

## **Manual of Operations**

This document is the Manual of Operations for the University Of Pittsburgh Coordinating Center (CC) IRB protocol entitled:

### **Testicular Tissue Cryopreservation**

In addition to this Manual of Operations, the Pittsburgh Coordinating Center will:

- Provide sample templates for the approved IRB protocol and informed consent forms
- Review and approve all IRB and consent forms for each individual recruitment site prior to submission
- Maintain records of IRB approval letters and current approved IRB protocols and consent forms for each individual recruitment site
- Review adverse event data for each individual recruitment site and provide an annual data safety monitoring summary to the University of Pittsburgh IRB and all sites
- Provide annual reports of subject enrollment to all recruitment sites
- Communicate protocol changes to all recruitment sites

## **PROTOCOL SUMMARY**

The “Testicular Tissue Cryopreservation” study is open to a subset of patients facing potentially fertility-threatening treatment regimens.

This study will harvest testicular tissues from eligible patients who are at risk of infertility and do not have standard of care options to preserve their future fertility. Separate portions of the harvested tissue will be 1) designated for research and 2) cryopreserved and maintained for participating patients as a resource for future elective procedures to achieve fertility. Research tissue will be de-identified and made available for research through the Coordinating Center at Magee-Womens Research Institute.

Research on testicular tissue will:

- 1) Optimize techniques for cryopreservation of testicular cells, including spermatogonial stem cells, from patients at high risk for infertility due to disease or prior to the initiation of therapy. Efficacy of cryopreservation techniques will be determined.
- 2) Determine presence and number of germ cells in the patients’ testicular tissue.
- 3) Develop methods to enrich spermatogonial stem cells and remove malignant contamination from testicular tissue.
- 4) Develop stem cell based therapeutics to restore fertility.

## SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations.

By this signature, the recruitment site agrees to comply with the following:

- Provide copies of IRB and consent forms to the CC prior to submission.
- Inform the CC about all modification to the IRB and consent forms in a timely manner and submit up-to-date forms annually.
- Adhere to the approved data safety monitoring procedures and provide adverse event data to the CC.
- Assure to provide testicular tissue for processing, storage, and research to the CC.
- Immediately report adverse events and unanticipated problems to the local IRB and the CC.

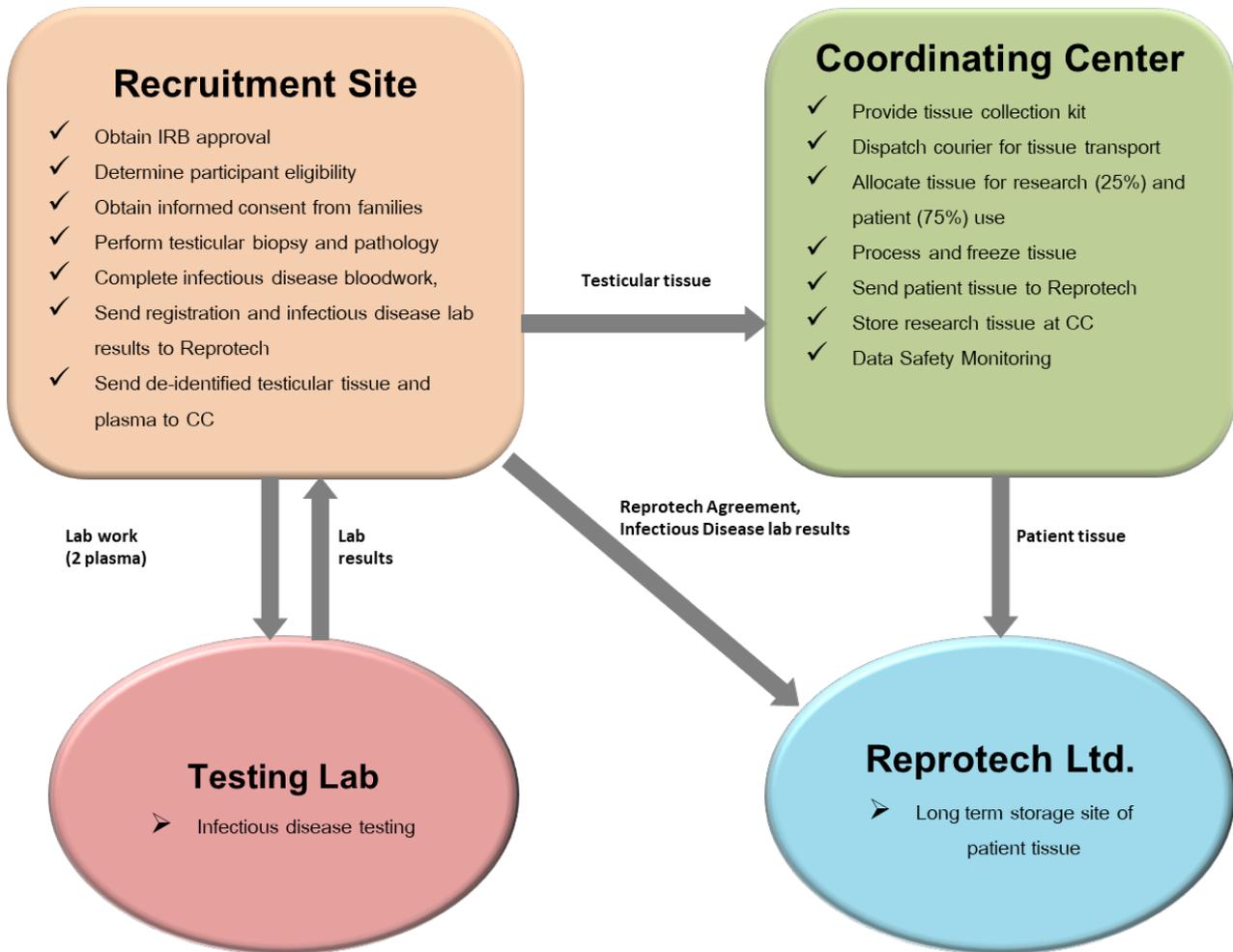
Site Investigator:

Signed: \_\_\_\_\_ Date: \_\_\_\_\_  
*Name*  
*Title*

(For CC use only)	
Received and reviewed:	Received and reviewed:
Date and Initial CC Official	Date and Initial CC IRB

<b>Table of Contents</b>		<b>Page</b>
Title Page		i
Protocol Summary		ii
Signature page		iii
Table of Contents		iv
Study Design Diagram		v
<b>1</b>	<b>Key Roles</b>	1
<b>2</b>	<b>Background information and scientific rationale</b>	2
2.1	Background Information	2
2.2	Scientific Rationale	2
2.3	Potential Risks and Benefits	4
	2.3.1 Potential Risks	4
	2.3.2 Potential Benefits	7
<b>3</b>	<b>Objectives</b>	9
<b>4</b>	<b>Study Population</b>	10
4.1	Patients in three categories will participate in this study	10
	4.1.1 Category 1	10
	4.1.2 Category 2	10
	4.1.3 Category 3	10
4.2	Inclusion/Exclusion Criteria	11
	4.2.1 Inclusion Criteria	11
	4.2.2 Exclusion Criteria	12
<b>5</b>	<b>Study Schedule</b>	13
5.1	Screening	13
5.2	Enrollment Baseline	13
5.3	Study Procedures	13
5.4	Follow-up and Final Visits	17
<b>6</b>	<b>Safety Assessment and Reporting</b>	18
6.1	Data Safety Monitoring Board	18
<b>7</b>	<b>Data Handling and Record Keeping</b>	19
<b>8</b>	<b>Appendices</b>	20
8.1	Patient Intake Form	
8.2	Eligibility Form	
8.3	Testicular Tissue Cryopreservation Study Enrollment Form	
8.4	Transportation Waiver Form	
8.5	Testicular Tissue Collection and Transport Form	
8.6	TTC Case Documentation Checklist	
8.7	Adverse Event Evaluation and Data Safety Monitoring Forms Infectious Disease Lab Specimen Collection Instructions and MBC Sample Form	
8.8	Testicular Tissue Cryopreservation Study – Follow-up Script	
8.9	ReproTech Forms	

## STUDY DESIGN



# 1 KEY ROLES

## Individuals:

### Principal Investigator:

**Kyle Orwig, PhD**  
Professor  
Ob/Gyn & Reproductive Sciences  
Magee-Womens Research Institute  
University of Pittsburgh  
204 Craft Avenue  
Pittsburgh, PA 15213  
Phone: 412-641-2415

### Coordinators:

**Kate McMahon and Sarah Steimer**  
Project Coordinators  
Magee-Womens Research Institute  
204 Craft Avenue  
Pittsburgh, PA 15213  
Phone: 412-641-2700

## Institutions:

### University of Pittsburgh Coordinating Center

Fertility Preservation Program in Pittsburgh  
Center for Reproduction and Transplantation  
Magee-Womens Hospital  
University of Pittsburgh Medical Center  
300 Halket Street, Suite 5150  
Pittsburgh, PA 15213  
Fertility Preservation Phone Line: 412-641-7475  
Fertility Preservation Email: [fertilitypreservation@upmc.edu](mailto:fertilitypreservation@upmc.edu)

## **2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE**

### **2.1 Background Information**

The cure rate of cancer in children, adolescents and young adults continues to increase with advances in chemotherapy and/or radiation protocols. As more oncology patients become long-term survivors, the consequences of their treatment on their quality of life have become an important focus of research in clinical oncology and reproductive medicine. One of the most common and most devastating side effects of cancer treatment is infertility. Many chemotherapy and radiation-containing regimens for cancer or prior to bone marrow transplantation can cause sterility in children and young adults. Semen cryopreservation is available as a fertility-preserving option for post pubertal boys and adult men, but many do not take advantage of this option due in part to lack of information, illness, and/or time constraints relative to their treatment plan. Currently, no fertility-preserving options are available for prepubescent boys who are not yet producing sperm. However, experimental techniques are currently being developed to provide future alternatives for patients that preserve their testicular tissue. In order to take advantage of these and future technologies, patients must harvest and preserve their testicular tissue prior to disease or treatment associated fertility decline. This study will be available to males of all ages who have a disease or will undergo a treatment that can cause infertility.

### **2.2 Scientific Rationale**

Over the last 30 years, advances in the survival of oncology patients have been made through the work of cooperative protocol-driven clinical research, particularly in young patient categories. Now that the overall event-free survival rate for child, adolescent and young adult cancer patients surpasses 75%, attention is focused on quality of life and long-term consequences of therapy. In particular, patients receiving chemotherapy and radiotherapy for cancer or other conditions are often at risk for infertility, placing fertility preservation at the forefront of these concerns. Progress to minimize the unwanted side effects of current treatment regimens without decreasing their effectiveness has allowed many cancer survivors to have children following spontaneous recovery of fertility (van den Berg et al., 2004). However, some oncological diseases require rigorous treatment regimens which will almost always lead to permanent infertility of the patient.

The primary causal factor for the risk of infertility in males is considered the treatment modality (i.e. the specific chemotherapy or radiotherapy regimen). Most of the available outcome data relating to fertility sequelae are from studies that examined the effects of single treatment agents.

In men, treatment with some chemotherapeutic agents and regimens induced prolonged azoospermia (complete absence of sperm in the ejaculate). The effects are likely the result of cytotoxicity to the spermatogonial stem cells that are responsible for maintaining spermatogenesis, possibly resulting in permanent infertility (Meistrich et al., 2005). In particular, alkylating chemotherapeutic agents such as procarbazine, busulfan, cyclophosphamide,

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chlorambucil, and melphalan, along with cisplatin are the most likely to produce prolonged infertility (Meistrich et al., 2005). Radiation fields that include the testes also produce prolonged and often permanent damage to spermatogenesis (Dubey et al., 2000; Meistrich and van Beek, 1990; Sandeman, 1966; Speiser et al., 1973). Other agents, particularly topoisomerase inhibitors (e.g., amsacrine), antimetabolites (e.g., methotrexate), and microtubule inhibitors can have additive effects on infertility risk when given with the highly gonadotoxic agents listed above (Meistrich et al., 1989). Combinatorial therapies, such as the busulfan-cyclophosphamide (BuCy) conditioning for bone marrow transplant, often result in permanent infertility (Socie et al., 2003). Furthermore, some agents that are administered in repetitive “fraction” treatments are more toxic in sum than single larger doses, and thus, for these agents a lower cumulative dose can lead to permanent infertility (Pont and Albrecht, 1997).

There is a paucity of data about the risk of infertility in prepubertal male patients. Anti-mitotic therapies (i.e. chemotherapy, radiation) cause infertility by targeting proliferating germ cells (e.g. spermatogonia, spermatocytes), the same mechanism by which they target neoplastic cells. In the prepubertal testis, these agents affect proliferating undifferentiated spermatogonia that are proliferating, but not yet producing complete spermatogenesis and sperm (Simorangkir et al., 2005). Rodent studies concur with this scenario and indicate that germ cells in the fetal, neonatal, prepubertal and adult testis are sensitive to chemotherapy (Brinster et al., 2003). While quantitative clinical data demonstrating the relative risk of male infertility between adults and children are not available, it is our best estimate that prepubertal patients exhibit similar sensitivities to potentially gonadotoxic agents as adults.

The main purpose of the proposed study is to develop techniques for long-term preservation of fertility through cryopreservation (freezing) of testicular tissue for patients with diseases or treatments (e.g., chemotherapy, radiation) that are likely to cause infertility. This study will store frozen testicular tissue for male patients as a potential resource to restore their fertility in the future using experimental techniques currently under development. The study will also provide a portion of the patient’s tissue for research to advance our understanding of testicular tissue freezing, cancer cell contamination and elimination in the testicular tissue, options for using stem cells to restore fertility, as well as the effects of chemotherapy/radiation on testicular stem cells.

## 2.3 Potential Risks and Benefits

### 2.3.1 Potential risks

#### Blood Draw

*Common Risks:* pain can occur

*Infrequent Risks:* bleeding can occur

#### Confidentiality

*Common Risks:* none

*Infrequent Risks:* Breach of confidentiality. Participation in this research is confidential and to minimize the risk of breach of confidentiality, all paper and electronic research records that contain identifiable information will be securely stored at the individual sites of recruitment. Access to identifiable information will be limited to the PI, co-investigators, study coordinator and research staff at the individual site. Personnel involved in this study are expected to protect the security and confidentiality of identifiable information. Tissue and blood samples will be de-identified by the individual sites, but in such a way that the Pittsburgh coordinating center will know which site sent the tissue (e.g., CHOC-001 from Children's Hospital of Orange County). Only the individual site PI, co-investigators and research staff will have access to their own files and these will not be available to Pittsburgh or other individual sites.

Authorized representatives of the USDA and the office for human research protections (OHRP) may review and/or obtain identifiable health information for the purpose of monitoring the accuracy of research data and to ensure that the research is being conducted according to FDA regulations. Testicular tissue designated for patient use will be stored at ReproTech, LTD, a third party tissue bank. Authorized representatives from ReproTech will have access to data, documents, blood plasma and tissue/cells generated by the study. Patients will sign a separate agreement with ReproTech.

#### Testicular Tissue Harvesting

*Common Risks:* none

*Infrequent Risks:*

- General anesthesia: the patient's risk of death from anesthesia is less than 1 in 100,000 in children older than 3 years and less than 1 in 10,000 in children less than 3 years (Arbous et al., 2001; Gibbs and Borton, 2006; Kawashima et al., 2003).

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- **Simple Orchiectomy:** Risks of simple orchiectomy are the same as other surgical procedures, including infection and bleeding as a result of surgical incision. The chance of the patient requiring hospitalization for complication(s) is less than 1%. The patient's chance of dying as a result of such complication(s) is less than 1 in 10,000.
  - **Testicular Wedge Resection:** Risks of testicular wedge resection are also the same as other surgical procedures, including infection and bleeding as a result of surgical incision. It is possible that the surgery itself could cause scar tissue or damage to the remaining testicular tissue, so that chances for producing sperm from that testicle could be reduced. Surgery in the pelvic region or on the testicles can damage the nerves that cause ejaculation. There is also a risk of bleeding within the resected testicle resulting from the surgical removal of tissue. The chance of the patient requiring hospitalization for complication(s) is less than 1%. The patient's chance of dying as a result of such complication(s) is less than 1 in 10,000.
  - **Removal of a Testicle:** There is a theoretical risk that the patient may experience a reduction in fertility due to the removal of a testicle, although the remaining testicle typically compensates for loss of one gonad. In that case, the surgery to remove testicular tissue would then have been unnecessary. Surgery in the pelvic region or on the testicles can damage the nerves that cause ejaculation. Removal of one testicle can lead to temporary reduction in production of testosterone, 90-95% of which is produced by the testicles (the balance is produced by the adrenal glands). The most common side-effects of reduced testosterone levels in adult men include lost or reduced sexual desire, impotence, hot flashes similar to those in menopausal women, mood swings or depression, enlargement and tenderness in the breasts, weight gain, osteoporosis, and fatigue. To address the potential psychological consequences of removing a testicle, some men opt to have a testicular prosthesis, or artificial testicles, placed inside the scrotum to replace the testicles removed during surgery. The prosthesis makes the scrotum look much as it did before surgery.
  - **Beginning therapy 2-3 days after surgery:** Patients will begin their treatments on a time-frame dictated by clinical management of their primary disease or condition, typically within one week after surgery. For patients who will receive chemotherapy or radiation for treatment of their primary disease, the patients' surgeon(s) will determine hemostasis and provide clearance indicating lack of complications prior to initiating therapy. It has been reported in some cases that chemotherapy or radiation treatments can begin as early as one day following testicular biopsy surgery (Bahadur et al., 2000).
  - **Delaying a patient's primary therapy:** In nearly all cases, there is no indication that there is an increased risk of delaying a patient's primary therapy for a window of time to permit surgical removal of testicular tissue and recovery (e.g., one day to one week).

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**Testicular Tissue/Cell Cryopreservation:**

*Common Risks:* none

*Infrequent Risks:* Testicular tissue will be cryopreserved following removal from subjects and, following an extended period of cryogenic storage, may be used for future procedures to attempt restoration of fertility. Although care will be taken, damage to the removed testicular tissue may occur during any part of the cryopreservation (freezing) or storage process. The exact method that might be used by the patient to achieve fertility in the future is unknown and is outside the scope of this protocol. The risk of birth defect(s) and/or genetic damage to any child who may be born following cryopreservation and long term storage of human testicular tissues is unknown. However, thousands of children have been born worldwide from frozen embryos and there only isolated reports of minor increased risk of some specific birth defects in these children (e.g., Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedeman syndrome). However, the potential risk of genetic mutations that could contribute to birth defects can only occur if subject tissues are used for experimental procedures to restore fertility, which is outside the scope of this protocol. Subjects will not be at direct risk during participation in this study.

The testicular tissue removed may not yield usable germ cells (i.e., functional spermatogonial stem cell or sperm from the testes), or pregnancy may not result when the spermatogonial stem cells or sperm are ultimately used. Some patients may have particular risks associated with their underlying disease. If a cancer or other disease already affects the testicles, it may reduce the options for using the tissue in the future. This may not be known until the patient wishes to use their tissue. Tissue could be lost or made unusable due to equipment failure, or unforeseeable natural disasters beyond the control of this program.

**Steps to Prevent or to Minimize the Severity of Potential Risks:**

All blood draws, surgical procedures, bone marrow aspirations, and tumor biopsies will be performed by skilled, experienced technicians/surgeons in a controlled environment. Testicular tissue processing and cryopreservation will be performed in the Fertility Preservation laboratories at Magee-Womens Hospital by certified technicians with experience processing testicular tissue. CFRE is an FDA-compliant and American Association of Tissue Banks-accredited long term storage facility for reproductive tissues and is FDA-registered as a HCT/P manufacturer, and thus, is an appropriate facility in which to process testicular tissue for potential future use by subjects. All tissue processing will be performed in accordance with good clinical practices, good laboratory practices (GLPs) and current good tissue practices (CGTPs) to minimize the risks for testicular tissue processing and cryopreservation. We have communicated our testicular tissue processing protocol to the Office of Cellular, Tissue and Gene Therapy at the FDA's Center for Biologics Evaluation and Research, which indicated that our protocol would be appropriate for the described homologous reproductive purpose under 21 CFR 1271 regulations. In all cases, suitable reagents and disposables will be employed for tissue processing in accordance with FDA recommendations. Individual sites may choose to perform testicular tissue cryopreservation at their own facilities. This might be beneficial when only limited or prolonged air travel between a recruitment site and the coordinating center is available. The coordinating center will provide protocols and training of local staff to ensure that tissue processing is done according to the protocol that was submitted to the FDA Center for

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Biologics Evaluation and Research, in order for all samples to be appropriately processed for the described homologous reproductive purpose under 21 CFR 1271 regulations. The coordinating center will ensure that all tissue processing will be performed in accordance with good clinical practices, good laboratory practices (GLPs) and current good tissue practices (CGTPs) to minimize the risks for testicular tissue processing and cryopreservation. The coordinating center will provide guidance to ensure that suitable reagents and disposables will be employed for tissue processing in accordance with FDA recommendations.

### **Steps Taken in the Event that a Clinically Significant, Unexpected Disease or Condition is Identified during the Conduct of the Study:**

If a subject is found to have a positive screen for an infectious disease (e.g., HIV), he will be informed and referred to the appropriate specialist. Infectious disease status will not be determined until after study enrollment. The storage of specimens designated for patient use from potentially infectious subjects (subjects for whom testing show a potential for an infectious disease) require certain additional safeguards for potentially infectious specimens only.

### **Endpoints:**

Since this is an observational study, there are no experimental endpoints that impact continued study participation. Continued storage of testicular tissue designated for patient use is governed by the ReproTech agreement and is not dependent upon continued study participation. Disposition of tissue designated for patient use at their death is also determined by the ReproTech agreement.

### **2.3.2 Potential for Direct Benefit:**

Established fertility preserving therapies are available for males that have undergone puberty, but these therapies are not accessible or appropriate for all adolescent or adult patients. Currently there are no therapies to preserve the future fertility of preadolescent boys. However, new reproductive therapies are under development and may one day offer “fertile hope” to those survivors that do not currently have access to fertility preserving therapies. When no established fertility sparing or preserving options are available, it is reasonable to offer harvesting and cryopreservation of testicular tissue as a possible means of fertility preservation. In this case, the potential direct benefits to the subject are two-fold, regardless of diagnosis or age. First, each subject will have tissue cryopreserved and dedicated for their own future use, a scenario that offers hope for patients that currently have limited prospects for future fertility. Retrospective studies indicate that most parents are interested in preserving fertility on behalf of their children with cancer (Ginsberg, 2011; van den Berg et al., 2007; Wyns et al., 2011). Thus, there is perceived acceptability and desire to undergo experimental therapy to preserve fertility, as long as treatment for the primary disease is not compromised (Oosterhuis et al., 2008). There is also likely a psychological benefit to the patient in terms of raising issues relating to their life after cure from their primary disease (e.g., cancer). Second, the subject may have the opportunity to utilize their stored testicular tissue or cells for fertility restoration procedures in the future.

### **3 OBJECTIVES**

The primary objective of the proposed study is to:

- 1) Optimize techniques for processing and cryopreserving testicular tissue.
- 2) Determine presence and number of germ cells in the patients' testicular tissue.
- 3) Develop methods to enrich spermatogonial stem cells and remove malignant contamination from testicular tissue.
- 4) Develop stem cell based therapeutics.

In addition, this study will process and cryopreserve tissue and/or cells for participating patients as a resource for future elective procedures to attempt fertility restoration.

## 4 STUDY POPULATION

### 4.1 Patients in three categories will participate in this study:

#### 4.1.1 **Category 1: Patients who are having all or part of one or both testicles removed for the treatment of a disease.**

- a. Clinical indications for removal of all or part of one or both testicles include (but are not limited to) the following: Advanced stage/grade testicular cancers; testicular metastases; Treatment of hormonally sensitive cancers (i.e., prostate) that necessitate bilateral orchiectomy

Note: removal of both testicles will limit options for fertility preservation.

#### 4.1.2 **Category 2: Patients who are having all or part of one or both testicles removed for the prevention of a disease.**

- a. Clinical scenarios for prophylactic bilateral orchiectomy include (but are not limited to) the following: Carriers of genes that predispose to hereditary cancers of the testicles or prostate; Patients with increased risk or personal history of hormonally sensitive cancers.

Note: removal of both testicles will limit options for fertility preservation.

#### 4.1.3 **Category 3: Patients having all or part of one testicle removed solely for the purpose of fertility preservation in the setting of a medical or surgical condition where the clinically indicated treatment is likely to cause infertility.**

- a. Clinical scenarios include (but are not limited to) the following: high- and intermediate-risk chemotherapy or radiation treatments for a variety of neoplastic and malignant disorders; conditioning for bone marrow transplantation for malignant diseases and non-malignant disorders.

Patients in Categories 1 and 2 will have testicular tissue removed for a clinically-indicated purpose. Only patients in Categories 1 and 2 may have both testes removed, which will only occur in clinically-indicated scenarios. Bilateral orchiectomy will not be performed for patients in Category 3 who are having testicular tissue removed solely for fertility preservation. The amount of tissue removed for clinical purposes will depend on the diagnosis and can include all or some of one or both testes. If there is no clinical indication for a unilateral orchiectomy a wedge resection will be performed. Each subject's surgeon will decide on a case-by-case basis if additional testicular tissue should be excised for the research purposes outlined in this protocol. Presence and extent testicular pathology in the clinically indicated portion of the gonad removed will help to determine whether additional tissue can or should be removed for the purposes of the research proposed in this protocol.

## 4.2 Inclusion/Exclusion Criteria

### 4.2.1 Inclusion Criteria

1. Be male at any age.
2. Be scheduled to undergo surgery, chemotherapy, drug treatment and/or radiation for the treatment or prevention of a medical condition or malignancy with risk of causing permanent and complete loss of subsequent testicular function. Investigators will employ two methods to calculate the risk of infertility (prolonged azoospermia) in boys/men. The first one is the cyclophosphamide equivalent dose (CED) calculator. Alkylating chemotherapy is the most toxic to fertility and therefore, the investigators will use the CED calculator to determine the risk of infertility from alkylating chemotherapy (see appendix 8.2). Patients with a CED of 4g/m<sup>2</sup> have significant risk of infertility (Green et al. 2014). Secondly, the investigators will use published data on radiation and other therapies not included in the CED to determine risk of infertility as follows:  
Significant risk:
  - Total body irradiation (TBI) (Wallace et al. 2005; Wallace et al. 2011)
  - Testicular radiation >2.5 Gy (Lambertini et al. 2016; Gordon et al. 1997)
  - Cisplatin 500 mg/m<sup>2</sup> (Lambertini et al. 2016)
  - Bone Marrow Transplantation (BMT) (Meacham et al., 2020)
3. Or, have a medical condition or malignancy that requires removal of all or part of one or both testicles.
4. Or, have newly diagnosed or recurrent disease. Those who were not enrolled at the time of initial diagnosis (i.e., patients with recurrent disease) are eligible if they have *not* previously received therapy that is viewed as likely to result in complete and permanent loss of testicular function.
5. Have two testicles if undergoing elective removal of a testicle for fertility preservation only (category 3). *Note: removal of both testicles will limit fertility preservation options.*
6. Sign an approved informed consent and authorization permitting the release of personal health information. The patient and/or the patient's legally authorized guardian must acknowledge in writing that consent for specimen collection has been obtained, in accordance with institutional policies approved by the U.S. Department of Health and Human Services.
7. Consent for serum screening tests for infectious diseases [i.e. HIV-1, HIV-2, hepatitis B, hepatitis C], to be performed at the time of testicular tissue harvesting.
8. Undergo a full history and physical examination and obtain standard pre-operative clearance (based on the most recent ACC/AHA Guideline for Perioperative Cardiovascular Evaluation for Noncardiac Surgery) as determined by their primary surgeon.

Eligibility will be recorded using a written checklist based on the criteria listed above and will be verified by the PI or co-investigator prior to initiating experimental interventions.

#### **4.2.2 Exclusion Criteria**

Patients will be ineligible for participation in this study if they are:

1. Diagnosed with psychological, psychiatric, or other conditions which prevent giving fully informed consent.
2. Diagnosed with an underlying medical condition that significantly increases their risk of complications from anesthesia and surgery.

## 5 STUDY SCHEDULE

### 5.1 Screening

Local investigators at each site will be informed by clinicians regarding patients who are planned to undergo treatment for a medical condition which may result in infertility; or have a medical condition known to be at high risk for infertility. The clinicians will approach the patient's family to inform the family about the study and that they may be approached by the investigators for potential enrollment in the study. If the patient's family agrees to being approached regarding entry into the study, their medical records will be reviewed to determine that all of the inclusion criteria are met and that none of the exclusion criteria are met. If this is so, written informed consent will be gained from the patient or their legal guardians. There are no specific screening tests to be performed for inclusion in the study.

### 5.2 Enrollment/Baseline

The only evaluation to be performed prior to enrollment is a review of the patient's medical records and discussion with the treatment team to ensure that the inclusion and exclusion criteria (see section 4.2) are met.

A baseline review will be performed at which time demographic details, past medical history, surgical history; family history, medications, etc. will be obtained and documented.

### 5.3 Study Procedures

The goal will be to remove healthy tissue for research and future patient use without compromising the health of any remaining tissue. This will be at the discretion of the surgeon and will be educated by discussion with the laboratory researchers listed as investigators on this protocol.

The surgical approach for removal of testicular tissue will be performed using the methods determined by the surgeon based on the medical/surgical diagnosis or treatment (see below). For instance, a trans-scrotal approach will be used for testicular tissue retrieval except in cases where an inguinal approach is not indicated (radical orchiectomy). Furthermore, surgery to harvest testicular tissue may be coordinated with another procedure such as placement of a central venous catheter for future chemotherapy, tumor biopsy, or laparotomy for another purpose. Testicular tissue designated for research will be de-identified by an honest-broker system.

**Timing of the Surgery and Starting Other Therapy:** Whenever possible, surgery to remove testicular tissue will be coordinated with other surgical procedures (e.g., central line placement). Whenever possible, surgery to obtain testicular tissue will be performed prior to any potentially gonadotoxic therapy (e.g., chemotherapy or radiation). Patients with previous exposure to gonadotoxic therapy may still be eligible for this protocol if the previous exposure was not associated with high risk of infertility (see section 4.2). For patients who will receive chemotherapy or radiation for treatment of their primary disease, the patients' surgeon(s) will determine hemostasis and provide surgical clearance for initiation of therapy. Subjects will begin

their treatments on a time-frame dictated by clinical management of their primary disease or condition, typically within one week. It has been reported in some cases that chemotherapy or radiation treatments can begin as early as one day following testicular biopsy surgery (Bahadur et al., 2000).

**Surgical Procurement of Testicular Tissue:** If a male patient chooses to participate and provides informed consent, he will be screened to determine eligibility. At early stages of technology development, simple orchiectomy (removal of one entire testicle) may give the best chance of preserving sufficient cells for effective therapy. However, incisional biopsy of up to 25% of tissue from one testis (wedge resection) will also be presented to the patient as an alternative option. The amount of testicular parenchyma removed will be at the discretion of the surgeon. The duration of surgical testicular tissue procurement is likely to be between 1 and 2 hours. The recovery time required prior to resuming normal activities or initiating other treatments (e.g., chemotherapy or radiation) is expected to be 2-3 days.

The decision whether to perform an orchiectomy or a wedge biopsy can be made by the surgical team at the recruitment site (if they wish to do so), or the options can be presented to the family and let the family decide how to proceed. The decision making process should be outlined in the protocol submitted to the recruitment site IRB. The coordinating center will provide guidance and recommendations.

#### **Wedge Resection (incisional biopsy) - Scrotal Approach**

Incision is made with scalpel in scrotum in direction of rugae. Dartos muscle is divided by electrocautery and the tunica vaginalis is divided sharply. The tunica albuginea is incised sharply with a scalpel and up to 25% of the testicular parenchyma is excised. The tunica albuginea is closed with a 5-0 absorbable suture. Then the tunica vaginalis is closed over the testicle with a 4-0 absorbable suture. Then the skin and dartos muscle are closed in a single layer with a 4-0 absorbable suture in a subcuticular fashion.

#### **Wedge Resection (incisional biopsy) - Subinguinal Approach**

Incision with scalpel is made 0.5 cm below external inguinal ring. The subcutaneous fat is divided by electrocautery. The spermatic cord is visualized and freed from its investing fascia by sharp dissection. The testicle is then delivered through the inguinal canal, leaving the gubernacular attachments intact. The tunica albuginea is incised sharply with a scalpel and up to 25% of the testicular parenchyma is excised. The testicle is returned back to its normal anatomic position. Scarpa's fascia is then closed with a 4-0 absorbable suture and the skin is closed with a 4-0 absorbable suture.

**Simple Orchiectomy** - The incision is made with scalpel in scrotum in direction of rugae. The dartos muscle is divided by electrocautery. The testicle and spermatic cord are then delivered through the incision. The cord is divided into 2 packets: one packet contains the vas deferens and the other contains the spermatic cord vessels. Each packet is tied off with a 2-0 non-absorbable suture. The skin and dartos are closed in a single layer with a 4-0 absorbable suture in a subcuticular fashion.

**Blood collection for infectious disease testing:** Tissue banking and subsequent use of testicular tissue is currently regulated by the Food and Drug Administration (FDA). In order to comply with current tissue banking regulations and to be prepared for any future changes in regulations while these testicular tissues are in storage, patients will be tested and screened for

a number of infectious diseases prior to banking testicular tissue. Two vials of blood (6 ml each) will be collected. The tubes will be sent to a testing lab for infectious disease testing. The immediate testing will include but not be limited to testing for Hepatitis B and C, and HIV. The testing that will be performed is the same as would be performed on a couple undergoing infertility treatment and storing sperm, eggs, or embryos for autologous use. Infectious disease testing is performed in this study to permit patient use of his own tissue and not for the purposes of research tissue or research study.

**Pathology:** A segment of each testicular specimen (~5%) will be removed at the recruitment site under sterile conditions, fixed in formalin, and sent to the Pathology Department to assess for contamination by neoplastic (malignant) cells. A full Pathology report detailing results of the histological and morphological examination of each tissue specimen will be included in the patient's medical record to provide information to counsel patients on the likelihood that the tissue obtained could be used for future fertility restoration. In cases where surgeons order intraoperative pathological examination of the patient's testicular tissue, additional tissue will not be reserved for pathological examination.

**Tissue transport:** Testicular tissue will be rapidly submerged in sterile ice-cold clinical grade tissue storage medium. The tissue container will be sealed and placed in double-redundant zip lock bags. The testicular tissue specimen will be placed in a Styrofoam shipping container with ice packs and will be shipped to the coordinating center in Pittsburgh (see shipping address below) for cryopreservation. Tissue will be de-identified at the individual site and labeled with a site specific identification number. No patient identifying information will be shipped to the Pittsburgh coordinating center.

**Tissue processing:** Testicular tissue will be processed at Magee-Womens Hospital. Upon arrival at the cryopreservation lab, testicular tissues will be weighed. The remaining tissue will be minced and cryopreserved as tissue fragments or digested to produce a cell suspension (see below). Approximately 75% of the resulting tissue pieces will be designated for patient use, and 25% will be de-identified and designated for research. The absolute amounts of testicular tissue designated for research and patient use will depend on the actual weight of tissue obtained.

### **Testicular Tissue:**

1) After obtaining the infectious disease test results, the primary study team at the recruitment site will inform the study team at the coordinating center regarding the infectious status of the samples, before testicular tissues designated for research use can be transferred to Magee-Womens Research Institute (MWRI; Pittsburgh, PA). Research tissue will not be stored with tissue designated for patient use.

2) After obtaining the infectious disease test results, the primary study team at the recruitment site will inform ReproTech regarding the infectious status of the samples. The recruitment site team and ReproTech will arrange for shipment of cryopreserved testicular tissue designated for patient use to ReproTech, Ltd. (RTL) in St. Paul, MN for storage and subsequent release. RTL is an FDA-compliant and American Association of Tissue Banks accredited long term storage facility for reproductive tissues. Based on the extended periods of time that these testicular tissues/cells are likely to be stored (patients may wait for five years from cancer treatment to be

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considered cancer free and begin a family; some may wait longer based on age), RTL provides maximum flexibility for the patients involved. In this way, patients are permitted to store their testicular tissues/cells as long as they wish and ship them to a fertility treatment center of their choice at the time of use. The patient can determine how the testicular tissue designated for his use will be utilized as technology changes and based on his unique circumstances. RTL does not perform fertility treatments and is not affiliated with any fertility center so there is no potential conflict of interest. Patients will execute a separate storage agreement with RTL which defines the length of storage, shipping requirements, infectious disease, screening and disposition of the tissues in the event of their death. In some circumstances, as determined by the subjects, it is possible for patient tissues to be donated to research prior to transfer to ReproTech, at which time the de-identified samples will be transferred to MWRI for storage and research use. In the event of their death, the individual site must send the coordinating center the identity of the patient, death certificate, and the page in the consent form designating tissue disposition in order to properly dispose of the tissue. Donation of subject tissue to research after transfer to ReproTech is governed by the subjects' agreement with ReproTech.

**Specimen Shipment**Shipping de-identified enrollment forms, tissue and blood to the Pittsburgh Coordinating Center:

Fertility Preservation Program of UPMC  
Center for Reproduction and Transplantation  
Magee-Womens Hospital  
204 Halket St. Suite 5150  
Pittsburgh, PA 15213  
Phone: 412-641-7475  
Email: fertilitypreservation@upmc.edu

Sending Cryostorage Agreement forms to ReproTech:

Attn: Jeanne Blank  
33 Fifth Ave NW, Suite 900  
St. Paul, MN 55112  
Phone: 651-489-0827  
Email: jeblank@reprotech.edu

**5.4 Follow-up and Final Visits, if applicable**

The follow up visit is typically done as a phone interview with the patient or their legal guardian. The physical examination of the surgical site is done by the primary treatment team.

After the results of the tissue pathology and lab work are resulted, a copy is made and mailed to the patient or legal guardians for their own personal records. Included in the send out are lab results, tissue pathology, ReproTech registration forms, number of vials cryopreserved and sent to ReproTech, and study consents. At this time, information about Verna's purse, a program offering discounted storage fees, is also sent to the family.

## **6 SAFETY ASSESSMENT AND REPORTING**

### **6.1 Data Safety Monitoring Board**

The Pittsburgh coordinating center will serve as the central data safety monitoring board (DSMB) for this study for the multicenter sites. The affiliated sites will send their adverse events to the coordinating center. The coordinating center will review this data at the bimonthly meeting. The coordinating center also has an independent Data Safety Monitoring Board that reviews reports from all the sites and provides an annual summary or a central DSMB report which will be sent to all the centers.

Dr. Orwig together with the other co-investigators and research team members listed on this protocol will meet on a bimonthly basis to conduct the data safety monitoring review for the Pittsburgh site.

Adverse events and surgical complications after an elective orchiectomy (Category 3 Patients-those not requiring surgery for clinical management of their primary disease) will be identified using the Common Toxicity Criteria for Adverse Events (CTCAE). A copy of the CTC version 4.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. The severity of the event should then be graded using the CTCAE criteria. Determination of whether the event was related to the surgical procedure and whether the adverse event was expected or unexpected will be made. Any instances of grade 3 or 4 adverse events are reported immediately to the University of Pittsburgh IRB using the standard forms and procedures established by the IRB.

## 7 DATA HANDLING AND RECORD KEEPING

**Participation in this research is confidential.** All research tissues will be de-identified by the individual centers; participants will be identified by number, not name. The Pittsburgh coordinating center will receive de-identified enrollment information, tissue and blood that is identified with a site-specific identification number. No information by which the patient can be identified will be published in connection with this study. Only the individual site PI and co-investigators will have access to files matching the patient information with tissue specimen numbers. Tissue and blood samples will be de-identified by the individual sites, but in such a way that the Pittsburgh coordinating center will know which site sent the tissue (e.g., CHOC-001 from Children's Hospital of Orange County or LCH-001 from Lurie Children's Hospital). Only the individual site PI, co-investigators and research staff will have access to their own files and these will not be available to Pittsburgh or other individual sites. Authorized representatives of the USDA and the office for human research protections (OHRP) may review and/or obtain identifiable health information for the purpose of monitoring the accuracy of research data and to ensure that the research is being conducted according to FDA regulations. Authorized representatives of a testing lab will have access to data, documents and blood samples in association with the FDA-mandated infectious disease screening. Testicular tissue designated for patient use will be stored at ReproTech, LTD, a third party tissue bank. Authorized representatives from ReproTech will have access to data, documents, blood plasma and tissue/cells generated by the study. Patients will sign a separate agreement with ReproTech.

### **Record keeping:**

The Pittsburgh Coordinating Center will maintain records of the IRB approval letter and the current approved IRB protocol and consent forms for each individual recruitment site.

The Pittsburgh Coordinating Center will act as the Data Safety Monitoring Board for all sites and will maintain a record of Data Safety Monitoring reports from each individual recruitment site.

### **Reporting:**

The Pittsburgh Coordinating Center will provide annual reports of data safety monitoring to all recruitment sites to the University of Pittsburgh IRB and all sites.

The Pittsburgh Coordinating Center will provide an annual summary of subject enrollment to all recruitment sites.

The Pittsburgh Coordinating Center will communicate protocol changes to all sites.

## **8 APPENDICES**

- 8.1 Patient Intake Form**
- 8.2 Eligibility Form**
- 8.3 Testicular Tissue Cryopreservation Study Enrollment Form**
- 8.4 Transportation Waiver Form**
- 8.5 Testicular Tissue Collection and Transport Form**
- 8.6 TTC Case Documentation Checklist**
- 8.7 Adverse Event Evaluation and Data Safety Monitoring Forms**
- 8.8 Testicular Tissue Cryopreservation Study – Follow-up Script**
- 8.9 ReproTech Forms**



## TESTICULAR TISSUE CRYOPRESERVATION INTAKE SHEET\*

How did you hear about us? \_\_\_\_\_

Date: \_\_\_\_\_ Email: \_\_\_\_\_

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

Address: \_\_\_\_\_

\_\_\_\_\_

Phone: (H) \_\_\_\_\_ (C) \_\_\_\_\_  
(W) \_\_\_\_\_

Date of Birth: \_\_\_\_\_ Age \_\_\_\_\_

Parents: \_\_\_\_\_

\_\_\_\_\_

Parent phone: \_\_\_\_\_

Diagnosis: \_\_\_\_\_

- Date diagnosed: \_\_\_\_\_

Previous treatment: \_\_\_\_\_

- Chemo: \_\_\_\_\_
- Radiation: \_\_\_\_\_
- Surgery: \_\_\_\_\_

Current treatment: \_\_\_\_\_

- Chemo: \_\_\_\_\_
- Radiation: \_\_\_\_\_
- Surgery: \_\_\_\_\_

Oncologist: \_\_\_\_\_

\_\_\_\_\_

Allergies: \_\_\_\_\_

Medications: \_\_\_\_\_

\_\_\_\_\_

Significant Medical History: \_\_\_\_\_

\_\_\_\_\_

# Eligibility Form

***Testicular tissue cryopreservation for fertility preservation  
in patients facing infertility-causing disease or treatment regimens***

IRB Protocol: \_\_\_\_\_

Subject Initials: \_\_\_\_\_

PI: \_\_\_\_\_

Subject #: \_\_\_\_\_

Date: \_\_\_\_\_

DOB: \_\_\_\_\_

Treatment Regimen: \_\_\_\_\_

Indication/Usage:    Malignancy         BMT/SCT         Other

Inclusion Criteria	Check at least one in each section
1. Male any age	<input type="checkbox"/>
2a. Scheduled to undergo surgery or medical treatment with risk of causing azoospermia and infertility.  <b>OR</b> 2b. Have a medical condition or malignancy that requires removal of all or part of one or both testicles	<input type="checkbox"/>  <input type="checkbox"/>
3a. Have newly diagnosed disease (see section 4a)  <b>OR</b> 3b. Have recurrent disease (see section 4b)	<input type="checkbox"/>  <input type="checkbox"/>
4. Subjects with recurrent disease or in the early stage of primary treatment are only eligible if they <u>have not</u> previously received therapy that would put them at high risk of azoospermia.  4a. Subject in early stage of primary treatment with significant risk regimen?  4b. Has subject received a previous treatment that would cause complete azoospermia?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> N/A  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> N/A
5. Patient in significant risk	<input type="checkbox"/> YES <input type="checkbox"/> NO

Qualify: Yes  No

Investigator Signature: \_\_\_\_\_ Date: \_\_\_\_\_

## Eligibility Form

*Testicular tissue cryopreservation for fertility preservation  
in patients facing infertility-causing disease or treatment regimens*

IRB Protocol:

Subject Initials: \_\_\_\_\_

PI:

Subject #: \_\_\_\_\_

Date: \_\_\_\_\_

DOB: \_\_\_\_\_

**Significant risk (Prolonged azoospermia after treatment):**

- Cyclophosphamide equivalent dose (CED) >4,000 mg/m<sup>2</sup> (Green et al., 2014)
- Total body irradiation (TBI) (Wallace et al. 2005; Wallace et al. 2011)
- Testicular radiation >2.5 Gy (Lambertini et al. 2016; Gordon et al. 1997)
- Cisplatin 500 mg/m<sup>2</sup> (Lambertini et al. 2016)
- Bone Marrow Transplant (BMT) (Meacham et al., 2020)

## Eligibility Form

***Testicular tissue cryopreservation for fertility preservation  
in patients facing infertility-causing disease or treatment regimens***

IRB Protocol: \_\_\_\_\_

Subject Initials: \_\_\_\_\_

PI: \_\_\_\_\_

Subject #: \_\_\_\_\_

Date: \_\_\_\_\_

DOB: \_\_\_\_\_

**How to calculate the Cyclophosphamide equivalent dose (CED) calculation (Green et al., 2014):**

Drug	Dose(cumulative dose in mg/m <sup>2</sup> )	Multiplier	Cyclophosphamide equivalent dose
Cyclophosphamide		1	
Ifosfamide		0.244	
Procarbazine		0.857	
Chlorambucil		14.286	
BCNU		15.0	
CCNU		16.0	
Melphalan		40	
Thio-TEPA		50	
Nitrogen mustard		100	
Busulfan		8.823	
		Total CED =	

**Example:**

Drug	Dose(cumulative dose in mg/m <sup>2</sup> )	Multiplier	Cyclophosphamide equivalent dose (mg/m <sup>2</sup> )
Cyclophosphamide	2000	1	2000*1 = 2000
Ifosfamide	5000	0.244	5000*0.244 = 1220
Procarbazine	0	0.857	0*0.857 = 0
Chlorambucil	0	14.286	0*14.286 = 0
BCNU	0	15.0	0*15 = 0
CCNU	300	16.0	300*16 = 4800
Melphalan	0	40	0*40 = 0
Thio-TEPA	0	50	0*50 = 0
Nitrogen mustard	0	100	0*100 = 0
Busulfan	0	8.823	0*8.823 = 0
		Total CED =	8020

Significant risk >4,000 mg/m<sup>2</sup>



Fertility Preservation  
IN  
Pittsburgh

## Testicular Tissue Cryopreservation Study Enrollment\*

Today's Date: \_\_\_\_\_  
Expected Date of Surgery: \_\_\_\_\_  
Consent form signed on: \_\_\_\_\_

### Site Information

Site Name: \_\_\_\_\_  
Primary Contact Person (Name and Phone): \_\_\_\_\_

### Patient Information

Patient Number: \_\_\_\_\_  
Date of Birth: \_\_\_\_\_

#### Race:

- American Indian/Alaska Native
- Asian
- Native Hawaiian or Other Pacific Islander
- Black or African American
- White
- More Than One Race
- Unknown or Not Reported

#### Ethnicity:

- Non-Hispanic
- Hispanic

Type of Cancer/Diagnosis: \_\_\_\_\_

Previous Cancer Treatment:

Reason for previous treatment:  Early stage of treatment       Recurrence

Chemotherapy received and doses: \_\_\_\_\_

Protocol name (if applicable): \_\_\_\_\_

Total cyclophosphamide equivalent dose (if applicable): \_\_\_\_\_

Radiation dose and field: \_\_\_\_\_

Surgery type: \_\_\_\_\_

Planned Cancer Treatment: \_\_\_\_\_

Please remove all patient identifiable information and forward a copy of this form to the Fertility Preservation Program in Pittsburgh at [fertilitypreservation@upmc.edu](mailto:fertilitypreservation@upmc.edu). For questions call 412-641-7475.



Fertility Preservation  
IN  
Pittsburgh

**Fertility Preservation Program in Pittsburgh  
Magee-Womens Hospital of UPMC Health System**

**TRANSPORTATION WAIVER\***

At your request:

\_\_\_\_\_ (Patient)

\_\_\_\_\_ (Parents)

We have provided shipping materials and arranged with your medical providers at:

\_\_\_\_\_ (Hospital)

to ship testicular tissue (tissue) in a cold storage container to the Fertility Preservation Program at Magee-Womens Hospital in Pittsburgh, Pennsylvania.

It must be understood by the parties signed below that there are inherent risks associated with the transport of the tissue, including but not limited to, container failure, travel delays, forces of nature, Acts of God and deviation in temperature that can cause adverse affects on the tissue.

Because of these possible transportation circumstances, the parties acknowledge that the events could compromise the viability of the tissue and that the Fertility Preservation Program in Pittsburgh, The Center for Fertility and Reproductive Endocrinology, Magee-Womens Hospital or UPMC Health System and its affiliates, can not make any representation or warranty of any kind concerning the quality of the tissue or any services related to the tissue.

\_\_\_\_\_  
Signature and Date

\_\_\_\_\_  
Signature and Date

\_\_\_\_\_  
Witness

Please remove all patient identifiable information and forward a copy of this form to the Fertility Preservation Program in Pittsburgh at [fertilitypreservation@upmc.edu](mailto:fertilitypreservation@upmc.edu). For questions call 412-641-7475.

\*Keep with patient records at recruiting site.



Fertility Preservation  
IN  
Pittsburgh

**Testicular Tissue Collection and Transport Form**  
for patient \_\_\_\_\_ (Case number)

**Date of Surgery:** \_\_\_\_\_

**Surgeon:** \_\_\_\_\_

**Time testicular tissue removed:** \_\_\_\_\_

**Name /Phone number of person shipping tissue:** \_\_\_\_\_

\_\_\_\_\_

**Comments:** \_\_\_\_\_

\_\_\_\_\_

For shipment to Pittsburgh, please follow these instructions and prepare the following contents in a thermos provided to you by the Coordinating Center:

1. We will coordinate tissue pick-up and transport with you the day before the scheduled surgery.
2. A return shipping label or a link to the courier's website for printing the return shipping label will be emailed to you.
3. Once pathology sample has been collected, place the remaining testicular tissue in a sterile specimen cup and add cold media into the specimen cup (about 2/3 full) prior to placement of tissue. The tissue should be placed into the container using sterile technique, and the tissue should not come in contact with formalin. The container should be labeled with patient tissue identification number and the side that the tissue was taken (left or right).
4. Place the specimen cup in the thermos and surround with ice packs (please place the ice pack in the freeze for at least 24 hours).
5. Turn on the temperature logger (LogTag) by holding down the Start/Mark button until the Alert and Ok lights flash red and green. Place the temperature logger next to the specimen cup.
6. Include filled Testicular Tissue Collection, Transport Form and Enrollment Form in the shipping box.
7. Add packing material as needed to stabilize the contents for shipping.
8. Include a copy of this filled form in the shipping box.
9. If there are any questions, please call our Fertility Preservation Phone Line at 412-641-7475 or email [fertilitypreservation@upmc.edu](mailto:fertilitypreservation@upmc.edu).

Version 2/2020



## TTC Case Documentation Checklist

Study ID \_\_\_\_\_  
Diagnosis \_\_\_\_\_  
Treatment: \_\_\_\_\_  
Oncology Clearance: \_\_\_\_\_  
DOB \_\_\_\_\_  
IDC-10: \_\_\_\_\_  
Azoospermia Risk: \_\_\_\_\_  
Surgery Date: \_\_\_\_\_

### **Consult Visit:**

\_\_\_\_\_ Fertility Options (Brochures - Fertile Hope, FPP, ASRM, etc...)  
\_\_\_\_\_ Give Testicular Tissue Cryo Study Consent (consent expires \_\_\_\_\_)

### **Pre-OP Coordinating Center Forms (Remove identifiable information and email copies to FPP):**

\_\_\_\_\_ Patient Intake Form  
\_\_\_\_\_ Eligibility criteria form (initiated by physician)  
\_\_\_\_\_ Enrollment Form  
\_\_\_\_\_ Testicular Tissue Collection Kit received on: \_\_\_\_\_ complete: Y / N

### **Pre-Op Visit:**

Surgeon \_\_\_\_\_  
Date \_\_\_\_\_ Location \_\_\_\_\_  
Procedure \_\_\_\_\_  
\_\_\_\_\_ FPP Transportation Waiver Form

### **Day of Surgery:**

\_\_\_\_\_ collect lab work (HIV 1/2, Hepatitis B, Hepatitis C); 2 plasma (purple top);  
TUBES EXPIRE \_\_\_\_\_  
\_\_\_\_\_ Contact pathology for path. Send path requisition with specimen.  
\_\_\_\_\_ Infectious disease testing done on: \_\_\_\_\_  
\_\_\_\_\_ FPP Testicular Tissue Collection and Transport Form  
\_\_\_\_\_ Testicular Tissue Collection Kit and form shipped at: \_\_\_\_\_ FPP received at: \_\_\_\_\_

### **Post-Op:**

\_\_\_\_\_ Reprotech registration to Jeanne Blank [jeblank@reprotech.com](mailto:jeblank@reprotech.com)  
\_\_\_\_\_ Infectious disease testing results faxed to ReproTech (copy to FPP)  
\_\_\_\_\_ Path report/Operative reports received  
\_\_\_\_\_ Adverse events review (copy to FPP)

### **FPP will send you:**

\_\_\_\_\_ Testicular tissue processing and freezing log  
\_\_\_\_\_ Immunohistochemistry results and report



Fertility Preservation  
IN  
Pittsburgh

**ADVERSE EVENT EVALUATION**

IRB#: \_\_\_\_\_  
Date of review: \_\_\_\_\_  
Subject ID: \_\_\_\_\_  
Diagnosis: \_\_\_\_\_  
Subject DOB: \_\_\_\_\_ Age \_\_\_\_\_  
Date of Procedure: \_\_\_\_\_ Procedure: \_\_\_\_\_  
Adverse effect: YES NO  
Describe adverse effect:

---

Name of the person obtaining this information	Signature	Date
---	-----------	------

Was the adverse event an unanticipated problem? YES NO

What caused the adverse event?

Is the adverse event related or possibly related to participation in the research? YES NO

Does the adverse event suggest that the research places subjects or others at greater risk or harm than was previously known or recognized?

Treatment?

---

Name of the person reviewing the AE	Signature	Date
-------------------------------------	-----------	------

Serious adverse events (eg. Hospitalization) and unanticipated adverse effects are to be reported to sponsor and IRB within 10 working days after becoming aware of the event.

Please forward a copy of this form to the Program Coordinator at **Fertilitypreservation@upmc.edu**  
Phone: 412-641-7475.

\* Keep with patient records at recruiting site.

**University of Pittsburgh  
Data Safety Monitoring Minutes**

**PI:**  
**Title:**  
**IRB #:**

**Date of Meeting:**

**Indicate the members of the staff that were present at the meeting:**

<b>The following information was discussed at the meeting</b>	
Recruitment and Retention	
Data Issues (timeliness and quality)	
Unanticipated Problems  Do these need to be reported to the appropriate oversight agencies (i.e. IRB, FDA, DoD)?	
Adverse Events and Serious Adverse Events  Do these need to be reported to the appropriate oversight agencies (i.e. IRB, FDA, DoD)?	
Confidentiality issues	
Change in risk benefit ratio	
Other issues addressed	

Signature Principal Investigator: \_\_\_\_\_ Date: \_\_\_\_\_

## Testicular Tissue Cryopreservation Study - Follow-up Questionnaire (Over 18)

Name:  Date of Birth:

Study ID #

Hello **(patient's name)**. This is **(my name)** from Fertility Preservation Program of Pittsburgh. We are contacting you about the testicular tissue that you had frozen here. We would like to ask you to complete a 5-10-minute survey to update your contact and health information and to ask you for some extra information for our research. Your participation in this survey is completely voluntary. This means that you do not have to participate in this survey unless you want to. There is a small chance that some of the questions may make you feel uncomfortable. You do not have to answer those questions if you do not want to. All the information I receive from you by phone will be strictly confidential.

You will only be able to type into areas in grey. You may also print it out and mail or fax it back to us.

### Questions:

1. Please verify your home address?

2. Is there an email address you would like us to have of file?

3. Do you have any questions?

*Note to Fertility Preservation Program Personnel: answers to questions 1-3 should be stored separately from the answers to the questions below to protect patient confidentiality. Please store this page separately from the questions that follow.*

4. Is the patient deceased:

- Yes, end call  
 No

**Health:**

5. Have you finished treatment yet?

- Yes  No

If No, what kind of treatment are you receiving? \_\_\_\_\_

6. How would you describe your current health?

- Excellent  
 Very good  
 Good  
 Fair  
 Poor

7. Have you been diagnosed with any other health condition since your initial diagnosis?

- Yes  No

If yes, diagnosis and treatment: \_\_\_\_\_

8. Had you started puberty before your treatment?

- Yes  No  N/A

If No, did your pediatrician tell you/your parents anything about your growth and development after your treatment?  
\_\_\_\_\_

**Fertility:**

9. Have you had a fertility consultation and/or a semen analysis since your treatment?"

- a.  Yes  No  N/A

If yes, what were the results: \_\_\_\_\_

10. Have you tried to achieve pregnancy with your partner since treatment stopped?

- Yes  No  N/A

11. Has your partner been pregnant since you started treatment?

- Yes  No  N/A

12. Is it important to you to have biological children?

- Yes  No  I don't know

**Satisfaction:**

13. Now that you've had some time to think about your decision, how are you feeling about the decision to store tissue?

\_\_\_\_\_

14. Would you recommend fertility preservation to a friend who was diagnosed with a disease or prescribed a medical treatment that could compromise fertility?

- Store tissue
- Do not store tissue
- Don't know

15. Although we cannot give you specific information on your tissue, would you like to have information about the research? Would you like to receive our newsletter?"

- Yes     No

16. Is there anything else we can help you with?

\_\_\_\_\_

Thank you for completing this survey. We appreciate you taking the time to answer the questions. We would like to contact you in one year, and annually after that, to repeat this survey. Is that acceptable to you?

- Yes     No

## Testicular Tissue Cryopreservation Study - Follow-up Questionnaire (Under 18)

Name: \_\_\_\_\_ Date of Birth: \_\_\_\_\_

Study ID # \_\_\_\_\_

Hello (patient's/parent's name). This is (my name) from Fertility Preservation Program of Pittsburgh. We are contacting you about the testicular tissue that you had frozen here for your son. We would like to ask you to complete a 5-10-minute survey to update your contact and health information and to ask you for some extra information for our research. Your participation in this survey is completely voluntary. This means that you do not have to participate in this survey unless you want to. There is a small chance that some of the questions may make you feel uncomfortable. You do not have to answer those questions if you do not want to. All the information I receive from you by phone will be strictly confidential.

You will only be able to type into areas in grey. You may also print it out and mail or fax it back to us.

For patients under the age of 18: complete survey with parent/legal guardian.

### Questions:

17. Please verify your home address?

\_\_\_\_\_

18. Is there an email address you would like us to have of file?

\_\_\_\_\_

19. Do you have any questions?

\_\_\_\_\_

*Note to Fertility Preservation Program Personnel: answers to questions 1-3 should be stored separately from the answers to the questions below to protect patient confidentiality. Please store this page separately from the questions that follow.*

20. Is the patient deceased:

- Yes, end the call  
 No

**Health**

21. Has your son finished treatment yet?

- Yes  No

If No, what kind of treatment is he receiving? \_\_\_\_\_

22. How would you describe your son's current health?

- Excellent  
 Very good  
 Good  
 Fair  
 Poor

23. Has your son been diagnosed with any other health condition since his initial diagnosis?

- Yes  No

If yes, diagnosis and treatment:

24. Has your son started puberty?

- Yes  No  N/A

25. Has your son's pediatrician told you anything about his growth and development?

- Yes  No  N/A

b. If YES, what were you told about your son's growth and development?"

**Fertility:**

26. Has your son had a fertility consultation and/or a semen analysis since his treatment?"

- c.  Yes  No  N/A

If yes, what were the results:

**Satisfaction:**

27. Now that you've had some time to think about your decision, how are you feeling about the decision to store tissue?

28. What would you recommend to a friend who was diagnosed with a disease or prescribed a treatment that could compromise his fertility?

- Store tissue
- Do not store tissue
- Don't know

29. Although we cannot give you specific information on your (son's) tissue, would you like to have information about the research? Would you like to receive our newsletter?"

- Yes     No

30. Is there anything else we can help you with?

Thank you for completing this survey. We appreciate you taking the time to answer the questions. We would like to contact you in one year, and annually after that, to repeat this survey. Is that acceptable to you?

- Yes     No



Dear Client Depositor,

ReproTech, Ltd. (RTL) is pleased to have been selected by the Center for Fertility & Reproductive Endocrinology as the facility to assume the storage responsibilities of your cryopreserved testicular tissue. ReproTech, Ltd. is licensed by the New York State Department of Health, the State of California Department of Health Services and accredited by the American Association of Tissue Banks. Our staff will provide you with the highest level of experience and professionalism to service your needs.

Our annual storage fee is \$275. You also have the option of paying quarterly or at our multi-year rates. The transfer fee to ship a tank from your clinic to RTL is \$215. RTL offers a financial assistance program (Verna's Purse) for clients who are experiencing financial hardship. If you are approved for the program, the annual fee will be reduced to \$75 and the transfer fee per shipping tank will be reduced to \$95. **The fee for the first storage period and the transfer fee must be prepaid before your specimens can be transferred to RTL for storage.**

Please complete the following forms:

**A. Client Depositor Registration;**

This form gives us information about you, the Client Depositor. On this form, you will choose a method of paying your annual storage fee and transfer fee. Regardless of the method chosen, this form needs a signature on the bottom, indicating that you accept and understand our billing policy.

**B. Testicular Tissue Cryostorage Agreement;**

Please read this agreement carefully. Please select one disposition option and sign and date your choice. Then print and sign your name to acknowledge the terms of the agreement.

**C. Medical History;** Please complete and sign this form.

**D. Specimen Transfer To RTL And Medical Data Release Authorization;**

Please read this 3 page document carefully. On this Authorization, you will initial to elect or decline to purchase shipping insurance. You will also initial to instruct us to use one or two shipping tanks for the shipment. The regular transfer fee rate is \$215 for one tank or \$430 for two tanks. Shipping insurance is assessed per tank. Please include your cryobank's information. You will complete the form by signing and providing your contact information.

**Please note: If the Client Depositor is under 18 years of age, a parent or guardian must complete and sign these forms.**

Prior to transfer, RTL requires evidence of your serology for Anti-HIV-1/2(AIDS). These testing results will be provided by your clinic.

In compliance with AATB Standards and RTL policies, the following tests must be completed and the results forwarded to RTL **prior to release** of your testicular tissue for your use in the future: Anti-HIV-1/2, HBsAg, and HCV.

Please call RTL at 888-489-8944 or email me if you have any questions or visit our website at [www.reprotech.com](http://www.reprotech.com). We will notify you via mail once the transfer has occurred and your testicular tissue is in storage at ReproTech, Ltd.

Sincerely,  
Lea Wilcox  
[lwilcox@reprotech.com](mailto:lwilcox@reprotech.com)

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Semen/  
Testicular Tissue

**REGISTRATION**

**PATIENT INFORMATION**

RTL Account # \_\_\_\_\_ (assigned by RTL staff)

Name \_\_\_\_\_ Date of Birth \_\_\_\_\_ SS# \_\_\_\_\_

Address \_\_\_\_\_ Home Phone (\_\_\_\_) \_\_\_\_\_

Street City State Zip

Name of Partner (if applicable) \_\_\_\_\_ Partner's SSN \_\_\_\_\_

Work Phone (\_\_\_\_) \_\_\_\_\_ Cell Phone Number(s) \_\_\_\_\_ Email Address \_\_\_\_\_

Have you ever **tested positive** for HIV, Hepatitis B, Hepatitis C, or HTLV I & II? \_\_\_\_\_

If yes, please specify \_\_\_\_\_

What month(s) and year(s) were your specimens cryopreserved? \_\_\_\_\_

**Privacy Policy:** RTL requires a Personal Identification Number (PIN) for release of information about your account.

Please enter your PIN (may be Social Security Number): \_\_\_\_\_

To whom, other than yourself, may we release information about your account (Print name & relationship) \_\_\_\_\_

**PERSON RESPONSIBLE FOR THIS ACCOUNT**

Name \_\_\_\_\_ Relationship to patient \_\_\_\_\_ Home Phone \_\_\_\_\_

Address \_\_\_\_\_ Work Phone \_\_\_\_\_

SS# \_\_\_\_\_

**PAYMENT POLICY**

Please indicate the billing interval for storage fees that you elect. Unused storage fees are non-refundable. Storage and shipping fees must be prepaid.

Quarterly  1 year  2 year  3 year

**CREDIT CARD AUTHORIZATION:** Your signature here authorizes ReproTech, Ltd. to charge your credit card for shipping and storage fees.  Check here if you are only authorizing RTL to use your credit card for the first annual or multi-year storage period and the shipping fees. Please note that quarterly storage fees are automatically billed and are not eligible for a one-time authorization.

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

Account Number \_\_\_\_\_ Name on Card \_\_\_\_\_ Expiration Date \_\_\_\_\_

**PHYSICIAN/CLINIC WHERE SEMEN/TESTICULAR TISSUE IS STORED**

Name \_\_\_\_\_ Telephone \_\_\_\_\_ Fax \_\_\_\_\_

Address \_\_\_\_\_

Street City State Zip

**PATIENT SIGNATURE BELOW IS REQUIRED**

Your signature below acknowledges acceptance of our payment and privacy policies and agreement to keep ReproTech, Ltd. updated with current address and contact information.

Signature of Patient \_\_\_\_\_ Date \_\_\_\_\_

If the Patient above is a minor, a parent or guardian of the minor must sign below:

Signature of Parent or Guardian, if applicable: \_\_\_\_\_

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## TESTICULAR TISSUE (UNDER 18 YEARS OLD) CRYOSTORAGE AGREEMENT

This AGREEMENT, Made between ReproTech, Ltd., a Minnesota corporation (the "Company"), and the person named below (the "Client Depositor").

1. **Collection and Storage:** With the assistance of the Client Depositor, and in accordance with the procedures for identification and testing established by the Company (as set forth in the Company's brochure and web site, [www.reprotech.com](http://www.reprotech.com)), the Company shall receive the Client Depositor's testicular tissue, which has been cryopreserved by the Client Depositor's physician/clinic (the "Clinic"), for long-term cryostorage until this Agreement is terminated pursuant to Paragraph 4. All procedures established by the Company may be modified at the sole discretion of the Company to reflect changes in industry practices, laws, or regulations.

2. **Storage Fees and Records:** The fee for each Storage Period shall be payable in advance and shall be adjusted from time to time by the Company based upon market factors. The current fees are set forth in the Company's brochure and web site, [www.reprotech.com](http://www.reprotech.com). A "Storage Period" begins with the month in which the Company receives specimens for storage. Unused storage fees are non-refundable. The Client Depositor shall keep the Company informed at all times, in writing, of his current address and telephone number for billing purposes and any other matter requiring notice to the Client Depositor. The Client Depositor's name and address, as well as other records relating to the subject of this Agreement, shall be kept on file at the Company.

3. **Account in Default:** If at any time the Company has not received full payment of all amounts due to the Company from the Client Depositor on or before the 60<sup>th</sup> day after the beginning of any storage Period, then the Client Depositor is in "default". In the event of default, the Company may, in its sole discretion, refer the Client Depositor's account to any attorney or collection agency for collection, and the Client Depositor agrees to pay all costs of such collection, including but not limited to any reasonable fees charged by the collection agency and reasonable attorney's fees. If the Client Depositor is in default, the Company may discard all stored specimens. The term "discard" means that the Company will thaw and destroy the specimens in a professional and ethical manner, as determined solely by the Company. Discarded specimens cannot and will not be used for reproductive purposes by or on behalf of any person or persons.

4. **Termination of Agreement:** This Agreement shall terminate and the Company's responsibilities for storage of specimens hereunder will cease:

- (1) upon the release of all specimens stored by the Company pursuant to Conditions of Release; or
- (2) upon the disposition of all specimens stored by the Company pursuant to a default under Paragraph 3; or
- (3) upon the notarized execution of Company's separate termination agreement by the Client Depositor; or
- (4) if the Client Depositor dies, as established by evidence deemed sufficient by the Company.

5. **Responsibilities and Liabilities of the Company:** The Client Depositor acknowledges that he has been fully advised concerning the state of the art of cryopreservation of specimens of testicular tissue. The Client Depositor acknowledges that he understands that the viability of the testicular tissue and the results from subsequent use depend almost in their entirety upon the Client Depositor and the recipient. Accordingly, the Client Depositor understands and agrees that the Company's responsibilities shall be limited hereunder solely to the adequate cryostorage of said testicular tissue consistent with the state of the art at the date of entering into this Agreement. The Client Depositor agrees to hold the Company harmless for any damage sustained while the testicular tissue specimens are not in the possession and control of the Company. In any event, the total liability of the Company for failure to meet any of its responsibilities to the Client Depositor shall not exceed the amount of storage and/or shipping fees theretofore paid by the Client Depositor. The parties agree that any claims relating to or arising out of this Agreement will be brought in the state courts of Minnesota. In the event the Company terminates the operation of its storage facility, it may, 30 days after written notice to the Client Depositor at his last known address, assign and transfer its obligations hereunder and the testicular tissue held on behalf of the Client Depositor to a similar storage facility.

6. **Additional Terms:** The Client Depositor promises and agrees to indemnify and save harmless the Company from any loss and/or expenses incurred in connection with the defense or payment of any claim by any other party relating to the subject of this Agreement. The Agreement shall be binding upon the Client Depositor and his assigns, heirs, executors, and administrators.

### 7. CONDITIONS OF RELEASE OF TESTICULAR TISSUE SPECIMENS FROM STORAGE DURING LIFETIME OF CLIENT DEPOSITOR

Release of testicular tissue may occur during the lifetime of the Client Depositor, only upon the occurrence of the following conditions;

- i. only to a licensed physician, and
- ii. only for use by the Client Depositor's spouse or sexually intimate partner ("Recipient"),
- iii. upon the express notarized authorization of the Client Depositor, and
- iv. upon the authorization of the Recipient's clinic, and
- v. upon the completion of serology/virology tests required by the Company.



Semen

**ADDENDUM TO SEMEN CRYOSTORAGE AGREEMENT**  
(Infectious Disease)

WHEREAS, the person named below (the "Client Depositor") has entered into a Semen Cryostorage Agreement for the cryostorage of semen by ReproTech Limited and

WHEREAS, certain additional terms apply to the storage of specimens from potentially infectious clients

WHEREFORE, the undersigned agrees that the following terms and conditions apply in addition to those set forth in Semen Cryostorage Agreement:

1. The storage of specimens from potentially infectious clients (clients for whom testing show a potential for an infectious disease) requires certain additional safeguards and procedures. The undersigned understands and agrees that his specimens will be stored in a separate vapor storage tank which is designated for potentially infectious specimens only.
  - a. Specimens from Client Depositors who have tested reactive for HIV will be stored in an HIV Only storage tank
  - b. Specimens from Client Depositors with non-HIV potentially infectious conditions may be stored in a separate non-HIV tank and their specimens will be physically segregated by use of disease specific canisters.
2. While specimens are normally divided for storage between two tanks (in order to reduce the risk of loss in the event one tank is destroyed), specimens from potentially infectious clients will all be stored in one tank.
3. The undersigned further understands that because of additional required precautions, storage fees and shipping fees will be higher than the fees charged to clients who are not potentially infectious. The undersigned acknowledges receipt of a fee schedule showing presently applicable fees.
4. The undersigned understands that unless other arrangements at increased cost are requested, specimens will be shipped to and from RTL using only one shipping tank (rather than the procedure for non-infectious specimens which split the shipments between two tanks to minimize the risk of loss).
5. **The undersigned further understand that the shipping fees must be pre-paid by the Client Depositor prior to the shipment of the tank to the clinic and that the shipping fees are non-refundable.**
6. The undersigned further understands that results of any testing for infectious diseases will be disclosed to the receiving physician and the recipient (spouse or sexually intimate partner) as part of an informed consent procedure before the specimens are used.

By: \_\_\_\_\_  
Client Depositor Name (Print) Client Depositor Signature Date

If the Client Depositor is a minor, a parent or guardian of the minor must sign below:

\_\_\_\_\_  
Name of Parent/Guardian, if applicable (Printed) Signature of Parent/Guardian, if applicable Date

By: \_\_\_\_\_  
ReproTech, Ltd. Representative Date RTL Account: \_\_\_\_\_

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Semen/  
Testicular Tissue

TREATMENT HISTORY

All information is REQUIRED, where applicable

Name: \_\_\_\_\_ Account: \_\_\_\_\_

Clinical Diagnosis: \_\_\_\_\_

Referring Physician (i.e. Oncologist, Urologist) who referred you for cryobanking:

Name: \_\_\_\_\_ Clinic Name: \_\_\_\_\_

Address: \_\_\_\_\_

Phone #: \_\_\_\_\_

Reason for Semen/Testicular Tissue Cryobanking (Please check the applicable selections.)

- |  |  |   |
|--|--|---|
| <b>Vasectomy:</b><br><input type="checkbox"/> Pre-vasectomy<br><input type="checkbox"/> Post-vasectomy   | <b>Cancer Treatment:</b><br><input type="checkbox"/> Pre-Radiation Therapy<br><input type="checkbox"/> Pre-Surgery<br><input type="checkbox"/> Pre-Chemotherapy<br><input type="checkbox"/> Between Treatments | <b>Fertility Treatment:</b><br><input type="checkbox"/> IVF Backup<br><input type="checkbox"/> Donation<br><input type="checkbox"/> Use by a Friend<br><input type="checkbox"/> Use by a Surrogate<br><input type="checkbox"/> Use by a Gestational Carrier<br><input type="checkbox"/> Other, Please specify _____ |
| <b>High Risk Occupation:</b><br><input type="checkbox"/> Military Service/Deployment<br><input type="checkbox"/> Other (Hazardous chemicals, etc.), Please specify _____ |  |   |

Treatment History: Please indicate applicable treatments or therapies and dates:

	None	Past	Future
Vasectomy			
Chemotherapy			
Radiation Therapy			
Surgery			

Fertility History:

Number of pregnancies: \_\_\_\_\_

Number of live births: \_\_\_\_\_

Comments: \_\_\_\_\_

Your signature below acknowledges that the semen/testicular tissue specimens provided to RTL for the purpose of long term storage have been produced by and are the property of the undersigned. It is understood and agreed that future serology testing may be required for storage and/or release of these specimens.

Signature \_\_\_\_\_ Date \_\_\_\_\_

If the Patient above is a minor, a parent or guardian of the minor must sign below:

Signature of Parent or Guardian, if applicable: \_\_\_\_\_

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**SPECIMEN TRANSFER TO RTL AND MEDICAL DATA RELEASE AUTHORIZATION - COURIER**

The undersigned client depositor(s) request(s) the transfer of his/her reproductive tissue specimens to ReproTech Ltd. (RTL) from the physician/clinic/"facility" listed below in accordance with RTL's current policies and procedures. It is understood that the facility acknowledges this request and will assist in the transfer of the reproductive tissue specimens. Furthermore it is recognized by the client depositor(s) that events beyond the control of RTL and the facility may occur during transfer and it is understood by all parties that neither the facility nor RTL are responsible for any losses in connection with or related to the shipment of the reproductive tissue specimens.

I (we) hereby authorize the transfer of my (our) reproductive tissue specimens from the facility to RTL for continued long term storage.  
I (we) understand that RTL and the facility cannot verify, nor guarantee, the viability of the transferred reproductive tissue specimens being placed into long term storage at RTL.  
I (we) agree to hold RTL harmless for any claims for damage to the reproductive tissue specimens arising from acts or omissions prior to RTL's possession of such specimens.  
I (we) agree that RTL shall not be liable for errors, including, specimen labeling errors, which occur prior to RTL's acceptance of the specimens for storage.  
I (we) have read and understand the policies above and hereby authorize the facility to release my (our) reproductive tissue specimens to the RTL.  
I (we) authorize the facility to release to RTL medical data, including but not limited to: Personal biographical data, serology/virology testing data and specimen processing/cryopreservation data. This includes information about human immunodeficiency virus-HIV, acquired immunodeficiency syndrome-AIDS, and AIDS related complex-ARC, as defined by Department of Community Health rules (1989 Public Act 174).

**Type of tissue to be transferred to RTL for continued storage**

Mark which type(s) of reproductive tissue(s) you want to be transferred to RTL for continued storage:

Embryo     Sperm     Testicular Tissue     Oocytes     Ovarian Tissue     Endometrial Tissue  
 Donor Embryo     Donor Semen     Donor Eggs     Other: \_\_\_\_\_

**Client Depositor Name(s)** \_\_\_\_\_

Client depositors have several options to mitigate the risks inherent in the shipment of reproductive tissue, including the use of two shipping tanks and the purchase of optional shipping insurance. The majority of shipments are sent by UPS. We understand that UPS provides a limit of \$100 of insurance for the contents of each shipment of human reproductive tissue. We have reviewed the optional Specimen Shipping Insurance information (page 3) and have selected to:

**Insurance: Choose one of these three options by initialing next to your choice**

\  I/We understand and accept that without the purchase of additional insurance, coverage for transfers is limited to a maximum of \$100 (UPS) and that other courier services may provide no insurance coverage at all. We decline to purchase additional insurance.

\  TIER 1: Purchase insurance at the \$15,000 level as described on page 3 at the cost of \$19.50. I/We understand that this insurance is for actual replacement costs up to \$15,000 and that it only insures the tissue against loss or loss of integrity due to an event that occurs during the shipment. I/We understand that payment for the insurance must be made in advance of the shipment for the insurance to be in effect.

\  TIER 2: Purchase insurance at the \$25,000 level as described on page 3 and at the cost of \$32.50. I/We understand that this insurance is for actual replacement costs up to \$25,000 and that it only insures the tissue against loss or loss of integrity due to an event that occurs during the shipment. I/We understand that payment for the insurance must be made in advance of the shipment for the insurance to be in effect.

**Tanks: Choose one of these two options by initialing next to your choice**

   \    I/We are requesting that our reproductive tissue specimens be divided into two shipping tanks for additional safety during shipping and understand that the additional cost of providing services by the way of two shipping tanks is an additional shipping fee of \$215.00. This option is only available if the reproductive tissue specimens are cryopreserved in more than one container.

   \    I/We have declined the use of two shipping tanks and accept the potential risk of using only one shipping tank.

I (we) have read and understand the policies and optional fees on page 1 and hereby authorize the cryobank listed below to release my (our) specimens to ReproTech Ltd.

Cryobank/Physician \_\_\_\_\_  
Address: \_\_\_\_\_  
Telephone: \_\_\_\_\_

Name (Printed): \_\_\_\_\_  
Signature(s): \_\_\_\_\_  
Address: \_\_\_\_\_  
Telephone: \_\_\_\_\_

Client Depositor  
Co-Client Depositor, if applicable

If the Client Depositor above is a minor, a parent or guardian of the minor must sign below:

\_\_\_\_\_  
Signature of the Parent or Guardian, if applicable

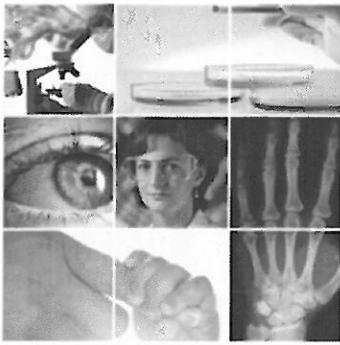
For clinic/cryobank use

We the undersigned cryobank\clinic agree to release to ReproTech, Ltd the reproductive tissue and. medical data, including but not limited to: Personal biographical/medical data.

Signatures: \_\_\_\_\_  
Cryobank/Physician \_\_\_\_\_  
Address: \_\_\_\_\_  
Telephone: \_\_\_\_\_

ReproTech, Ltd.

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# Specimen Shipping Insurance

Protecting Assets. Making a Difference.<sup>SM</sup>

**IMA**, a premier insurance broker in the United States, has developed a shipping insurance program exclusively available to clients of **ReproTech, Limited**, a leader in long term storage of reproductive tissues. While every precaution and effort is taken to ensure safe and timely delivery of specimens, shipping accidents can happen. **Specimen Shipping Insurance** provides an inexpensive insurance solution to help minimize the financial impact of an adverse event during shipping.

### Coverage for:

- Compromised specimens due to damaged or destroyed shipping tanks
- Compromised specimens due to dramatic change in temperature

\*Coverage begins once received by designated shipping carrier and ends once received at final destination.

The following coverage options are available if selected at the time of Specimen Transfer Authorization:

#### Tier 1:

**Semen Account** - Coverage will pay expenses associated with a replacement cycle or a Testicular Sperm Extraction (TESE) procedure up to a total cost not to exceed \$15,000. Charge \$19.50.

**Oocyte Account** - Coverage will pay expenses associated with a replacement cycle or for an IVF cycle up to a total cost not to exceed \$15,000. Charge \$19.50

**Embryo account** - Coverage will pay expenses associated with a replacement cycle or for an IVF cycle up to a total cost not to exceed \$15,000. Charge \$19.50.

**Donor Semen Account** - Coverage will pay expenses associated with a replacement cycle including replacement cost of the donor sperm up to a total actual cost not to exceed \$15,000. Charge \$19.50

#### Tier 2:

**Embryo or Semen account** - Coverage will pay for Testicular Sperm Extraction (TESE) procedure and a replacement IVF cycle up to a total cost not to exceed \$25,000. Charge \$32.50.

**Donor Oocyte Account** - Coverage will pay expenses associated with a replacement cycle including replacement cost of the donor eggs up to a total cost not to exceed \$25,000. Charge \$32.50

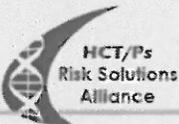
**Embryo account** - Coverage will pay for a replacement IVF cycle including donor egg expenses up to a total cost not to exceed \$25,000. Charge \$32.50.

\*Falvey, IMA or ReproTech cannot verify, nor guarantee, the viability of the specimens being shipped



IMA identifies, manages and mitigates the most challenging risk management & insurance problems in your industry. This is accomplished by understanding your industry and ultimately making your organization a better risk while saving you premium dollars. IMA accomplishes this through:

- HCT/PS Industry Focus & Expertise
- Exposure Evaluation & Risk Transfer Strategies
- Customized Loss Control & Claims Management Services
- Contractual Risk Transfer Analysis
- Insurance, Risk Management & Employee Benefits



IMA offers an exclusive program, HCT/PS Risk Solutions Alliance, that provides a unique one-stop solution for your insurance and risk management needs. Tapping into these resources allows your business to not only realize savings in premium dollars but gain access to invaluable regulatory expertise and enhanced coverage custom designed for reproductive facilities.

Mark Ware - Director of Client Services  
303-615-7505 / 1-800-813-0203  
mark.ware@imacorp.com  
www.imacorp.com

Dallas | Denver | Kansas City | Topeka | Wichita

CA: IMA of Colorado, Inc., dba IMA of Colorado Insurance Services LLC #0608704 | IMA of Texas, Inc., dba IMA of Texas Insurance Services LLC #PC04115 | IMA of Kansas, Inc. dba IMA of Kansas Insurance Services LLC #C022748