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DALLAS IVF

# *Informed Consent for Assisted Reproduction: Frozen Embryo Transfer*

Please place your signatures below to indicate which components of FET treatment you agree to undertake in your upcoming treatment cycle. Also, initial each page to indicate that you have read and understand the information provided. If you do not understand the information provided, please speak with your treating physician. There are a few locations within the consent form where you are being asked to make a decision. Please initial your choice and sign where requested.

### ***Chosen Elements of Treatment:***

**Printed patient name** **date of birth**

**Printed partner's name** **date of birth**

**Signatures:** (please sign ONLY in the presence of a notary or a Dallas IVF Representative or via e-signature on patient portal)

<b>Patient Signature:</b>	<i>Signature</i>
<b>Partner Signature:</b>	<i>Signature</i>
<b>Witness Signature:</b>	<i>Signature</i>

## OVERVIEW

In Vitro Fertilization (IVF) has become an established treatment for many forms of infertility. The main goal of IVF is to allow a patient the opportunity to become pregnant using her own eggs and sperm from her partner or from a donor. This is an elective procedure designed to result in the patient's pregnancy when other treatments have failed or are not appropriate.

This consent reviews the IVF process from start to finish, including the risks that this treatment might pose to you and your offspring. While best efforts have been made to disclose all known risks, there may be risks of IVF which are not yet clarified or even suspected at the time of this writing.

An IVF cycle typically includes the following steps or procedures:

- Medications to grow multiple eggs
- Retrieval of eggs from the ovary or ovaries
- Insemination of eggs with sperm
- Culture of any resulting fertilized eggs (embryos)
- Placement ("transfer") of one or more embryo(s) into the uterus
- Support of the uterine lining with hormones to permit and sustain pregnancy

In certain cases, these additional procedures can be employed:

- Intracytoplasmic sperm injection (ICSI) to increase the chance for fertilization
- Assisted hatching of embryos to increase the chance of embryo attachment ("implantation")
- Embryo Cryopreservation (freezing)
- Frozen Embryo Transfer

*Note: At various points in this document, rates are given which reflect what are believed to be U.S. national averages for those employing IVF treatments. These include items such as pregnancy rates, Cesarean delivery rates, and preterm delivery rates. These rates are not meant to indicate the rates of these outcomes within individual practices offering IVF and are not to be understood as such. Individual practices may have higher or lower pregnancy and delivery rates than these national averages, and also higher or lower risks for certain complications. It is appropriate to ask the practice about their specific rates.*

*Also note that while this information is believed to be up to date at the time of publication (2008), newer reports may not yet be incorporated into this document.*

### a. Frozen Embryo Transfer

- Frozen embryos can be thawed
- The number chosen influences the pregnancy rate and the multiple pregnancy rates
- A woman's age and the appearance of the developing embryo have the greatest influences on pregnancy outcome
- Embryos are placed in the uterine cavity with a thin tube
- Excess of embryos of sufficient quality that are not transferred can be frozen

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After a few hours of development, one or more embryos are selected for transfer to the uterine cavity. Embryos are placed in the uterine cavity with a thin tube. Ultrasound guidance may be used to help guide the catheter or confirm placement through the cervix and into the uterine cavity. Although the possibility of a complication from the embryo transfer is very rare, risks include infection and loss of, or damage to the embryos.

The number of embryos transferred influences the pregnancy rate and the multiple pregnancy rate. The age of the woman and the appearance of the developing embryo have the greatest influence on pregnancy outcome and the chance for multiple pregnancy. While it is possible, it is unusual to develop more fetuses than the number of embryos transferred. It is critical to discuss the number to be transferred before the transfer is done.

In an effort to help curtail the problem of multiple pregnancies (see multiple pregnancies), national guidelines published in 2006 recommend limits on the number of embryos to transfer (see Tables below). These limits differ depending on the developmental stage of the embryos and the quality of the embryos and take into account the patient's personal history.

**Recommended limits on number of 2-3 day old embryos to transfer**

Embryos	age <35	age 35-37	age 38-40	age >40
favorable	1 or 2	2	3	5
unfavorable	2	3	4	5

**Recommended limits on number of 5-6 day old embryos to transfer**

Embryos	age <35	age 35-37	age 38-40	age >40
favorable	1	2	2	3
unfavorable	2	2	3	3

## b. Hormonal support of uterine lining

- Successful attachment of embryo(s) to the uterine lining depends on adequate hormonal support
- Progesterone, given by the intramuscular or vaginal route, is routinely given for this purpose

Successful attachment of embryos to the uterine lining depends on adequate hormonal support of the lining. The critical hormones in this support are progesterone and estradiol. Normally, the ovary makes sufficient amounts of both hormones. However, in IVF cycles, this support is not always adequate. Therefore, progesterone is routinely given, and some clinics also prescribe estradiol. Progesterone is given by the intramuscular or vaginal route. Estradiol is given by the oral, vaginal, or intramuscular route. The duration of this support is from 2 to 10 weeks.

## c. Additional Elements and their risk

### 1. Assisted Hatching

- Assisted Hatching involves making a hole in the outer shell (zona pellucida) that surrounds the embryo
- Hatching may make it easier for embryos to escape from the shell which surrounds them

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The cells that make up the early embryo are enclosed within a flexible membrane (shell) called the zona pellucida. During normal development, a portion of this membrane dissolves, allowing the embryonic cells to escape or "hatch" out of the shell. Only upon hatching can the embryonic cells implant within the wall of the uterus to form a pregnancy.

Assisted hatching is the laboratory technique in which an embryologist makes an artificial opening in the shell of the embryo. The hatching is usually performed on the day of transfer, prior to loading the embryo into the transfer catheter. The opening can be made by mechanical means (slicing with a needle or burning the shell with a laser) or chemical means by dissolving a small hole in the shell with a dilute acid solution.

Some programs have incorporated artificial or "assisted hatching" into their treatment protocols because they believe it improves implantation rates, and ultimately, live birth rates although definitive evidence of this is lacking.

Risks that may be associated with assisted hatching include damage to the embryo resulting in loss of embryonic cells, or destruction or death of the embryo. Artificial manipulation of the zygote may increase the rates of monozygotic (identical) twinning which are significantly more complicated pregnancies. There may be other risks not yet known.

## 2. Frozen Embryos

- Freezing of viable embryos not transferred after egg retrieval provide additional chances for pregnancy
- Frozen embryos do not always survive the process of freezing and thawing
- Freezing of eggs before fertilization is currently much less successful than freezing of fertilized eggs (embryos)
- Ethical and legal dilemmas can arise when couples separate or divorce; disposition agreements are essential
- It is the responsibility of each couple with frozen embryos to remain in contact with the clinic on annual basis

Freezing (or "cryopreservation") of embryos is a common procedure. Since multiple eggs (oocytes) are often produced during ovarian stimulation, on occasion there are more embryos available than are considered appropriate for transfer to the uterus. These embryos, if viable, can be frozen for future use. This saves the expense and inconvenience of stimulation to obtain additional eggs in the future. Furthermore, the availability of cryopreservation permits patients to transfer fewer embryos during a fresh cycle, reducing the risk of high-order multiple gestations (triplets or greater). Other possible reasons for cryopreservation of embryos include freezing all embryos in the initial cycle to prevent severe ovarian hyperstimulation syndrome (OHSS), or if a couple were concerned that their future fertility potential might be reduced due to necessary medical treatment (e.g., cancer therapy or surgery). The pregnancy success rates for cryopreserved embryos transferred into the human uterus can vary from practice to practice. Overall pregnancy rates at the national level with frozen embryos are lower than with fresh embryos. This, at least in part, results from the routine selection of the best-looking embryos for fresh transfer, reserving the 'second-best' for freezing. There is some evidence that pregnancy rates are similar when there is no such selection.

**Indications:**

- To reduce the risks of multiple gestation
- To preserve fertility potential in the face of certain necessary medical procedures
- To increase the chance of having one or more pregnancies from a single cycle of ovarian stimulation
- To minimize the medical risk and cost to the patient by decreasing the number of stimulated cycles and egg retrievals

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- To temporarily delay pregnancy and the risks of OHSS occurs by freezing all embryos, when this risk is high.

**Risks of embryo cryopreservation:** There are several techniques for embryo cryopreservation, and research is ongoing. Traditional methods include “slow,” graduated freezing in a computerized setting, and “rapid” freezing methods, called “vitrification.” Current techniques deliver a high percentage of viable embryos thawed after cryopreservation, but there can be no certainty that embryos will thaw normally, nor be viable enough to divide and eventually implant in the uterus. Cryopreservation techniques could theoretically be injurious to the embryo. Extensive animal data (through several generations), and limited human data, do not indicate any likelihood that children born of embryos that have been cryopreserved and thawed will experience greater risk of abnormalities than those born of fresh embryos. However, until very large numbers of children have been born following freezing and thawing of embryos, it is not possible to be certain that the rate of abnormalities is no different from the normal rate.

## d. Risks to the Woman

### 1. Risks of Pregnancy

Pregnancies that occur with IVF are associated with increased risks of certain conditions (see Table below from the Executive Summary of a National Institute of Child Health and Human Development Workshop held in September 2005, as reported in the journal Obstetrics & Gynecology, vol. 109, no. 4, pages 967-77, 2007). Some of these risks stem from the higher average age of women pregnant by IVF and the fact that the underlying cause of infertility may be the cause of the increased risk of pregnancy complications. There may be additional risks related to the IVF procedure per se, but it is difficult to assign the relative contributions.

#### Potential Risks in Singleton IVF-conceived Pregnancies

	Absolute Risk (%) in IVF-conceived Pregnancies	Relative Risk (vs. non IVF-conceived Pregnancies)
Pre-eclampsia	10.3%	1.6 (1.2--2.0)
Placenta previa	2.4%	2.9 (1.5--5.4)
Placental abruption	2.2%	2.4 (1.1--5.2)
Gestational diabetes	6.8%	2.0 (1.4--3.0)
Cesarean delivery	26.7%	2.1 (1.7--2.6)

In this table, the Absolute risk is the percent of IVF Pregnancies in which the risk occurred. The Relative Risk is the risk in IVF versus the risk in non-IVF pregnancies; for example, a relative risk of 2.0 indicates that twice as many IVF pregnancies experience this risk as compared to non-IVF pregnancies. The numbers in parentheses (called the “Confidence Interval”) indicate the range in which the actual Relative Risk lies.

Currently more than 30% of IVF pregnancies are twins or higher-order multiple gestations (triplets or greater), and about half of all IVF babies are a result of multiple gestations. Identical twinning occurs in 1.5% to 4.5% of IVF pregnancies. IVF twins deliver on average three weeks earlier and weigh 1,000 gm less than IVF singletons. Of note, IVF twins do as well as spontaneously conceived twins. Triplet (and greater) pregnancies deliver before 32 weeks (7 months) in almost half of cases.

Additionally, while embryos are transferred directly into the uterus with IVF, ectopic (tubal, cervical and abdominal) pregnancies as well as abnormal intra-uterine pregnancies have occurred either alone or concurrently with a normal intra-uterine pregnancy. These abnormal pregnancies oftentimes require medical treatments with methotrexate (a weak chemotherapy drug) or surgery to treat the abnormal pregnancy.

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Side effects of methotrexate include nausea or vomiting, diarrhea, cramping, mouth ulcers, headache, skin rash, sensitivity to the sun and temporary abnormalities in liver function tests. Risks of surgery include the risks of anesthesia, scar tissue formation inside the uterus, infection, bleeding and injury to any internal organs.

## 2. Risks to Offspring

- IVF babies may be at a slight increased risk for birth defects
- The risk for a multiple pregnancy is significantly higher for patients undergoing IVF, even when only one embryo is transferred
- Multiple pregnancies are the greatest risk for babies following IVF
- Some risk may also stem from the underlying infertility state, or from the IVF techniques, or both

## 3. Overall risks

Since the first birth of an IVF baby in 1978, more than 3 million children have been born worldwide following IVF treatments. Numerous studies have been conducted to assess the overall health of IVF children and the majority of studies on the safety of IVF have been reassuring. As more time has passed and the dataset has enlarged, some studies have raised doubts about the equivalence of risks for IVF babies as compared to naturally conceived babies.

A major problem in interpreting the data arises from the fact that comparing a group of infertile couples to a group of normally fertile couples is not the proper comparison to make if one wants to assess the risk that IVF technology engenders. Infertile couples, by definition, do not have normal reproductive function and might be expected to have babies with more abnormalities than a group of normally fertile couples. This said, even if the studies suggesting an increased risk to babies born after IVF prove to be true, the absolute risk of any abnormal outcome appears to be small.

Singletons conceived with IVF tend to be born slightly earlier than naturally conceived babies (39.1 weeks as compared to 39.5 weeks). IVF twins are not born earlier or later than naturally conceived twins. The risk of a singleton IVF conceived baby being born with a birth weight under 5 pounds nine ounces (2500 grams) is 12.5% vs. 7% in naturally conceived singletons.

### e. Birth Defects

The risk of birth defects in the normal population is 2-3 %. In IVF babies the birth defect rate may be 2.6-3.9%. The difference is seen predominately in singleton males. Studies to date have not been large enough to prove a link between IVF treatment and specific types of birth defects.

**Imprinting Disorders.** These are rare disorders having to do with whether a maternal or paternal gene is inappropriately expressed. In two studies approximately 4% of children with the imprinting disorder called Beckwith-Wiedemann Syndrome were born after IVF, which is more than expected. A large Danish study however found no increased risk of imprinting disorders in children conceived with the assistance of IVF. Since the incidence of this syndrome in the general population is 1/15,000, even if there is a 2 to 5-fold increase to 2-5/15,000, this absolute risk is very low.

**Childhood cancers.** Most studies have not reported an increased risk with the exception of retinoblastoma: In one study in the Netherlands, five cases were reported after IVF treatment which is 5 to 7 times more than expected.

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**Infant Development.** In general, studies of long-term developmental outcomes have been reassuring so far; most children are doing well. However, these studies are difficult to do and suffer from limitations. A more recent study with better methodology reports an increased risk of cerebral palsy (3.7 fold) and developmental delay (4 fold), but most of this stemmed from the prematurity and low birth weight that was a consequence of multiple pregnancy.

#### Potential Risks in Singleton IVF Pregnancies

	Absolute Risk (%) in IVF Pregnancies	Relative Risk (vs. non-IVF Pregnancies)
Preterm birth	11.5%	2.0 (1.7--2.2)
Low birth weight (< 2500 g)	9.5%	1.8 (1.4--2.2)
Very low birth weight (< 1500 g)	2.5%	2.7 (2.3--3.1)
Small for gestational age	14.6%	1.6 (1.3--2.0)
NICU admission	17.8%	1.6 (1.3--2.0)
Stillbirth	1.2%	2.6 (1.8--3.6)
Neonatal mortality	0.6%	2.0 (1.2--3.4)
Cerebral palsy	0.4%	2.8 (1.3--5.8)
Genetic risks		
-imprinting disorder	0.03%	17.8 (1.8--432.9)
-major birth defect	4.3%	1.5% (1.3--1.8)
-chromosomal abnormalities (after ICSI):		
-of a sex chromosome	0.6%	3.0
-of another chromosome	0.4%	5.7

In this table, the Absolute risk is the percent of IVF Pregnancies in which the risk occurred. The Relative Risk is the risk in IVF versus the risk in non-IVF pregnancies; for example, a relative risk of 2.0 indicates that twice as many IVF pregnancies experience this risk as compared to non-IVF pregnancies. The numbers in parentheses (called the "Confidence Interval") indicate the range in which the actual Relative Risk lies.

#### f. Risks of a Multiple Pregnancy

The most important maternal complications associated with multiple gestation are preterm labor and delivery, pre-eclampsia, and gestational diabetes (see prior section on Risks to Woman). Others include gall bladder problems, skin problems, excess weight gain, anemia, excessive nausea and vomiting, and exacerbation of pregnancy-associated gastrointestinal symptoms including reflux and constipation. Chronic back pain, intermittent heartburn, postpartum laxity of the abdominal wall, and umbilical hernias also can occur. Triplets and above increase the risk to the mother of more significant complications including post-partum hemorrhage and transfusion.

Prematurity accounts for most of the excess perinatal morbidity and mortality associated with multiple gestations. Moreover, IVF pregnancies are associated with an increased risk of prematurity, independent of maternal age and fetal numbers. Fetal growth problems and discordant growth among the fetuses also result in perinatal morbidity and mortality. Multifetal pregnancy reduction (where one or more fetuses are selectively terminated) reduces, but does not eliminate, the risk of these complications.

Fetal death rates for singleton, twin, and triplet pregnancies are 4.3 per 1,000, 15.5 per 1,000, and 21 per 1,000, respectively. The death of one or more fetuses in a multiple gestation (vanishing twin) is more common in the first trimester and may be observed in up to 25% of pregnancies after IVF. Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus or mother. No excess perinatal or maternal morbidity has been described resulting from a "vanishing" embryo.

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Demise of a single fetus in a twin pregnancy after the first trimester is more common when they share a placenta, ranging in incidence from 0.5% to 6.8%, and may cause harm to the remaining fetus.

Multiple fetuses (including twins) that share the same placenta have additional risks. Twin-twin transfusion syndrome in which there is an imbalance of circulation between the fetuses may occur in up to 20% of twins sharing a placenta. Excess or insufficient amniotic fluid may result from twin-to-twin transfusion syndrome. Twins sharing the same placenta have a higher frequency of birth defects compared to pregnancies having two placentas. Twins sharing the same placenta appear to occur more frequently after blastocyst transfer.

Placenta previa and vasa previa are more common complications in multiple gestations. Abruptio placenta also is more common and postpartum hemorrhage may complicate 12% of multifetal deliveries. Consequences of multiple gestations include the major sequelae of prematurity (cerebral palsy, retinopathy of prematurity, and chronic lung disease) as well as those of fetal growth restriction (polycythemia, hypoglycemia, necrotizing enterocolitis). It is unclear to what extent multiple gestations themselves affect neuro-behavioral development in the absence of these complications. Rearing of twins and high-order multiples may generate physical, emotional, and financial stresses, and the incidence of maternal depression and anxiety is increased in women raising multiples. At mid-childhood, prematurely born offspring from multiple gestations have lower IQ scores, and multiple birth children have an increase in behavioral problems compared with singletons. It is not clear to what extent these risks are affected by IVF per se.

***The Option of Selective Reduction:*** Pregnancies that have more than 2 fetuses are considered an adverse outcome of infertility treatment. The greater the number of fetuses within the uterus, the greater is the risk for adverse perinatal and maternal outcomes. Patients with more than twins are faced with the options of continuing the pregnancy with all risks previously described, terminating the entire pregnancy, or reducing the number of fetuses in an effort to decrease the risk of maternal and perinatal morbidity and mortality. Multifetal pregnancy reduction (MFPR) decreases risks associated with preterm delivery, but often creates profound ethical dilemmas. Pregnancy loss is the main risk of MFPR. However, current data suggest that such complications have decreased as experience with the procedure has grown. The risk of loss of the entire pregnancy after MFPR is approximately 1%.

In general, the risk of loss after MFPR increases if the number of fetuses at the beginning of the procedure is more than three. While there is little difference between the loss rates observed when the final number of viable fetuses is two or one, the loss rate is higher in pregnancies reduced to triplets. Pregnancies that are reduced to twins appear to do as well as spontaneously conceived twin gestations, although an increased risk of having a small for gestational age fetus is increased when the starting number is over four. The benefit of MFPR can be documented in triplet and higher-order gestations because reduction prolongs the length of gestation of the surviving fetuses. (This has been demonstrated for triplets; triplets have a 30-35% risk of birth under 32 weeks compared to twins which is 7 to 10%)

### **g. Legal Considerations and Legal Counsel**

The law regarding embryo cryopreservation, subsequent thaw and use, and parent-child status of any resulting child(ren) is, or may be, unsettled in the state in which either the patient, spouse, partner, or any donor currently or in the future lives, or the state in which the ART Program is located. We acknowledge that the ART Program has not given us legal advice, that we are not relying on the ART Program to give us any legal advice, and that we have been informed that we may wish to consult a lawyer who is experienced in the areas of reproductive law and embryo cryopreservation and disposition if we have any questions or concerns about the present or future status of our embryos, our

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individual or joint access to them, our individual or joint parental status as to any resulting child, or about any other aspect of this consent and agreement.

## **h. Reporting Outcomes**

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The 1992 Fertility Clinic Success Rate and Certification Act requires the Centers for Disease Control and Prevention (CDC) to collect cycle-specific data as well as pregnancy outcome on all assisted reproductive technology cycles performed in the United States each year and requires them to report success rates using these data. Consequently, data from my/our IVF procedure will be provided to the CDC, and to the Society of Assisted Reproductive Technologies (SART) of the American Society of Reproductive Medicine (ASRM) (if my/our clinic is a member of this organization). The CDC may request additional information from the treatment center or contact me/us directly for additional follow-up. Additionally, my/our information may be used and disclosed in accordance with HIPAA guidelines in order to perform research or quality control. All information used for research will be de-identified prior to publication. De-identification is a process intended to prevent the data associated with my/our treatment being used to identify me/us as individuals.

## **i. References:**

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### *General IVF overviews available on the internet*

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<http://www.sart.org/>

<http://www.cdc.gov/art/>

<http://www.resolve.org/site/PageServer>

### *Number of Embryos to Transfer*

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Guidelines on number of embryos transferred. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. *Fertil Steril* 2006; 86 (suppl 4): S51-S52.

### *Embryo hatching*

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The role of assisted hatching in in vitro fertilization: a review of the literature. A Committee opinion. The Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. *Fertil Steril* 2006; 86 (suppl 4): S124-S126.

### *Risks of pregnancy*

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Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. *Obstet Gynecol* 2007; 109(4):967-77.

### *Risks to offspring*

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Infertility, assisted reproductive technology, and adverse pregnancy outcomes. Executive Summary of a National Institute of Child Health and Human Development Workshop. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. *Obstet Gynecol* 2007; 109(4):967-77.

Multiple pregnancy associated with infertility therapy. The Practice Committees of the American Society for Reproductive Medicine *Fertil Steril* 2006; 86 (suppl 4): S106-S110.

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We (I) acknowledge that we have read and understood the information provided below regarding the Frozen Embryo Transfer process and its risks and agree to go forward with this treatment as our signatures below testify.

Patient Signature:	   <small>Signature</small>
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Partner Signature:	   <small>Signature</small>
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*If signed outside of Dallas IVF, this document requires a Notary.*

*If signed at Dallas IVF, both parties must be present, and this document must be signed in the presence of a DALLAS IVF employee and witnessed below.*

Patient Signature

Date

Patient Printed Name

Date of Birth

**Notary Public**

Sworn and subscribed before me on this \_\_\_\_\_ day of \_\_\_\_\_, \_\_\_\_\_.

Notary Signature

Date

Spouse / Partner Signature

Date

Spouse / Partner Printed Name

Date of Birth

**Notary Public**

Sworn and subscribed before me on this \_\_\_\_\_ day of \_\_\_\_\_, \_\_\_\_\_.

Notary Signature

Date

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**Statement by Witness**

I declare that the person who signed this document is personally known to me and appears to be of sound mind and acting of his or her own free will. He or she signed (or asked another to sign for him or her) this document in my presence.

Witness Name: \_\_\_\_\_

Witness Signature: \_\_\_\_\_ Date: \_\_\_\_\_