendations by professional fertility center / cryostorage facility guidelines, then REACH reserves the right to dispose of my cryopreserved eggs.

I acknowledge that technical, mechanical or power failures can occur at any point in the freezing process which could result in the loss of the future viability of the eggs. Likewise, once the eggs are in storage, terrorism, fire, technical difficulties and certain acts of nature (earthquake, prolonged loss of power, etc) could result in the loss of frozen eggs. Therefore,REACH is not liable for the loss of frozen eggs caused by or arising from such events.

If I opt to transfer cryopreserved eggs to another fertility center or long-term storage facility, I understand that I have full and sole responsibility for the transport and disposition of the cryopreserved eggs and hereby release REACH from any and all responsibility relating to the transport of the cryopreserved eggs.

I agree to release and hold harmless REACH, its trustees, directors, officers, shareholders, employees, servants, agents, affiliates, management companies and representatives for any and all damages, expenses, causes of action, suits and claims made or initiated with respect to the legal custody, rights and/or physical defect or abnormality of the egg as a result of the ovarian stimulation, egg retrieval, cryopreservation, and storage to the extent that such liabilities are not attributable to the negligence or willful misconduct of REACH and with respect to any claimed emotional injury or cost arising out of my participation in the above mentioned services.

I acknowledge that I have been provided with sufficient information about assisted reproductive technology and cryopreservation methods as well as the risks, benefits, and alternatives for ovarian stimulation, egg retrieval, and egg cryopreservation and storage. I have had the opportunity to consult with my physician and healthcare team. My physician and healthcare team have answered any and all questions I have posed to my satisfaction.

I acknowledge that I have read this document in its entirety and have had ample time to reach my decision, free from pressure and coercion, to proceed with my participation in the assisted reproductive services stated above.

_____ _____
Patient signature Date

_____ _____
REACH Representative verifying completion of consent Date

REPRODUCTIVE ENDOCRINE ASSOCIATES OF CHARLOTTE, P.C.

If signed outside of REACH facility, then patient's signature need notary attestation.

STATE OF _____
COUNTY OF _____

I, , a Notary Public of _____ County and State of

_____, certify that _____

personally appeared before me this day and acknowledged the execution of the foregoing instrument

consisting of _____ pages.

Witness, my hand and official seal, this, the _____ day of _____, 20___.

Notary Public: _____

My Commission Expires: _____