# ANALYSIS OF THE INFORMED CONSENT PROCESS IN PANCREATIC ISLET CELL TRANSPLANTATION

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# CHAPTER 1

## INTRODUCTION

In partial fulfillment of curriculum requirements for Masters in Clinical Research Management, I did six months internship, June 1, 2009 to November 18, 2009, in Transplant Administration located at Baylor All Saints Medical Center, Fort Worth, TX. I was under the supervision of my onsite mentor, Betsy Stein, CCRC and research nurse Kerri Purcell, RN. During my internship I performed day to day activities expected from a clinical research coordinator. I helped Kerri Purcell, RN, the research nurse for this study by filling out IRB forms, organizing patient charts, and filling out case report forms on subjects. With Betsy, I attended multiple commercialization, financial, and managerial meetings related to this project and other aspects of Baylor Regional Transplant Institute. Bearing witness to such meetings was truly a learning experience. Through witnessing individuals from varying backgrounds come together to develop and implement plans for overarching programs and observing human behavior in such meetings, I discovered that clinical research management requires a knowledge base of not only research and regulations but also business savvy, psychology, and excellent verbal and written communication skills.

The other project I was actively involved with was the UT Southwestern Acute Liver Failure Study Group (ALFSG). I worked with Dr. Natalie Murray (Medical Director of Liver Transplantation) and Sonnya Coultup (Transplant Clinical Research Coordinator) on drafting a resubmission letter to renew Baylor University Medical Center's participation as a site in the

NIH funded study. ALFSG is a group which examines the rare, orphan disease of Acute Liver Failure. This multi-site study collects samples and information on the history, causes and outcomes of Acute Liver Failure in the United States. Currently, ALFSG is conducting a clinical trial to test whether the drug N-acetylcysteine (NAC) improves outcome (survival) for patients with Acute Liver Failure not caused by acetaminophen overdose. Also, this group is responsible for publishing data on acetaminophen overdoses causing Acute Liver Failure which led to the recent U.S. FDA scrutiny and reevaluation of warning labels on medications containing acetaminophen.

For this study, I collected information about site personnel and facilities, statistics on liver transplant recipients, and publications. I had an opportunity to work and speak with a variety of personnel in Baylor Research Transplant Institute Research.

Transplant Administration consists of varied organizations and personnel who work together to ensure smooth office operations. The Baylor Regional Transplant Institute consists of pre- and post-transplant nurses for liver and kidney transplants, dietitians, social workers, islet cell research staff, research nurses, data specialists, physicians, and surgeons. Also, under the Transplant Administration umbrella are the hepatologists of the Liver Consultants of Texas, the financial coordinators TPAS, nephrologists, and the staff of Health Texas Provider Network.

The islet cell research team at Baylor All Saints in Fort Worth, Texas consists of the project PI, Dr. Marlon Levy (Surgical Director of Transplant), Dr. Shinichi Matsumoto (Director of Islet Cell Research), research nurses Kerri Purcell and Erin Fassett, post doctoral fellow Dr. Morihito Takita, and consultant Mr. Yasutaka Fujita.

My on site mentor has the responsibility of establishing a solid operational and financial foundation for the allogeneic islet cell transplantation program. After meeting with the research

nurses and investigators on the project, reading all the active islet cell transplantation protocols, and reviewing all current literature on the topic, I began to formulate my research topic. Pancreatic islet cell transplantation is a novel investigational treatment for type 1 diabetes. However, there are many complex issues and a lot of complicated material for the subject to digest. As result, it is necessary to scrutinize the process responsible for educating the patient about their study, the informed consent process. In order to address this problem, interviews with pancreatic islet cell transplantation subjects, research nurses and coordinators, and IRB members about the informed consent process and research may yield solutions to these problems.

## LITERATURE REVIEW

### Diabetes

Glucose is the main source of fuel for the body. After digestion, glucose passes into the bloodstream, where it is used by cells for growth and energy. For glucose's entry into cells and conversion into energy, insulin must be present. Insulin is a hormone produced by the beta cells within the islets of Langerhans of the pancreas, a large gland that lies behind the stomach. Increased blood glucose concentrations stimulate insulin secretion, whereas reduced blood glucose concentrations reduce insulin secretion.[1] However, in diabetics the pancreas either produces little or no insulin, or cells do not respond appropriately to the insulin that is produced[6]. Glucose accumulates in the bloodstream, overflows into the urine, and leaves the body through urine.[2] Thus, the body loses its main source of fuel even though the blood contains large amounts of glucose while cells are starved of energy.

Diabetes is a metabolic disease characterized by a high blood glucose concentration caused by insulin deficiency, often combined with insulin resistance. Hyperglycemia, which is high blood glucose or sugar concentration, occurs because of inadequate insulin release, uncontrolled hepatic glucose output and/or reduced glucose uptake by skeletal muscle with reduced glycogen synthesis.[1] When the renal threshold for glucose reabsorption is exceeded, glucose spills into the urine and causes osmotic diuresis which results in dehydration and increased thirst.[1] Insulin deficiency causes protein wasting through increased breakdown and reduced protein synthesis. Diabetes may be caused by genetic defects of the beta cells, defects in insulin receptors, diseases of the pancreas, and excessive amounts of hormones that work against the actions of insulin.[1] Over the years, various complications arise as a consequence of diabetes. Hyperglycemia damages nerves and blood vessels, which can lead to complications such as

hypertension, heart disease, stroke, kidney disease, blindness, nerve problems, gum infections, and amputation.[3]

The two main types of diabetes are called type 1 and type 2. A third form of diabetes is called gestational diabetes. Type 1 diabetes, formerly called juvenile diabetes, is usually first diagnosed in children, teenagers, and young adults, but can appear at any age.[2] Type 1 diabetes is an autoimmune disease where the immune system attacks and destroys the insulin-producing beta cells in the pancreas. The pancreas then produces little or no insulin, and Type 1 diabetics must take insulin daily to live. At present, it is not certain what causes the body's immune system to attack the beta cells, but autoimmune, genetic, and environmental factors, possibly viruses, are involved.[4] Type 1 diabetes accounts for about 5 to 10 percent of diagnosed diabetes in the United States.[5] Symptoms develop over a short time period, although beta cell destruction may begin years earlier. Symptoms may include increased thirst and urination, constant hunger, weight loss, blurred vision, and extreme fatigue.[1] If not diagnosed and treated with insulin, type 1 diabetics can lapse into a life-threatening diabetic coma known as diabetic ketoacidosis.[1, 6]

Type 2 diabetes, formerly called adult-onset diabetes, is the most common form of diabetes. People can develop type 2 diabetes at any age. This form of diabetes usually begins with insulin resistance, a condition in which muscle, liver, and fat cells do not use insulin properly. The pancreas is usually producing enough insulin, but for unknown reasons the body cannot use the insulin effectively. As result, the body needs more insulin to help glucose enter cells to be used for energy. At first, the pancreas keeps up with the added demand by producing more insulin. In time, however, the pancreas loses its ability to secrete enough insulin in response to meals. The result is the same as for type 1 diabetes where glucose accumulates in the blood and the body cannot utilize glucose for energy.

About 90 to 95 percent of people with diabetes have type 2.[5] This form of diabetes is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity, and certain ethnicities. About 80 percent of people with type 2 diabetes are overweight.[5] Type 2 diabetes is increasingly being diagnosed in children and adolescents. The symptoms of type 2 diabetes develop gradually, and their onset is not as sudden as in type 1 diabetes. Symptoms may include those of type 1 and the slow healing of wounds or sores, but some people display no symptoms.[2]

Gestational diabetes may develop in women during the late stages of pregnancy. This is caused by pregnancy hormones or an insulin shortage.[2] Although this form of diabetes usually goes away after the baby is born, women who have had gestational diabetes have a 40 to 60 percent chance of developing type 2 diabetes within 5 to 10 years.[5]

Pancreas

The pancreas is an organ about 6 inches (15 cm) long that stretches across the back of the abdomen, behind the stomach.[7] The head of the pancreas is on the right side of the abdomen and is connected to the duodenum, the first section of the small intestine. The pancreas serves exocrine and endocrine functions.[8] The exocrine function of the pancreas involves the synthesis and secretion of pancreatic juices. The pancreatic juices are enzymes and bicarbonate ions that help digest food in the small intestine. As pancreatic juices are made, they flow into the main pancreatic duct.[7] This duct joins the common bile duct, which connects the pancreas to the liver and the gallbladder. The common bile duct, which carries bile (a fluid that aids in lipid digestion), connects to the small intestine near the stomach.[7]

The endocrine function of the pancreas resides in the islets of Langerhans embedded between the exocrine units of the pancreas. Approximately 1 million islets constitute the 1-2 percent of the total human pancreas.[9] The islets are composed of alpha, beta, delta, F, epsilon, and G cells.[8] Alpha cells of the islets secrete glucagon that counters the action of insulin. Beta cells of the islets secrete insulin, which helps control carbohydrate metabolism. They make up about three fourths of the cells of the islets.[9] Delta cells secrete somatostatin, which inhibits the release of glucagon and insulin. F cells secrete pancreatic polypeptides which regulate pancreas secretion activities. Epsilon cells produce ghrelin that stimulates hunger. G cells secrete gastrin that stimulates HCl production by the stomach.[10]

Allogeneic Islet Transplantation

Researchers are working on solutions for type 1 diabetics to live without daily insulin injections. In an experimental procedure called pancreatic islet transplantation, islets are taken from a cadaveric donor pancreas and transferred into a person with type 1 diabetes.[3] Once implanted, the beta cells in these islets begin to make and release insulin.

Although scientists have made many advances in islet transplantation in recent years, transplanted islets tend to lose function over time, and few transplant recipients are able to stop using insulin for very long.[3] However, partial islet function can help patients reduce their need for insulin, achieve better glucose stability, and reduce problems with hypoglycemia.[11] Also, islet transplantation appears to eliminate hypoglycemia unawareness.[11] Diabetics with hypoglycemia unawareness are vulnerable to dangerous episodes of severe hypoglycemia because they are not able to recognize that their blood glucose levels are too low.[3]

A pancreas is procured from a deceased organ donor. First, the pancreas is offered for whole-organ pancreas transplantation, and, if declined, it can be offered for islet isolation.[12] Also, pancreases from obese donors not used for pancreas transplantation are one source for islets. If the donor is older than 50 years or has a body mass index (BMI) of more than 30 $kg/m^2$, the pancreas can be offered for islet isolation directly.[13] Islet cell yield, size, and functionality vary among these pancreases. Procured pancreases are preserved using a two-layer method composed of an ET-Kyoto solution and oxygenated perfluorocarbon solution.[14]

Specialized enzymes, such as collengenase and liberase, digest the donor pancreatic tissue and separate the islets from the tissue.[13] Islets are purified by density gradient centrifugation. This method allows the separation of islets from exocrine tissue according to the differences of density because the islet tissue is lighter than the exocrine tissue. However, the density of the islet and exocrine tissue vary in each individual, and they must be measured to adjust the separation parameters.[12] Islets are assessed for quantity, quality, and sterility before transplantation. Since islets are fragile and susceptible to degradation, transplantation occurs soon after they are removed. Normally, a patient receives at least 10,000 islet "equivalents" per kilogram of body weight, which is extracted from two donor pancreases.[14] To achieve insulin independence, subjects often require two transplants at the same time. However, some transplants only require a single donated pancreas.

Transplants are often performed using x-ray and ultrasound to guide placement of a catheter through the upper abdomen and into the hepatic portal vein.[15] This is because the liver has good regenerative capacity, is one of the major sites of insulin action, and appears to confer some immunological privilege to the islets.[16] Other possible methods of islet cell transplantation used in clinical studies include transplantation under the kidney capsule and into the spleen,

pancreas, gastrointestinal mucosa, and immunologically privileged sites. However, due to inappropriate oxygen conditions, the high number of islet cells required to achieve insulin independence, and ongoing animal studies, these options are not the best sites for transplantation at this time.[16] The islets are then infused slowly through the catheter into the liver. This is usually performed as an outpatient procedure where the patient receives a local anesthetic and a sedative.[17] In some cases, a surgeon may perform the transplant through a small incision, using general anesthesia.[3] After transplantation, islets begin to release insulin immediately. However, full islet function and new blood vessel growth associated with the islets take time. The doctor will order many tests to check blood glucose levels after the transplant, and insulin is given until the islets are fully functional.[17]

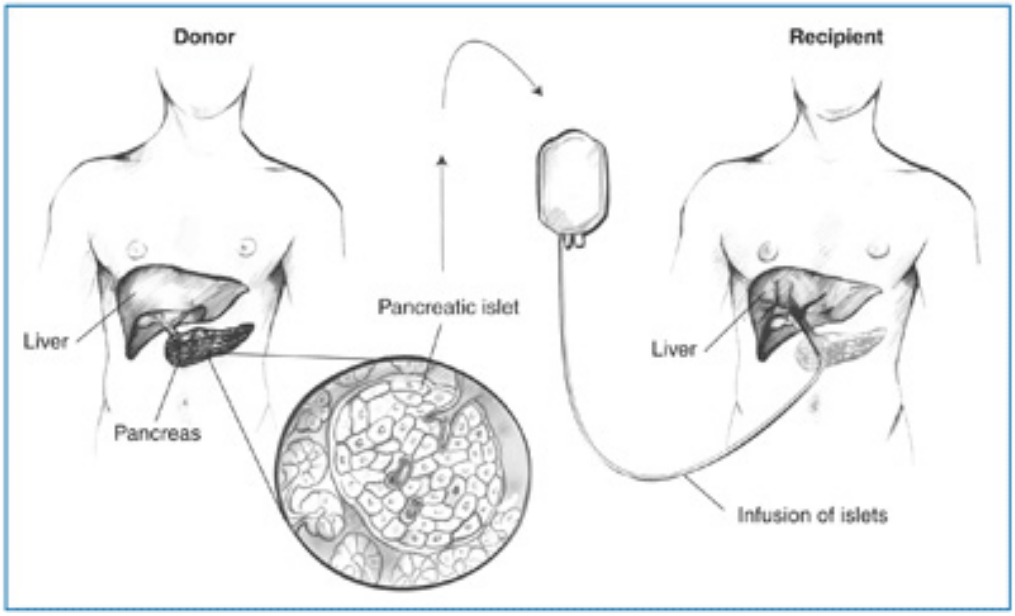


Figure 1-1: Islet Transplant Procedure Illustration: Islets extracted from a donor pancreas are infused into the liver. Once implanted, the beta cells in the islets begin to make and release insulin.[3]

Risks of islet transplantation include the risks associated with the transplant procedure, particularly bleeding and blood clots, and side effects from the immunosuppressive drugs that

recipients take to prevent rejection of the transplanted islets.[13] A major obstacle to widespread use of islet transplantation is the shortage of islets. Although organs from about 7,000 deceased donors become available each year in the United States, fewer than half of the donated pancreases are suitable for whole organ pancreas transplantation or for harvesting of islets.[18] However, researchers are exploring various approaches to solve this problem, such as transplanting islets from a single donated pancreas, from a portion of the pancreas of a living donor, or from pigs.[13, 17] Other alternative cells sources for insulin producing beta pancreatic cells include existing pancreatic cells (endocrine, acinar or ductal cells), regeneration from human embryonic stem cells, and cells from other tissues of endodermal origin by transdifferentiation.[19]

Rejection

The major challenge facing any transplant is rejection. The immune system destroys bacteria, viruses, and any tissue it recognizes as "foreign," including transplanted islets. In addition, the autoimmune response that destroyed transplant recipients' own islets in the first place may recur and attack the transplanted islet cells.

Islets will be lost immediately after transplantation if an instant blood-mediated inflammatory reaction (IBMIR) occurs.[20] IBMIR is responsible for the loss of the majority of islets through ABO-compatible blood interaction with islets causing the release of proinflammatory cytokines from islets, tissues, or cells in the blood. Platelets bind to islets while granulocytes and leukocytes infiltrate the islets. In this process, the liver's Kupffer cells, islets' macrophages, and blood neutrophils release inflammatory cytokines that injure transplanted

islets.[15] The cytokines responsible for islet damage include IL-1 (interleukin-1), TNF-α (tumor necrosis factor-alpha), and IFN-γ (interferon-gamma).[15]

IL-1 is an inflammatory cytokine that induces fever, controls lymphocyte migration to sites of infection, increases the number of bone marrow cell proliferation, and causes the degeneration of bone joints.[21, 22] It is produced by macrophages, monocytes, and dendritic cells in response to an infection.[22, 23]

TNF-α is a systemic inflammatory cytokine that stimulates the acute phase reaction.[24] It is produced by macrophages, lymphoid cells, mast cells, and monocytes.[24] TNF-α regulates immune cell activation and movement, induces apoptic cell death, causes inflammation, and inhibits tumorgenesis and viral replication.[9, 24] It works with IL-1 and IL-6 to accomplish these functions. Large amounts of TNF-α are released in response to IL-1, lipopolyssacharides and bacterial proteins.[21]

IFN-γ is an inflammatory cytokine that plays a role in intracellular viral and bacterial infections and tumorgenesis control.[24] Its plays a critical role in the innate and adaptive immune responses. IFN-γ is produced by natural killer cells, dendritic cells, and CD4 and CD8 T cells.[21]

Currently, islet transplantation does not require performing human leukocyte antigen (HLA) matching between the donors and recipient islets because human islets do not express HLA class II under normal conditions. However, inflammation leads to induced expression of HLA class II on transplanted islets.[20]

Immunosuppressant Drugs

To combat the problem of rejection, immunosuppressive drugs are administered to keep the transplanted islets functioning.[3] Immunosuppressant drugs that inhibit the body's immune response are given to prevent rejection of transplanted organs and are also used to treat autoimmune diseases such as lupus, rheumatoid arthritis, eczema and psoriasis. [26] Autoimmune diseases cause the immune system to attack healthy, normal tissue as if it were a foreign substance.

To prevent rejection after islet cell transplantation, islet cell patients use a combination of immunosuppressive drugs, also called anti-rejection drugs, including daclizumab (Zenapax), sirolimus (Rapamune), and tacrolimus (Prograf).[3] This drug regimen is referred to as the Edmonton protocol.[27] It is standard regimen across all islet cell transplant protocols at Baylor and at other institutions conducting islet cell transplant research. However, each institution, like BUMC, contains a longer, distinctive drug combination that is unique and confidential to their protocol. Daclizumab is given intravenously right after the transplantation and then discontinued. Sirolimus and tacrolimus, the two main drugs that prevent the immune system from destroying the transplanted islets, must be taken for life or for as long as the islets continue to function.

Daclizumab is a humanized IgG1 monoclonal antibody that binds specifically to IL-2 receptor on activated lymphocytes, thereby inhibiting IL-2-mediated activation of allograft rejection pathway.[22, 28] Sirolimus is an immunosuppressive lactone that blocks IL-2-dependent T lymphocyte proliferation and stimulation, possibly by blocking activation of a kinase referred to as mammalian target of rapamycin, or “mTOR,” a serine-threonine kinase that is important for

cell cycle progression.[23] Tacrolimus (Prograf or FK506) binds intracellular receptor, FKBP-12, preventing IL-2 transcription and inhibiting T-lymphocyte activation.[29]

These drugs have significant side effects and their long-term effects are not fully known. Immediate side effects of immunosuppressive drugs may include mouth sores and gastrointestinal problems.[1] Other side effects may include nephrotoxicity, neurotoxicity, and hyperglycemia.[1] Also, patients may have increased blood cholesterol levels, hypertension, anemia, fatigue, decreased white blood cell counts, decreased kidney function, and increased susceptibility to bacterial and viral infection.[3] Furthermore, taking immunosuppressive drugs increases the risk of tumors and cancer.[3]

Researchers continue to develop and monitor modifications to the Edmonton protocol drug regimen, including the use of new drugs and new combinations of drugs designed to help reduce destruction of transplanted islets and promote their successful implantation.[30] These therapies may help transplant recipients achieve better function and durability of transplanted islets with fewer side effects. The ultimate goal is to achieve immune tolerance of the transplanted islets, where the patient's immune system no longer recognizes the islets as foreign. If achieved, immune tolerance would allow patients to maintain transplanted islets without long-term immunosuppression. Currently under investigation are new approaches that will allow successful transplantation without the use of immunosuppressive drugs. For instance, one study is testing the transplantation of islets that are encapsulated with a special coating designed to prevent rejection.[3]

Informed Consent

The informed consent process recognizes that patients and "human subjects" share the need to understand and make autonomous decisions. It is the most important aspect of ethical conduct in research. The informed consent process is an ongoing exchange of information between the investigator and the subject.[31] Informed consent is a process that is designed to give the subject all information including risks and benefits, ensure the subject understands this information, discuss the individual's rights as a research subject, and give the subject an opportunity to agree or decline to participate in the trial.[32]

Informed consent must be obtained prior to the start of the study. The investigator must give subjects sufficient time and information to consider participation, respond to questions and be certain that the subject understands the risks and responsibilities, ensure that the subject is aware of alternative options, and obtain the subject's voluntary consent.[32]

The FDA's Code of Federal Regulations specifically addresses the content of the informed consent form in Title 21 Part 50.25 (21 CFR 50.25). This includes the eight required elements of 1) research, 2) foreseeable risks, 3) benefits, 4) alternative procedures, 5) confidentiality, 6) compensation, 7) contacts, and 8) voluntariness.[33] Also, it includes six additional elements of 1) unforeseeable risks, 2) termination circumstances, 3) additional costs, 4) withdrawal consequences and procedures, 5) new findings, and 6) number of subjects.[33] Additional elements are not optional but must be included when applicable. The form should define all medical/technical terminology; be of an appropriate reading level; avoid jargon, abbreviations and acronyms; and use graphics, simple sentences, short paragraphs, and subject headers.[33]

Moreover, the Department of Health and Human Services' Code of Federal Regulations details the required components of the informed consent form in Title 45 Part 46 Subpart A (45 CFR 46).[34] These include all the aforementioned components of 21 CFR 50.25 except purpose of the trial, subject responsibilities, trial procedures, contacts, and duration of subject participation.[34]

The IRB reviewing the study protocol may require additional guidelines such as the initialing of all pages of the consent document by the subject and the investigator, the investigator's signature and date on the consent form, or the addition of elements to the form.[32] There are several general guidelines that are part of the consent process.[33] The subject must sign and date the informed consent form and the HIPAA authorization form. Also, a signed copy of the consent must be given to subjects and the original signed consent must be maintained in Investigator files. A notation documenting the informed consent process must appear in the medical record to verify the subject consented prior to participation. The consent form must be amended to incorporate new information gained during the study. Moreover, participating subjects should be re-consented if new information could affect willingness to continue participation, but the IRB has final word on whether to re-consent.[33, 34]

Moreover, there are international guidelines which attempt to provide a consistent set of rules for clinical researchers. The International Conference on Harmonization Good Clinical Practices (ICH GCP) section 4.8.10 lists 22 items to inform subjects about in the informed consent process.[31, 35] These items include all the informed consent components of U.S. regulations 21 CFR 46 and 21 CFR 50, but makes additional demands of the process.[36] Also, in the 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects, which was published by CIOMS/WHO (Council for Investigational Organizations of Medical

Sciences/ World Health Organization), Guideline 5 lists information that should be contained in the informed consent process. Their requirements encompass all required and additional elements of aforementioned regulations and guidelines, but require additional informational components be included in the informed consent process.

Of all four sets of regulations only one defines informed consent. The Good Clinical Practice: Consolidated Guidance (E6) provides a definition of the "informed consent" in section 1.28[35]:

> "A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate."

# CHAPTER 2

# SPECIFIC AIMS AND SIGNIFICANCE

## Specific Aim 1

To analyze issues related to the pancreatic islet cell transplantation informed consent process and propose suggestions for improvement.

## Significance

In an experimental procedure such as allogeneic islet cell transplantation there are many complex issues to take into consideration. When a patient consents to this study they receive a large quantity of complicated material from research staff during the informed consent process that shapes their decision making. Many factors must be taken into consideration because this is a long-term study that may affect the subject for life.

## Specific Aim 2

To compare and contrast the informed consent process in this experimental study with other long-term and short-term experimental studies involving human subjects

## Significance

Comparing the informed consent process in pancreatic allogeneic islet cell transplantation to a variety of investigational studies will highlight common issues. One study may have found

a solution to a common protocol problem or a more efficient means of conducting business than another.

**Specific Aim 3**

To conduct interviews on attitudes about the informed consent process and research with allogeneic islet cell subjects, research nurses, coordinators, and IRB members.

**Significance**

An examination of the informed consent process and education process from patient and administration perspectives will supply information that may be useful for improving the current informed consent process. Also, it has the potential to improve the patient's quality of life through informational empowerment.

# CHAPTER 3

# METHODOLOGY

## Study Design

To compare the informed consent process of islet cell transplantation to that of others, this project examined the informed consent process from various perspectives including those of islet cell transplantation patients, Baylor All Saints Medical Center (BAS) and Baylor University Medical Center (BUMC) research nurses and coordinators, and Baylor Research Institute (BRI) Institutional Review Board (IRB) members. Patients were assessed through open-ended interviews about their informed consent process, their treatment experience, the issues they considered prior to consent and still consider, and changes they would like to see made to the process. Research nurses and coordinators were interviewed about issues that may arise during the informed consent process and the differences between long-term and short-term protocols and other transplant protocols. IRB members were interviewed about ethical and risk-benefit considerations concerning this type of study and other long-term studies.

The study intended to examine the perspectives of 3-5 islet cell transplant subjects, 5-10 research nurses or coordinators, and 3-5 IRB members across two different islet cell transplant protocols.

Data Collection

No identifiers were collected that link the collected data to the subject's identity. Subjects were contacted by phone or through e-mail about the interview or questionnaire by the islet cell research nurse or the corporate director of transplant. Those willing to participate sent an e-mail or phone response to the student researcher with the completed questionnaire or information regarding how they would like to be interviewed. For islet cell transplant subjects that came in for their regular monthly visit, their research nurse asked them if they would like to participate in an interview during the visit or if they would rather take the questionnaire via e-mail.

Those consenting to the study answered questions in an interview or through a questionnaire. Each interview was conducted using an IRB approved script of questions. The same questions comprised the questionnaire. Each interviewee had the option of choosing to not answer any question he or she felt uncomfortable answering. Islet cell transplant subjects answered questions in the presence of their coordinator who was a research nurse. Each interview took about 15-30 minutes. Interviews occurred in an enclosed office, in the clinic, over the phone, or by e-mail depending on the subjects' availability.

All the data collected from the questionnaires and interviews were separated based on subject subset (patient, research nurse/coordinator, or IRB member) and all identifiers removed. All identifiers were removed from e-mail questionnaires upon receipt. E-mail answers were transcribed onto another form and the original e-mail with a visible address was deleted.

Data Analysis

The questionnaires and interview notes were analyzed using sociological grounded theory analytic strategies designed to elicit topics for discussion from the data. Grounded theory is a systematic qualitative research method that produces theory from data in the process of conducting research.[37] In the social sciences, it is used to derive themes from interview data in a manner similar to a reverse engineered hypothesis. Grounded theory or the "constant comparisons" analytic method consists of 3 stages: open, axial, and selective coding.[38] Constantly comparing categories allow the investigator to understand the construction of their interrelationships.[38] During open coding, text segments that are related to a theme or idea are identified and given a conceptual label.[40] Open coding involves line by line analysis to determine codes or labels from the interview data.[39] These codes indicate similarities which are labeled as concepts. Concepts are then grouped into similar categories. During axial coding, related concepts among answers are grouped into conceptual categories.[40] This stage determines relationships between and within categories, and collapses them into larger categories. During selective coding, core categories emerge as central themes by grouping categories under a larger theme or a narrative spine.[39] As is customary in qualitative research, data analysis began after the first interview or questionnaire and continued after all the interviews and questionnaires were completed.[40]

Moreover, answers to questions regarding the informed consent process were compared to established Code of Federal Regulations, Baylor Research Institute's policies and procedures, and BRI allogeneic islet cell transplantation protocols. The interview and questionnaire questions can be found in Appendix B.

Study procedures were approved by the Baylor Institutional Review Board Dallas, TX and by the University of North Texas Health Science Center Institutional Review Board, Fort Worth, TX. The IRB protocol is found in Appendix C.

# CHAPTER 4

# RESULTS AND DISCUSSION

## Results

Of the intended populations, answers were collected from 3 IRB members, 9 research nurses or coordinators, and 5 islet cell subjects. All 3 IRB members were interviewed over the phone. Five research nurses and coordinators were interviewed in- person, while 5 were interviewed over the phone. Two islet cell subjects were interviewed in-person and 3 through e-mail questionnaires.

### IRB Member Interviews

It is not the policy of the IRB to release the individual identity of the IRB membership to the public. In compliance with 21 CFR 56 and 45 CFR 46, the BRI IRB publishes a list of IRB member credentials and affiliations. Of the listed 27 members, 3 members were identified and contacted by the corporate director to determine if they were interested in being interviewed. The 3 members came from varying backgrounds and areas of expertise.

IRB Concerns. Common IRB member concerns involved study adherence to Data Safety and Monitoring Board (DSMB) findings and guidelines and maintaining a record of severe adverse events. In general, the IRB is concerned that personnel may become complacent and neglect their responsibilities in long-term studies. IRB members fear that record keeping and

protocol adherence may fall by the way side. As a study progresses, the number of deviations increase and research staff must keep track of changes in personnel and subject drop out numbers. Moreover, in long-term studies it is important that subjects continue to understand that the informed consent process is ongoing. In such studies, subjects may forget that they are still part of an investigational study.

Site as Sponsor Issues. In the relatively few cases where Baylor serves as both site and the sponsor, as in the allogeneic islet cell transplant protocol, the IRB is concerned about budgetary services. These concerns involve whether or not the study has sufficient funding to conduct research for the projected amount of time detailed in the protocol and if they will be able to cover the costs of procedures, medical visits, and medications for each subject. Because those protocols tightly regulate their budgets it is difficult for IRB to get involved from a financial standpoint. These studies involve personnel that are well versed in research and run their studies very smoothly. Typically these studies do not involve investigational drug protocols. Moreover, these protocols involve an objective external monitor who is an expert in their area, but does not serve on site. Monitors provide additional safety monitoring and ensure that rules are followed and prevent data manipulation. Also, project integrity is preserved through follow-up reports which may be once a year or more frequently depending on the protocol under investigation. Furthermore, all forms, data analysis, and data collection should proceed as directed by the IRB and the DSMB.

Remedying Conflicts of Interest. There are potential sources for conflicts of interest in an investigator initiated studies like allogeneic islet cell transplantation. To prevent conflicts of

interest and undue influence, all conflicts of interest must be disclosed up front. There are a series of forms designed by BRI in accordance with FDA regulations to ensure accordance with the law. Individuals with financial relationships to the study may not be objective, so the IRB may have an individual step down as the PI on a protocol and ask a co-investigator or sub-investigator to assume the role of lead PI. Also, the IRB may tell an investigator not to refer or recruit patients.

Issues Associated with Transplant Protocols. Transplant protocols constitute a significant number of BRI's IRB approved studies. The most prevalent issues associated with transplant protocols involve logistics and readmission of transplant patients. In transplant protocols, things must be done quickly, so coordination and communication between research nurses or coordinators, physicians, and pharmacy staff is essential. In the readmission of transplant recipients, communication becomes very important between staff and the IRB to guarantee observance of the appropriate policies and procedures.

Another common concern of the IRB associated with transplant protocols is that the line between standard of care and investigation may be blurred. The same group of physicians and nurses treated the subject as a patient when the subject was off study. In many cases, the transplant physician and staff become the subject's primary healthcare provider because other physicians believe that the transplant physician is better informed about the patient's new condition. This may increase the chances for problems to arise in subject understanding of investigational aspects of a study and delineating between standard of care versus investigational care. However, transplant protocols and personnel employ strong parameters, delineate thoroughly roles and responsibilities, and work diligently on the informed consent process.

There are lots of potential for problems, but transplant protocols are usually very clear, and protocol personnel are thorough in their implementation of the protocol and all research guidelines.

Compliance with the Law. To ensure FDA and ICH compliance of all informed consent forms and the informed consent process a series of events occur. IRB members review all documents with FDA and ICH guidelines in mind. Moreover, all members have been educated on what should be included in submissions and the standards to which they are held. Furthermore, BRI provides required educational seminars to ensure that clinical research personnel know the rules, their roles and follow them. Upon receipt of a protocol, the IRB has a checklist where all conditions must be met. BRI has a series of templates with carefully chosen language that complies with FDA and ICH requirements. These templates contain very detailed instructions about what has to be done and the kind of language that should be used. Also, the IRB has the capacity to send an auditor in the rare event it suspects data manipulation and /or noncompliance.

IRB Perspectives on the Informed Consent Process. When asked to define the informed consent process, IRB members provided similar responses that underscore the importance of subject safety. To IRB members, the informed consent process is established to protect patients by examining safety measures in place and the risk to safety ratio. They emphasized that it as an ongoing discussion informing the subject of their voluntary choice to participate or continue to participate in a study. This process includes everything from recruitment advertisements to the signing of the actual informed consent document and continues through the course of the study.

Another issue highlighted by IRB members was the readability of the informed consent form. It should be understandable and written at an eighth grade reading level. The consent form should not be too long or unwieldy, otherwise no subject will go through every page and read it carefully. Also, careful attention must be paid to special risk groups such as the elderly and those who do not speak English. In such cases, the informed consent form should be written in a larger font and a translated version of the informed consent form should be readily available. Unlike other IRBs, the BRI IRB requires all protocols to include a translated version of the informed consent form in the event of the enrollment of a non-English speaking subject.

Research Nurse and Coordinator Interviews

Research nurses and coordinators from a variety of research fields were interviewed at BAS and BUMC. Some interview participants had research experience in multiple areas of research and with short-term and long-term studies. Other participants have spent the majority of their career in one discipline and had experience in either short-term or long-term studies depending on the discipline.

Oncology Protocols. In short-term oncology prevention studies, questionnaires are distributed to assess quality of life and are not related to investigational drugs. These questionnaires are similar in nature to quality of life questionnaires distributed to allogeneic islet cell subjects during follow-up visits. Long-term cancer prevention studies are related to investigational drugs and usually involve subjects with a genetic predisposition to a particular disease. In late stage oncology studies involving cancer patients with a bleak diagnosis, the nature of investigational treatment is an emotionally charged issue that influences the informed

consent process. Research personnel must work with the subject's family members to ensure subject understanding of the study, while addressing fears and concerns.

In neuro-oncology protocols, there are several quality of life issues associated with studies. Like other oncology studies, subjects are aware of their poor prognosis. One of their investigational drugs is administered intravenously 2-5 times a week each week until the tumor progresses and the subject no longer meets protocol inclusion criteria. Many of the side effects of chemotherapy such as hair loss and GI dysfunction may be embarrassing and uncomfortable for subjects. In another study, the subject's head is shaved for a procedure and they are the subject of unwanted attention when in public.

Bone Marrow Transplant Protocols. All bone marrow transplant studies are long-term studies, where the patients are followed for life. Subjects are patients who have received a life threatening prognosis like those in oncology trials. The entire situation is emotionally charged and shapes the informed consent process. Similar to islet cell transplantation, there are two varieties of the procedure: allogeneic and autogenic. Like allogeneic islet cell transplant protocols, the majority of investigational trials in this field are associated with experimental immunosuppressant drug regimen protocols. Subjects who agree to these studies are willing to undergo a very painful procedure and subject themselves to experimental drug regimens in an attempt to cure their condition. Bone marrow transplant has multiple long-term studies which follow subjects for life or until they switch to a new therapy due to increased metastasis, but the physician must determine whether or not it is safe to remove the subject from the study.

Women's Health Protocols. In a geographic region where a large portion of the subject population does not speak or understand English, the language barrier can prove to be an impediment to the informed consent process. However, through the use of a translator and the short-form consent form some of the challenges involved can be overcome. Subject retention is difficult because subjects do not see the need for extended information that is collected after the patient is discharged. Once they have obtained the procedure or treatment they no longer feel the need to continue returning to the clinic. Only in scenarios where there is a compensated healthcare component, such as extended visits and tests, do they see the need to continue returning to the study facility.

Solid Organ Transplant Protocols. In solid organ transplant protocols, most of the research studies revolve around the evaluation of various immunosuppressant regimens. Immunosuppressant medications may have side effects that affect a subject's quality of life in ways similar to islet cell transplant recipients. As in allogeneic islet cell transplantation, financial issues are also a cause for concern in solid organ transplant recipients. If insurance coverage is lost and Medicare ceases to cover anti-rejection medication after 36 months the solid organ transplant recipient could go into organ rejection without a means to pay for those medications.

Weight Loss Protocols. The attainment of enrollment goals is easier in weight loss studies than in others. Often, the consent form and protocol need to be revised to increase the allotted number of subjects enrolled in the study. In weight loss studies, subject retention is difficult since many of these patients seek a quick fix to their problem. When they do not obtain

instantaneous positive results, they tend to leave the study and not reconsent. Unfortunately, these subjects fail to understand how important it is for them to lose weight to prevent the onset of diabetes and complications which arise from that disease.

Diabetes Protocols. Like weight loss studies it is easier to reach enrollment goals in diabetes studies than in surgical studies. However, subject retention in diabetes studies is better than that of weight loss studies. Research nurses attribute this to two reasons. The first reason is that many subjects have managed their diabetes for most of their life and are vigilant about managing their diabetes. The second reason suggests that continual follow-ups with an endocrinologist reinforce commitment to the management of their diabetes and participation in their study.

Islet Cell Transplant Protocols. This investigational treatment aims to improve a patient's quality of life and decreases diabetic complications down the line. Also, it increases hypoglycemic awareness and C-peptide levels. For study participants long-term quality of life gains outweigh short-term quality of life discomforts. This may be seen as a preventative measure to avert diabetic complications late in life.

Investigator Initiated Studies versus Sponsor Initiated Studies. Investigator initiated studies are defined as studies developed and conducted by an investigator. Although an industry sponsor may provide drugs, devices, biologics, or funds, such a sponsor has no role in the conduct of the study.

In investigator initiated studies, like the allogeneic islet cell transplant, the entire study staff is more familiar with the protocol, the science supporting it, and all the details of the study. This may be attributed to resources about the study being more accessible to staff such as the research nurse or coordinator. These resources include the principal investigator of the project, the scientists responsible for laboratory manufacturing of the investigational treatment, published scientific articles, in-progress scientific articles, and a host of other sources. In the opinion of one research nurse, study personnel appear better educated on investigator initiated studies than in industry sponsored studies.

In sponsor-initiated research, staff needs to research the disease, treatment, drug, or device themselves. Personnel have no choice but to follow the protocol and the established system of reporting and recording data. In contrast, in PI initiated studies, elements of the protocol and forms can be revised as needed to meet standard of care or make a process more efficient. In investigator initiated research like allogeneic islet cell transplant, changes are made to the protocols and the informed consent form more often than industry sponsored studies because there is greater control by the research staff over the study. Revisions can be made quickly and efficiently to remedy any situation.

In investigator initiated studies, all processes are mandated by the protocol. The investigator and staff are responsible for designing case report forms, orders, subject binders and all other study related documents. However, sponsor driven protocols cover one aspect of a transplant such as a drug or a device, and in such studies personnel are afraid to deviate from the protocol.

In other transplant protocols such as liver, kidney, and pancreas, which are mostly sponsor initiated studies, subjects have difficulty discerning between standard of care and

investigational care, at times. Coordinators and research nurses must constantly remind subjects which aspects of care are experimental. Investigational features may range from a single device or drug to an entire procedure or drug regimen. In allogeneic islet cell transplantation, an investigator initiated study, subjects appear to correctly distinguish between standard of care and investigational aspects of their study. This may be due to the fact that the entire allogeneic islet cell transplantation study is experimental. Everything from the transplant procedure to immunosuppressant regimens to laboratory methods for islet procurement and preservation are under investigation. Moreover, many islet cell subjects continue to see other specialists such as endocrinologists and cardiologists, as part of their standard of care, during the course of their enrollment in the trial. Patient visits to physicians, other than the PI, may help islet cell subjects further differentiate between standard of care and investigational care.

Research Nurses/ Coordinators Perspectives on the Informed Consent Process. When defining the informed consent process words such as "understanding," "ongoing," and "conversation" were common to all responses. Topics common to all answers included managing risks and benefits, subject comprehension of the investigational clinical trial, educated decision making, and expectations of a trial. One research nurse claimed that, "the informed consent process is the most important part of a clinical trial and the most time consuming if done right." The more complex a process and emotionally charged a situation, such as those involving life threatening illness, the more vigilant the staff, subject, and the subject's family must be about the study.

All research nurses or coordinators designated their duties and responsibilities when defining the informed consent process. However, only two interview participants emphasized

that the PI is ultimately responsible for the informed consent process, but can delegate duties to the research nurse or coordinator. The lack of emphasis on the role of the PI may suggest that the research nurse or coordinator is responsible for many of the duties pertaining to the informed consent process. In long-term studies, especially in transplant and oncology protocols, research nurses and coordinators require the patient to bring a family member to their visits and patient orientations. The family member acts as a source of moral support, another set of eyes and ears, and someone to help the subject remember what is discussed during the visit.

Informed Consent in Short-Term and Long-Term Studies. Subjects in long-term studies must be very motivated to continue their commitment to the study. It is easier to recruit subjects for short-term studies because there is little or no commitment or follow-up.

In long-term studies, the consent form and the informed consent process is longer. There is an added emphasis on what happens at later visits and the need to update contact information often. Subjects tend to drop out because the coordinator cannot contact subjects anymore or because subjects refuse to participate in the study any longer.

In short-term studies, the informed consent forms are shorter than those in long-term studies. The informed consent form is at most 5 pages in length in these studies. Normally, reconsent does not occur in most short-term studies because the chance of new information presenting itself is not likely in the short time frame. In long-term studies, the informed consent forms are longer and vary from 5-20 pages in length. Of all informed consent forms used in islet cell transplantation protocols at Baylor, the longest one is 18 pages in length. In such cases, patient attention and comprehension wanes while reading the lengthy informed consent form. In situations like these, research nurses and coordinators encourage the subject to take home the

informed consent form and read through it carefully. Also, they encourage a family member or friend to review the form with them and make a list of questions, concerns and comments they need answered by the coordinator, research nurse, or PI.

Informed Consent in Pancreatic Islet Cell Transplantation. The informed consent form is typically changed every 4 months, but this depends on how often changes are made to the islet cell protocol. At the very least, changes are made to the protocol and informed consent form at least once a year. Normally, the subject does not ask why they have to sign the document again during a reconsent because they trust the research nurse. However, before the subject signs the informed consent form during a reconsent, the research nurse will go over the entire informed consent and place emphasis on what changes were made to the informed consent form and the protocol and how those changes may or may not affect the subject.

Informed Consent Commonalities. Across all protocols, changes are made to the informed consent form at least once a year as a result of the IRB continuing review. Changes are made to both the protocol and informed consent form with the discovery of new findings, changes in safety information, and when the sponsor requests it. Signing of the informed consent form can only occur in person, so the research nurse will reconsent the subject during clinic visits. If there is a more pressing need to reconsent the subject, the coordinator or research nurse will call the subject to come into the clinic or office to sign the consent form.

Patient Interviews

In a breakdown of all allogeneic islet cell transplant recipients currently monitored by the islet transplant program, 2 subjects are off study, 2 subjects are pending transplants, and 5 subjects are currently active. After the islet cell transplant, subjects were slowly weaned off insulin until the cells were able to function themselves. However, over the course of a few months islet cell function decreases and eventually ceases in some subjects. All subjects agreed that if given the chance to be transplanted again they would agree to the procedure. In fact, all are hoping to be transplanted a third time. The enthusiasm for this investigational transplant is largely due to positive gains in other areas related to their diabetes. Even after islet cell function decreased or ceased to function altogether, there was a dramatic decrease in the units of insulin consumed by subjects, a decrease in the number of hypoglycemic episodes, a redevelopment of the ability to detect hypoglycemic episodes, increased amounts of energy, a decrease in HbA1c values and an increase in C-peptide levels. [11,41]

Subject Initiated Education. Many of the islet cell transplant subjects are well versed on their disease condition, type I diabetes mellitus, because they have managed this disease for the majority of their lives. Thus, it comes as no surprise that the majority of islet cell transplant recipients conduct their own research on the investigational treatment before signing up for the study. This includes internet searches, speaking to transplant recipients, coordinators and PIs at other universities and hospitals conducting islet cell transplantation trials, and observing the laboratory manufacturing process. One subject commented that he "knew more about the islet cell transplant process than his diabetes" after performing an exhaustive background research on the topic. However, 2 subjects did not do any prior research because they wanted to go into the

process with an open mind, were suspicious of the internet, and did not want to over analyze the situation. However, after their initial meeting with the islet cell transplant research nurse and PI, they did their own research

Subject Concerns. Immunosuppressant medications were the most frequently mentioned cause of concern prior to providing consent for the islet cell transplantation. The dangers associated with hypoglycemic unawareness outweighed the risks associated with the side effects of the immunosuppressant medications. Prior to their transplant, many of these subjects were experiencing very low blood sugar levels, but were asymptomatic. The inability to discern hypoglycemic episodes resulted in feelings of irritability, unawareness of surroundings, and fainting or passing out in unlikely places. For one patient in particular, the incidence of cancer associated with the use of immunosuppressant medication was a cause of great concern early on in the informed consent process. However, he was reassured by the PI on the project that such incidences were very low.

Another issue to consider is the level of commitment this study requires on the subject's part. Subjects who lived farther away from the Dallas-Fort Worth area carefully scheduled visits ahead of time and made arrangements to stay with family in the area. Subjects who worked full-time jobs had to ensure that their employer would provide leave for the procedure, recuperation time, and time for follow-up visits and tests.

Other factors considered prior to consenting to the transplant study included how this study would affect their family. Family members that were skeptical about the transplant study were convinced by facts and studies provided by the PI and individual literature searches they had done on online.

Another concern exhibited by the subjects includes the ability to pay for medications and follow-up care when they are off study. Baylor Health Care System pays for medications and medical care associated with the islet cell transplantation study while the subject is active in the study for 2 years. Once the subject is off study, Baylor may continue to provide financial support for immunosuppressant mediations and follow-up medical care due to a sense of moral obligation. However, this is proving to be more of a financial strain than the islet cell program intended. At present, administration is formulating a subject transition plan to ensure that islet transplant subjects have the means to afford their medications once they are off study.

Suggestions for Improvement. Most islet cell transplant subjects were satisfied with the informed consent process and did not believe any changes needed to be made to the process. None of the subjects thought that a model of the procedure or a diagram of the process is necessary for the understanding of the procedure or clinical trial. They were very satisfied with the informed consent process and felt comfortable enough to call or e-mail the research nurse and PI with all their concerns and questions at any time. One subject did suggest that greater emphasis should be placed on what could go wrong and the side effects. However, this subject incurred the greatest number of severe adverse reactions and eventually developed antibodies against her transplant. Another subject felt that a chart detailing the schedule of assessments and procedures was confusing in the informed consent form.

## Discussion

Informed Consent Process

Even though U.S. regulations 45 CFR 46 and 21 CFR 50 do not provide a definition of the phrase “informed consent” or “informed consent process,” most research personnel have a basic understanding of its meaning. Although the two sets of U.S. regulations do not define “informed consent” they do contain specific lists of information elements required for the informed consent process to meet legal standards.

When asked to define the informed consent process, IRB members, research nurses and coordinators identified certain elements more often than others. Most answers identified the investigational nature of the study, the purpose of the study, foreseeable risks and benefits, and the voluntary nature of the study. Some answers included duration of participation, identifying which aspects of the study are experimental, trial procedures, subject responsibilities, the investigator’s decision to terminate subject participation, and consequences of the decision to withdraw.

These elements of the informed consent process appear to be more important to the process than others. The elements identified most often by research nurses and IRB members appear to be directly relevant to protecting the subject’s wellbeing and immediate needs. Interview answers indicate the importance of subject safety and subject comprehension of the fundamentals of an investigational study.

The 45 CFR 46 elements of the informed consent process that were not included in subject answers were alternative courses of treatment, record confidentiality, and compensation in case of injury. Twenty-one CFR 50 elements of informed consent, which were not mentioned in interview answers, consist of the aforementioned excluded 45 CFR 46 elements, contact

person in case of injury, and approximate number of patients. Excluded answers indicate that the study particulars that do not directly affect the wellbeing of the subject and contingency measures are of lesser importance.

The informed consent process is especially important in transplant protocols like pancreatic allogeneic islet cell transplantation where it becomes difficult for a patient to delineate between standard of care and investigational therapeutics. The islet cell transplant recipients interviewed in this study all appear to understand the experimental nature of this study. They understand the difference between the care received at a follow-up visit to the transplant clinic with the PI and research nurse versus a visit to their personal physician, endocrinologist, or cardiologist. Also, islet transplant subjects understand that the informed consent process is an ongoing process between them, the research nurse and the PI.

The subject's relationship with the coordinator or research nurse is key in any kind of experimental study. Since the PI delegates the majority of his or her informed consent process responsibilities to the research nurse or coordinator, it is important that the subject feels comfortable enough to share all pertinent information with the nurse and inquire about everything study related.

Allayed Concerns

Since the transplanted islet cells will die without immunosuppressant medications, one may ask if it is ever really safe for a subject to leave the study. One patient said that if she had a bad reaction to the medications or if her transplanted islet cells were rejected by her body or ceased to function, she always felt as if she could leave the study without any consequences. The patient can always return to exogenous insulin administration and careful glucose

monitoring of hypoglycemic episodes. In the event that a patient chose to leave the study while his or her cells were functioning, the subject would have to undergo rejection reeducation to detail what can go wrong and what steps he or she should take to correct the situation.

Financial Complications Resolved

In an investigator initiated study, like allogeneic islet cell transplantation, a number of funding issues arise. Providing coverage for all clinical visits, visits to specialists, and name brand immunosuppressant medications is costly. Without adequate planning, funds for continued research and medications may run out. As a result, a variety of strategies are employed to replenish funds. To increase awareness of the study and the type of investigational research being conducted by Baylor Health Care System, investigators on the islet cell project publish multiple scientific articles and posters on their work. Also, they attend scientific conferences and fundraising events and make educational presentations to attract new investors and investigational partners. To retain investors and attract new investors to the project, updates and newsletters are sent to current and potential financiers. Investigators and fellows on the project apply for multiple private and government agency grants to ease the financial burden of the work.

Presently, off study subjects receive immunosuppressant medications if their transplanted islet cells continue to function. Even though such a decision may not make financial sense, Baylor believes that this is the most responsible and humane course of action. Currently, plans are being developed to ensure that the subject has the financial means to afford immunosuppressant medications and follow-up care.

These plans integrate many of the financial strategies already in place for solid organ transplant studies. They inform the patient of the costs associated with their transplant, follow-up visits, and anti-rejection medications prior to transplant. Then, financial coordinators make certain that transplant recipients have a form of medical coverage in place prior to and after being transplanted. A financial clearance process occurs prior to enrolling in the study, so subjects have coverage for other types of medical expenses not related to the study. Also, financial coordinators develop plans for individual transplant recipients to help alleviate financial burdens in special need situations.

For allogeneic islet cell transplant subjects this includes working with pharmaceutical companies with prescription assistance programs and ensuring that the subject has an adequate form of healthcare insurance prior to leaving the study.

Limitations

Over the phone interviews and in-person interviews yielded more information than e-mail questionnaires. E-mail questionnaire answers were short, simple, and to the point. However, in-person and phone interview subjects tended to elaborate on answers with examples and personal anecdotes. In-person interviews yielded the greatest amount of information about the informed consent process and the islet cell transplantation process.

Like all qualitative research, the results are specific to the subjects who were interviewed. They are not generalizable to all subjects or all protocols utilizing the informed consent process. The elements of informed consent noted by the interview or questionnaire participant were shaped by their individual experience and areas of expertise. Nevertheless, they provide insight into the subject's experience and viewpoint, and they enrich the understanding of the informed consent process.

With responses from more than half of the entire pancreatic allogeneic islet cell transplant subject population monitored by the allogeneic islet cell program , this study suggests that islet cell transplant recipients  are satisfied with their current informed consent process. Much of this is due to subject education either on his or her own or through the informed consent process and the research nurse.

## Conclusion

Diabetes was the seventh leading cause of death listed on U.S. death certificates in 2006.[5] In adults, type 1 diabetes accounts for 5 to 10 percent of all diagnosed cases of diabetes.[5] The investigational study of pancreatic allogeneic islet cell transplantation attempts to improve a subject's quality of life and decrease diabetic complications that arise late in life. Also, it increases hypoglycemic awareness and decreases the need for large amounts of exogenous insulin. In spite of its benefits, this investigational study involves complex and confusing issues which may cause potential subjects to turn away from the study. However, through a well developed informed consent process that educates the subject on all aspects of the trial that are relevant to the subject's decision, complexity and confusion can be overcome.

# APPENDIX A

# INTERNSHIP LOG

# INTERNSHIP DAILY ACTIVITY JOURNAL

Internship Start Date: June 1, 2009

Internship End Date: November 18, 2009

June 1

- Reviewed employee orientation manual
- Set up a Baylor University Medical Center e-mail account
- Met staff in Transplant Administration and BRI
- Read protocols 008-095 and 008-189

June 2

- Completed BLN lessons
- Toured All Saints facility with Emelia Bittenbinder
- Started researching for background section for Proposal

June 3

- Received ID badge and parking permit
- Attended Transplant Administration staff meeting on media relations and progress management
- Continued research for Proposal

June 4

- Started background section for Proposal
- Study Manager training

June 5

- Established a RefWorks account and continued work on background section

- Reviewed available Internship Practicum reports on file

June 8

- Continued work on background section for Proposal

June 9

- Filled out IRB forms 7 and 14 for access to protocols
- Meeting with Kerri Purcell, RN and research nurse
- Attended video-conference with the entire islet transplant team
- Read protocol 006-069

June 10

- Continued work on background and references
- Attended Dr. Yasunami video-conference on Islet Graft Rejection

June 11

- Meeting with Betsy regarding possible thesis topics
- Outlined possible thesis topics
- Attended islet transplant meeting with PI, RN, director, and operations manager regarding funding issues

June 12

- Outlined possible thesis topics
- Meeting with Dr. Matsumoto and members of his team
- Shadowed Kerri on patient visit

June 15

- Shadowed Kerri on patient visit
- Completed draft #1 of the thesis proposal

June 16

- Submitted thesis proposal to committee members
- Reviewed BRI  informed consent guidelines and IRB guidelines
- Reviewed BRI  templates for informed consent

June 17

- Reviewed human subjects protection material in the Baylor Research Institute

June 18

- Read protocol 005-029

June 19

- Obtained short term protocols from the BRI
- Filled out IRB form 7 on all transplant protocols

June 22

- Meeting with Betsy
- Filled out patient CRFs

June 23

- Attended IRB Coordinator Training hosted by the director of BRI's Office of Research Subject Protection
- Filled out patient CRFs

June 24

- Worked on proposal corrections
- Filled out patient CRFs

June 25

- Attended NIH Grant Seminar

- Filled out patient CRFs

June 26

- Filled out patient CRFs
- Worked on proposal corrections

June 29

- Attended Transplant Education Meeting #1 for newly transplanted patients
- Worked on proposal corrections

June 30

- Worked on proposal corrections
- Reviewed material on human subject protection

July 1

- Worked on proposal corrections

July 2

- Worked on proposal corrections
- Oversaw lab equipment moved into Islet team's UNTHSC lab

July 6

- Worked on proposal corrections

July 7

- Attended weekly Islet Transplant Meeting
- Completed CRFs

July 8

- Watched Kerri consent a patient
- Formulated questions for subject, research nurse, and IRB member scripts

July 9

- Completed proposal
- Obtained all signatures for proposal paperwork

July 10

- Filed completed proposal in the Graduate School

July 13

- Attended Transplant Education Meeting #2: Learning to Love the Lean Life for newly transplanted patients

July 14

- Attended weekly Islet Transplant Meeting

July 15

- Obtained and reviewed patient education material on liver and kidney transplants

July 16

- Meeting with Betsy

July 17

- Researched informed consent process for thesis

July 20

- Attended Transplant Education Meeting #3: Food Safety for newly transplanted patients
- Attended Liver Pre-Transplant Orientation

July 21

- Filled out 6 months of CRFs

July 22

- Organized chart for a newly transplanted patient

- Attended Staff Meeting

July 23

- Organized charts for a newly transplanted patient

July 24

- Organized charts for a newly transplanted patient
- Filled out 6 months of CRFs on a new transplant patient

July 27

- Attended Transplant Education Meeting #4: Diabetes and Your Transplant for newly transplanted patients
- Attended Manager Retreat Meeting
- Attended Allo Islet Financial Issues Meeting

July 28

- Looked for medications and prescriptions in old patient charts
- Created a list of prescription medications for each islet cell transplant protocol

July 29

- Filled out patient CRFs

July 3

- Attended Transplant Administration staff meeting
- Compared and contrasted informed consent forms for all islet cell transplant protocols

July 31

- Filled out patient CRFs
- Started on IRB submission for patient interviews

August 3

- Filled out patient CRFs
- Worked on IRB submission for patient interviews

August 4

- Filled out patient CRFs

August 5

- Filled out patient CRFs on a re-transplanted subject

August 6

- Filled out CRFs and organized patient charts on a new transplant candidate

August 7

- Shadowed Kerri on a patient visit and physician consult
- Filled out patient CRFs

August 10

- Shadowed Kerri and Erin on a patient visit and physician consult
- Worked on patient interview research protocol for IRB submission

August 11

- Attended Islet Cell Transplant meeting
- Worked on patient interview research protocol for IRB submission

August 12

- Worked on patient interview informed consent form for IRB submission

August 13

- Meeting with Betsy regarding IRB submission
- Made Betsy's suggested revisions for the IRB submission

August 14

- Made Betsy's suggested revisions for the IRB submission

August 17

- Asked Kerri for a list of possible subjects and research nurses for thesis project and brainstormed alternative means of conducting the interviews
- Made new revisions to IRB submission

August 18

- Attended a Kidney orientation for pre-transplant patients

August 19

- Conference call with Betsy regarding new changes to the IRB submission

August 20

- Attended meeting between Transplant managers
- Attended meeting between Transplant and Health Texas managers
- Meeting with Betsy regarding possible subjects for the thesis project and other opportunities in transplant

August 21

- Revised IRB submission for thesis
- Set a date and time to watch an islet cell isolation and kidney transplant

August 24

- Attended meeting for Transplant Finance Review for Fiscal Year 2009
- Meeting with Betsy regarding transplant financial terms
- Received a sample marketing plan and clinical research handout about islet cell

August 25

- Revised IRB submission for thesis and submitted it to Betsy for proofreading

- Finished patient CRFs on a patient that is no longer in the islet cell study
- Attended Islet Cell Transplant meeting

August 26

- Attended Liver Selection Committee
- Reviewed sample marketing plan

August 27

- Revised IRB submission and obtained signatures

August 28

- Reviewed sample marketing plan
- Attended Kidney Selection Committee

August 31

- Reviewed sample marketing plan and brainstormed islet cell marketing ideas

September 1

- Brainstormed islet cell marketing ideas using the Inventor's Commercialization Toolkit
- Attended Islet Cell Transplant meeting

September 2

- Attended Billing Compliance Meeting
- Attended Staff meeting for Transplant Administration staff meeting

September 3

- Attended meeting between Transplant and Health Texas managers
- Met with Betsy about IRB submission

September 8

- Attended Islet Cell Transplant Meeting

September 9

- Attended Islet Cell Financial Meeting

September 10

- Attended Allo Islet Meeting

September 11

- Outlined thesis sections

September 14

- Reviewed recently published articles related to islet transplant
- Attended a pharmaceutical presentation

September 15

- Reviewed the Informed Consent process for thesis
- Attended a pharmaceutical presentation

September 16

- Attended Baylor Research Institute's Investigator Breakfast
- Attended Islet Cell Marketing Meeting
- Attended Financial Meeting with All Saints Health Foundation

September 17

- Attended Investigator Breakfast
- Completed additional documents requested by IRB for submission

September 18

- Filled out patient CRFs
- Compiled additional research and information on the informed consent process in transplant patients

September 21

- Baylor IRB submission was sent to IRB in Dallas
- Filled out patient CRFs

September 22

- Baylor IRB coordinator requested additional documents for submission
- Prepared additional IRB documents and obtained additional signatures

September 23

- Baylor IRB coordinator determined additional documents are not necessary and original submission was complete
- Filled out patient CRFs

September 24

- Filled out patient CRFs
- Compiled additional research and information on the informed consent process from surgeon, coordinator, and nurse perspectives

September 25

- Selected a thesis presentation date, time, and room
- Arranged an end of block appointment with major professor

September 28

- Started working on UNTHSC IRB submission

September 29

- Shadowed Kerri on a possible islet subject evaluation and physician consultation
- Received Baylor IRB approval letters

- Betsy arranged a side project with Dr. Murray who requires assistance in writing a NIH submission

September 30

- Met with UNTHSC IRB coordinator to determine what paperwork is needed for research submission
- Met with Dr. Murray to discuss drafting of a NIH submission
- Continued work on UNTHSC IRB submission
- Filled out patient CRFs

October 1

- Continued work on UNTHSC IRB submission
- Started compiling information on NIH submission for acute liver failure program
- Completed CITI training

October 2

- Continued work on UNTHSC IRB submission
- Compiled all information on NIH submission for acute liver failure program

October 5

- Continued work on UNTHSC IRB submission
- Read new FDA guidance practices for Allogenic Islet Cell Transplantation

October 6

- Attended Islet Cell meeting
- Continued work on UNTHSC IRB submission

October 7

- Submitted study submission to UNTHSC IRB

October 8

- Toured UNTHSC laboratory with All Saints Foundation
- Observed rat pancreas dissolution and rat pancreas islet isolation
- Met with Betsy about thesis and viewing a human auto isolation
- Obtained signatures on defense paperwork

October 9

- Outlined thesis topics
- Created copies of questionnaires and cover letters

October 12

- Attended Breast Cancer Lecture
- Met with Dr. Murray regarding the UTSW-ALFSG NIH proposal draft
- Met with Kerri on how to approach islet patients for study

October 13

- Sent additional documents to UNTHSC IRB
- Received UNTHSC IRB approval

October 14

- Attended Baylor Research Transplant Institute's Town Hall meeting
- Set up interview times and dates with BAS coordinators and RNs

October 15

- Met with Dr. Murray regarding the NIH letter drafting
- Set up interview times and dates with BAS coordinators and RNs
- Worked on draft of ALFSG NIH letter

October 16

- Shadowed Kerri on patient visit
- Interviewed a patient and 3 RNs/coordinators for thesis study
- Worked on draft of ALFSG NIH letter

October 19

- Met with Dr. Murray regarding the ALFSG NIH proposal draft
- Worked on ALFSG NIH letter draft

October 20

- Set up remainder of interviews with BAS nurses and coordinators
- Completed draft of ALFSG NIH letter

October 21

- Met with Dr. Murray regarding the NIH letter
- Interviewed 2 research nurses

October 22

- Met with Betsy about thesis
- Observed auto islet cell processing procedure at islet lab in Dallas

October 23

- Outlined elements of my thesis
- Met with Betsy about thesis
- Started work on background section of the thesis
- Complete NIH letter for submission to UTSW-ALFSG

October 26

- Interviewed 5 coordinators on different research fields
- Interviewed an IRB member and a patient

- Completed background section of the thesis

October 27

- Interviewed 2 patients
- Interviewed 2 IRB members
- Continued working on thesis

October 28

- Met with Betsy about thesis and data collection for interviews
- Continued working on thesis

October 29

- Continued working on thesis

October 30

- Continued working on thesis
- Attended a Town Hall meeting for all Baylor Staff
- Interviewed 2 patients

November 2

- Continued working on thesis

November 3

- Continued working on thesis
- Attended Islet Cell meeting

November 4

- Continued working on thesis
- Attended Transplant Staff meeting

November 5

- Attended Nurses' Journal Club Luncheon
- Started preparing oral presentation for the defense
- Obtained PowerPoint slides from Dr. Matsomoto

November 6

- Shadowed Kerri on patient visit
- Shadowed Kerri on follow-up for newly transplanted patient
- Conducted 2 in-person patient interviews
- Spoke with Betsy about the organization of Transplant Administration
- Continued preparing oral presentation and thesis

November 9

- Observed a thesis presentation
- Shadowed Kerri on a patient visit
- Discussed thesis revisions with Betsy
- Continued working on oral presentation
- Attended pharmaceutical luncheon

November 10

- Continued working on oral presentation
- Made arrangements to observe a meeting of the BRI IRB on 11/19/09

November 11

- Continued working on oral presentation
- Observed monitor and Kerri review all study related documents

November 12

- Continued working on oral presentation

- Observed monitor and Kerri review all study related documents
- Observed Dr. Levy perform a kidney transplant

November 13

- Met with Dr. Oglesby to practice presentation and review thesis revisions
- Continued working on oral presentation and thesis

November 16

- Continued working on oral presentation and thesis

November 17

- Continued working on oral presentation

November 18

- Defended thesis to committee members and members of the public

# APPENDIX B

# QUESTIONNAIRES

IRB Protocol Number: 008-095/006-069
Date: Version # 1
Time: Revised: August 26, 2009

Script for Research Nurses and Coordinators

1. How often do you update the informed consent form and why or under what circumstances do you need to update it?

2. How often do you reconsent?

3. Does the patient ask why they are being reconsented?

4. Does the reconsent occur during a normal patient visit?

5. Has a patient ever refused to reconsent? What happens then?

6. When you reconsent, is it similar to the initial consent or is it an abbreviated version of the initial consent where emphasis is placed on what has been changed in the protocol and consent?

7. What are the similarities and differences between consenting patients in islet cell transplants vs. other kinds of transplants? Are there more drugs, models, longer post-monitor window? (for research nurses and coordinators in transplant)

8. What are the similarities and differences between consenting patients in long-term studies (like islet cell transplants) vs. short-term studies?

9. Currently, there is no standard definition for the "informed consent process," but a series of federal regulations outline the idea. How would you define the "informed consent process"?

Script for Patients

1. How long ago did you have your islet cell transplant?

2. What do you remember about your informed consent process?

3. Who did you identify as being part of your informed consent process?

4. Do you have any ideas how to change the informed consent process?

5. Can you think of anything we can do better in reference to the informed consent process?

6. Did you feel as if the informed consent process was truly an ongoing process? Were all your concerns and questions addressed?

7. The consent form reflects that this is a special circumstance where Baylor is the site and sponsor. Did you have any specific questions about that in the informed consent process?

8. What things did you consider prior to consenting to your islet cell transplant?

9. What if any independent research about islet cell transplant did you do prior to enrollment?

10. Show an informed consent form from their protocol and ask if there is anything that was unclear in form or what questions they had prior to consent.

Script for IRB Members

1. What are common concerns you have for long-term studies vs. short-term studies?

2. What issues arise in protocols where Baylor is both the sponsor and the site?

3. What safeguards do you put in place to prevent conflicts of interest or undo influence of subjects?

4. What are the issues associated with transplant protocols?

5. How do you ensure FDA and ICH compliance with all informed consent forms and the informed consent process?

6. In the cases where Baylor serves as both the site and the sponsor, how do ensure project integrity?

7. Currently, there is no standard definition for the informed consent process, but a series of federal regulations outline the idea. How would you define the informed consent process?

# APPENDIX C

# IRB DOCUMENTS

*iversity of North Texas Health Science Center*

**fice for the Protection of Human Subjects (OPHS) / Institutional Review Board (IRB)**

**quest for Review of Expedited Category Research Project**

IRB # _____
**(Staff Use Only)**

search activities that (1) present **no more than minimal risk** to human subjects and (2) involve **only** procedures listed in one or more of the egories below in Section One may be reviewed by the IRB through the expedited review procedure. *Minimal risk means that the risks of harm icipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or ing the performance of routine physical or psychological examinations or tests.*

ou believe that your research falls into one of the following categories, please indicate which category or categories you believe is or are propriate. The IRB Chairperson (or designee) will review your research to determine if expedited review is warranted and if approval can be nted. If you have any questions, you may contact the OPHS Office at 817-735-0409.

*le of Research Activity:* Analysis of the Informed Consent Process in Parcratic Islet Cell Transplantation

*me of Principal Investigator (Faculty Member):* Dr. Patricia Gwirtz, Ph.D.

*partment/Program:* Integrative Physiology

**tegories Eligible for Expedited Review: (You can check more than one category, as needed.)**

| *Category 1:* | **Check if applicable:** | **Check if applicable:** | **Note:** Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is **NOT** eligible for expedited review. |
|---|---|---|---|
| ☐ **Clinical studies of drugs and medical devices ONLY when condition (a) or (b) is met:** → | ☐ (a) Research on drugs for which an investigational new drug application is not required. | ☐ (b) Research on medical devices for which:<br>(i) an investigational device exemption application is NOT required **OR**<br>(ii) medical device is **cleared/ approved** for marketing and it is being used in accordance with its cleared/approved labeling. | |
| *Category 2:* | **Check applicable box:** | ☐ (b) Other adults and children*, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. | **Indicate volumes and frequency of blood draws.** |
| ☐ **Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture from:** → | ☐ (a) Healthy, non-pregnant adults who weigh at least 110 pounds.<br>**Contact OPHS Staff for criteria** | **Contact OPHS Staff for criteria** | |
| *Category 3:* | **Check all that apply:** | ☐ Amniotic fluid obtained at the time of membrane rupture prior to or during labor | ☐ Hair and nail clippings in a non-disfiguring manner |
| ☐ **Prospective collection of biological specimens for research purposes by noninvasive means.** → | ☐ Placenta removed at delivery<br>☐ Deciduous teeth taken during exfoliation or routine patient care<br>☐ Permanent teeth if routine patient care indicates a need for extraction<br>☐ Excreta and external secretions (including sweat)<br>☐ Uncannulated saliva | ☐ Supra- and subgingival dental plaque and calculus. [Collection is not more invasive than routine prophylactic teeth scaling and it is done according to accepted techniques]<br>☐ Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings | ☐ Sputum collected after saline mist nebulization<br>**If research does not include any of the given specimen collections, give a brief description:** |
| *Category 4:* | **Check all that apply:** | ☐ Magnetic resonance imaging (MRI) | **NOTE** *Studies intended to evaluate the safety and effectiveness of a medical device are NOT eligible for expedited review, including studies of cleared medical devices for new indications.* |
| ☐ **Collection of data through noninvasive procedures routinely done in clinical practice. Where medical devices are employed, they must be cleared/approved for marketing.** → | ☐ Physical sensors applied to the body surface or at a distance AND do not involve input of significant amounts of energy into the subject or an invasion of subject's privacy<br>☐ Weighing or testing sensory acuity<br>☐ Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography | ☐ Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing (appropriate to age, weight, and health of the individual)<br>**If research procedures do not include any of the given procedures, please enclose a brief description:** | *To qualify for this subcategory, the study **CANNOT** involve general anesthesia, sedation or procedures with X-rays or microwaves (such as CT/CAT Scan, etc).* |

| | | | |
|---|---|---|---|
| *ategory 5:*<br>Research involving materials (data, documents, records, or specimens) that: | **Check if applicable:**<br>☐ (a) Have already been collected for some other purpose, | **Check if applicable:**<br>☐ (b) Will be collected for non-research purposes (such as medical treatment or diagnosis) | **Does the research protocol fit under this category and is condition (a) or (b) met?**<br>☐ Yes ☐ No |
| *ategory 6:*<br>Collection of data from voice, video, digital, or image recordings made for research purposes | **Check all those applied for research study:**<br>☐ Voice ☐ Video<br>☐ Digital ☐ Image | **Will subjects be informed about the recordings?**<br>☐ Yes ☐ No | **Include in the protocol a detailed description of how, when and what extent subjects will be recorded. In addition, describe data storage and confidentiality of the recorded data.** |
| *ategory 7:*<br>Research where condition (a) or (b) is applicable: | **Check if applicable:**<br>☐ (a) Individual or group characteristics or behavior (research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) | **Check if applicable:**<br>☒ (b) Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. | **Does the research protocol fit under this category?**<br>☒ Yes ☐ No |

*ecall: 'Children' in (b) above is defined in the HHS regulations as "persons who have not attained the legal age for consent r treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will e conducted" [45 CFR 46.402(a)]. In Texas, this is typically under 18 years old.*

oes the study nvolve storage or banking of human specimens or identifiable private information for use in future studies?

'es ☐ No ☒

oes the study involve genetic testing or DNA/RNA extraction? Yes ☐ No ☒

**any of the answers to the above questions are yes, please ensure that this information is discussed in the informed onsent form (if applicable).**

laximum number of subjects recruited for participation: 40 Age range of the subjects recruited: 30-80

Will this study include any of the following subject pools?

☐ Pregnant Women ☐ Cognitively Impaired ☐ Prisoners ☐ Genetics ☐ Military Personnel

☐ Minors (<18) ☐ UNTHSC employees ☐ Fetuses ☐ UNTHSC students ☒ Patients

☐ Economically Disadvantaged (homeless, evacuees)

low will you recruit and correspond with subjects for this study?

☒ Telephone (please submit telephone script with your submission) ☐ Referrals

☒ Advertising (newspaper, email, Daily News, website, brochure, radio, etc.) ☐ Other

Will subjects be compensated for their participation? Yes ☐ No ☒

**Document payment schedule in the protocol synopsis, and if applicable, the informed consent.**

Will any of the following instruments or methods be used? ***Check all that apply. Include copies of these materials with your submission:***

☒ Interview (attach script/guide) ☒ Surveys/Questionnaires

☐ Standardized (published) tests or assessments ☐ Focus Group (attach guide)

Does the study involve (**check all that apply**):

☐ Painful or aversive stimuli ☐ False Feedback ☐ Emotional Stress

☐ Withholding of critical information ☐ Deception ☐ False Information

**st all OTHER KEY PERSONNEL associated with this project (co-investigators, study coordinator, study physician, etc.)**

there a **STUDENT INVESTIGATOR** associated with this project? ☒ Yes ☐ No

ame of student investigator: Sonia Kakade

nal address of student investigator: skakade@live.unthsc.edu Contact number of student investigator: 332-289-6686

ole/ Responsibilities: interview subjects, distribute the e-mail questionnaire, collect and de-identify the data, and analyze the data

**O-INVESTIGATOR:**

ame & Degree: Betsy Stein, CCRC Department: Transplant

ole/ Responsibilities: contacts coordinators, research nurses, and IRB members to arrange interview times and questionnaire

dministration method

**O-INVESTIGATOR:**

ame & Degree: _____ Department: _____

ole/ Responsibilities: _____

**TUDY COORDINATOR:**

ame & Degree: Kerr Purcell, RN Department: Transplant Research

ole/ Responsibilities: witnesses patient interviews and contacts patients to arrange interview times and questionnaire

dministration method

***When submitting your Expedited research to the OPHS Office, please submit 2 complete packets with the following information contained within EACH packet.***

***f the IRB materials you submit fail to capture the most necessary information for a complete/thorough review, or if the application packet is incomplete, your IRB materials will be sent immediately back to you. Please ensure that the ollowing information is submitted in each packet for a more streamlined "speedy" review of your research project. In ddition, please keep in mind that the review process takes time, and research may not be initiated until the application as been approved.***

1) IRB Application Form (with original PI signature on one copy)
2) Protocol Synopsis
3) Informed Consent Form (if applicable)
4) Conflict of Interest Form
5) CITI Training Certificates

*If applicable:*

(6) Grant Application
(7) Recruitment Materials (flyers, emails, advertisements, etc.)
(8) Surveys/Questionnaires
(9) Telephone scripts/oral scripts
(10) Assent Forms/Parental Permission Forms
(11) Research Agreements
(12) Letters of permission/cooperation, and/or approvals from oth IRBs

Patricia A Gaunty
**Principal Investigator Signature**

10/5/09
**Date**

DATE: 13 October 2009

TO: Patricia Gwirtz, PhD
Sonia Kakade (student)
CRM (Clinical Research Management) Program

PROTOCOL: # 2009-109

**Analysis of the Informed Consent Process in Pancreatic Islet Cell Transplantation**

**IRB BOARD ACTION AND NOTICE OF APPROVAL**

The Institutional Review Board (IRB) of the University of North Texas Health Science Center (UNTHSC) has reviewed your protocol and has granted approval.

**Approval is effective October 13, 2009 through October 13, 2010**

You are responsible for complying with all UNTHSC IRB and OPHS policies, decisions, conditions and requirements. You are responsible for insuring that the research is implemented as specified in the approved protocol. Unless otherwise authorized by the UNTHSC-IRB, you are responsible for obtaining and documenting informed consents in accordance with applicable Federal Regulations (45 CFR 46 and 21 CFR 50) using ONLY the IRB approved consent forms designated for this protocol.

You must report to the Chair of the IRB any changes affecting the protocol upon which this certification is based. **No changes may be made without prior approval by the IRB** except those necessary to eliminate immediate hazards.

Should your project period extend beyond this expiration date, you must submit a Progress Report for Continuing Review to the IRB. You must allow sufficient time for the request for renewal to be reviewed and approved **before expiration of the current approval.** Be sure to *prepare for a renewal 2 months prior to the protocol expiration date.* If the project is finished before the approval expiration date, you must submit a final Progress Report (Continuing Review) either at the time the project is completed or before the expiration.

The Office for the Protection of Human Subjects (OPHS) will send out a reminder notice for your Progress Report (Continuing Review), however it is the responsibility of the Principal Investigator to prepare such a report in order for continuing review to occur BEFORE the expiration date.

Sincerely,

Brian Gladue, PhD
Chair, UNTHSC Institutional Review Board

**IRB Board Action**

2009-109 Patricia Gwirtz, PhD CRM Program
(with Sonia Kakade, CRM Student)
Analysis of the Informed Consent Process in Pancreatic Islet Cell Transplantation

Brief 2-page survey research instrument to be completed by patients who have undergone a research project involving pancreatic islet cell transplantations, as well as ancillary personnel involved with that project (research coordinators and nurses associated with the consenting process, IRB members who conducted the protocol review). Survey to be completed at clinic visits (in-person interviews with patients/subjects), and via e-mail and/or telephone. Research to be conducted at Baylor All Saints in Fort Worth and was approved by Baylor Research Institute (BRI) IRB, September 17, 2009. Given that the study will be conducted only at Baylor facilities as described in the protocol submitted, protocol synopsis and survey instruments approved by BRI-IRB accepted as submitted for use. NO UNTHSC IRB-Approved stamp is required or provided. It is also noted that only data collected after the protocol was approved by UNTHSC-IRB can be used for this UNTHSC graduate student project. Thus, only those data collected on or after October 13, 2009 may be used in any research report, presentation, thesis, dissertation or publication by any UNTHSC faculty, staff, or student.

As reviewed by UNTHSC IRB Chair, and in concurrence with the findings of BRI-IRB, this study meets the criteria for Expedited Review, under the provisions of 45 CFR 46.110 (b) (1) category # 7, research employing survey, interview methodologies. In addition, a request for waiver of documentation of informed consent was submitted and approved under the provisions of 45 CFR 46.117(c)(2) research presents no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context (emails, phone interviews). Request approved in accordance with Expedited review by Dr. Gladue, as IRB Chair, on October 13, 2009.

UNIVERSITY of NORTH TEXAS HEALTH SCIENCE CENTER at Fort Worth
TEXAS COLLEGE OF OSTEOPATHIC MEDICINE
INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS

# BOARD ACTION

IRB PROJECT #: 2009-109 DATE SUBMITTED: October 7, 2009

PRINCIPAL INVESTIGATOR: Patricia Gwirtz, PhD (with Sonia Kakade, CRM Student)

PROJECT TITLE: Analysis of the Informed Consent Process in Pancreatic Islet Cell Transplantation

PROTOCOL #: n/a

DEPARTMENT: Clinical Research Management (CRM) TELEPHONE EXTENSION: x 2079

In accordance with UNT Health Science Center policy on the protection of human subjects, the following action has been taken on the above referenced project:

---

Approval, when given, is **only** for the project as submitted. **No changes** may be implemented without first receiving IRB review and approval.

✓ Project has received approval through October 13, 2010.

____ Informed Consent approved as submitted on _____.
You **MUST** use this version (attached) rather than previously approved versions. In addition, only consent documents which bear the official UNTHSC IRB approval stamp can be used with subjects.

✓ Study Protocol dated October 8, 2009 approved as submitted.

____ Protocol Synopsis approved as submitted on _____.

____ Amendment _____ to the protocol approved as submitted.

____ Based upon the recently completed Continuing Review (IRB Form 4), project has received continued approval through _____.

____ Project has been reviewed. In order to receive approval, you must incorporate the attached modifications. You must submit one "highlighted" copy and one "clean" copy of the revised protocol synopsis, informed consent and advertisements to the IRB for review. YOU MAY NOT BEGIN YOUR PROJECT UNTIL NOTIFIED BY THE IRB.

____ Consideration of the project has been tabled pending resolution of the issue(s) outlined below.

____ Project is disapproved for the reason(s) outlined below.

____ Completion of project is acknowledged and all required paperwork has been received.

✓ Special Findings:

See attached page for findings related to protocol approval

_____ October 13, 2009
Chairman, Institutional Review Board Date

IRB Form 2 revised 12-03 MA 04-1487

BAYLOR
Research Institute
Affiliated with Baylor Health Care System

3310 Live Oak
Suite 501
Dallas, Texas 75204
(214) 820-2687
(214) 820-4952 Fax
BaylorHealth.com

## IRB APPROVAL - Revisions to Previously Approved Projects

September 17, 2009

Marlon F. Levy, MD
Transplant Svc-Surgical Director, Transplantation
Baylor All Saints Hospital
1400 Eighth Avenue
Fort Worth, TX 76104

Re: Pancreatic Islet Transplantation - A Novel Approach to Improve Islet Quality and Engraftment
Project#: 008-095 Protocol#: N/A Protocol Dt: 08/27/2009

The following items received expedited review:

- Request for Revisions - IRB007 (07/27/2009)
- Questionnaire / Survey (08/26/2009; 1)
- Proposed Revisions Summary
- Survey Cover Letter
- Correspondence from PI to IRB - From Research Staff

On behalf of the Institutional Review Board, I have reviewed the above referenced research project in accordance with 45 CFR 46 & 164 and 21 CFR 50 & 56. This review was conducted in accordance with the expedited review process as outlined in 45 CFR 46.110(b). Based on the information presented, I have determined that the study meets the criteria specified below.

45 CFR 46.110(b)(2):
(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized

Based on this review, the above referenced items are approved for implementation.

The Board reminds you that Baylor Policy requires that that unless waived, fully documented informed consent must be obtained in accordance with 45 CFR 46.116 and 21 CFR50.20 from all human subjects involved in this research study. Informed consent must be obtained by the principal investigator or other key personnel as listed in this submission. Documentation of informed consent must be kept on file for a period of three years past completion or discontinuation of the study and will no doubt be subject to inspection in the

In addition, 45 CFR 164 requires that, unless waived by the IRB, authorization must be obtained for use and disclosure of Protected Health Information. If this project is currently open to new enrollment, the approved version of the consent form(s) is listed above. The document(s) reviewed in this submission has been determined to satisfy the requirements as outlined in 45 CFR 164.508.

DHHS and FDA regulations require you to submit periodic and terminal progress reports to Baylor's Institutional Review Board and to receive at least annual approval of your activity from this Committee.

You are also required to report to this Committee immediately any death, unanticipated problems invoving risks to subjects or others, or serious adverse incidents resulting from your study. These events must be reported in accordance with current BRI Policies 830 and 838.

Federal regulations and institutional policies require that the IRB review any and all changes in your research activity. This includes amendments, revisions, administrative changes, advertisements, or ANY other change in the information as presented at initial review. In other words, should your project change, another review by the Board is required. Failure to comply with any of the above requirements, federal regulations, or institutional policy may result in severe sanctions being placed on the Medical Center and on you as the Principal Investigator. These sanctions could result in your research being permanently terminated for non-compliance.

Receipt of approval does not convey institutional authority to gain additional patient information. It is your responsibility as Principal Investigator to abide by institutional and/or departmental policies regarding confidentiality, access, and release of patient data.

Please be advised: there may be additional administrative requirements from Baylor Research Institute that must be met before the study may begin enrolling subjects.

Sincerely,

Lawrence R. Schiller, MD, Chair
Institutional Review Board – Blue

RECEIVED
SEP 16 2009

**BAYLOR RESEARCH INSTITUTE**
***INSTITUTIONAL REVIEW BOARD***
**Application for Revision to IRB Approved Study– IRB Form 7**
**This form must by TYPED – Handwritten copies not accepted**

**Revisions to research projects may not be instituted until written approval from the IRB has been given.**

IRB Project # 008-095 Date Submitted: 07/27/09

Project Title: Pancreatic Islet Cell Transplantation- A Novel Approach to Improve Islet Cell Quality and Engraftment

Principal Investigator: Dr. Marlon Levy, MD Department: Transplant Research

Telephone Extension: 4649 FAX: 817-922-4655

Mailing Address: 1400 Eighth Ave. Fort Worth, TX 76104 E-Mail Address: MarlonL@baylorhealth.edu

Contact Person (if different from PI): Kerri Purcell, RN Department: Transplant Research

Telephone Extension: 4640 E-Mail Address: KerriP@BaylorHealth.edu

---

***Materials Revised in this submission:***

a. ☐ **Protocol**
If checked, list below the date, version, and title of the modification (i.e. Amendment, Revision, Administration Change).

b. ☐ **Consent Form**
If checked, attach a copy of the revised Consent Form with changes highlighted. In addition, list the version date of the attached document **and** outline the plan to provide this new information to subjects who are currently participating, but who have already given informed consent.

c. ☒ **Questionnaire/Survey** ***
If checked, attach a copy with changes highlighted and provide the version date of the new document.
See attached patient, research nurse/coordinator, and IRB member scripts all of which are dated August 26, 2009, Version 1.

d. ☐ **Advertisement**
If checked, attach materials and specify where, when and how advertisement is going to be used. These should include a version date on all materials. The IRB can review a draft advertisement, but approval of a draft does not constitute final approval to use the advertisement. The IRB must also review the final layout for newspaper or tape (audio/video) for radio or television.

e. ☐ **Change in PI or addition/removal of other study staff**

f. ☐ **Other Change (list specifics below)**

**BAYLOR RESEARCH INSTITUTE**
***INSTITUTIONAL REVIEW BOARD***
**Application for Revision to IRB Approved Study- IRB Form 7**

Describe the proposed revision(s). Attach any documentation associated with this revision. If this revision is a protocol amendment or consent form revision with extensive changes, please **summarize** below, be specific but brief ***(do not just state "See Attached").*** If this project is sponsored by an outside agency, we require that you also provide us with a copy of the cover letter or other supporting documentation from the sponsor regarding this revision. This allows us to confirm that this change is indeed supported by the sponsor.

A sub-study will investigate the pancreatic islet cell transplantation informed consent process. Data will be collected through interviews with patients, research nurses, coordinators, and IRB members. Interviews will be conducted in person, by phone, or by e-mail. Each interview use a script of questions.

3. Provide the rationale for the proposed revision. Be brief but specific *(i.e. protocol and consent revised due to DSMB identification of new risks, protocol revised due to administrative changes at company, etc., change in study staff or addition of investigator).*

In accordance with UNTHSC graduate school requirements, the student researcher will conduct a sub-study to collect data for her thesis.

4. This revision includes the following:

a. ☐ Significant change in the scope or research objectives of the project.
b. ☐ Change in the overall risk/benefit ratio.
c. ☐ Increase in dosage of investigational drug (larger dose or longer treatment period)
d. ☐ Newly identified risk or an increase in the occurrence of risk since last approval.
e. ☐ Addition of vulnerable population to study
f. ☐ Addition of study procedures which involve greater than minimal risk
g. ☐ Reopening the study to enrollment (study was closed to enrollment prior to this amendment)
h. ☐ Some increases in number of subjects being enrolled (some increases - contact IRB office for determination)
i. ☒ None of the above

**If this study was originally reviewed by the Full IRB and A, B, C, D, E, F or G is checked, this revision must be reviewed by the Full IRB. If H is checked, contact the IRB office to determine if Full Board review is required. If Full Board review is required, submit original and three copies, at least three working days prior to the packet deadline for the IRB that manages this project. Other changes could also require review by the Full IRB, if in the opinion of the IRB Chair/Vice Chair they are considered more than minor or constitute greater than minimal risk. If this is the case, you will be contacted.**

**CERTIFICATION OF PRINCIPAL INVESTIGATOR:**

I certify that the information in this application is complete and correct.

I understand that as Principal Investigator, I have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the IRB.

The requested changes will not be implemented until approval has been received and I have received confirmation of such in writing from the IRB.

PI Signature _____ Date 10 SEP 08 1530

**BAYLOR RESEARCH INSTITUTE**
***INSTITUTIONAL REVIEW BOARD***
**Application for Revision to IRB Approved Study– IRB Form 7**

**DO NOT WRITE BELOW THIS LINE – FOR IRB USE ONLY**

This submission has received administrative review:

Elizabeth Cothran, M.S., CIP, Director ORSP (or designee) — Date: 9/17/09

This submission has been reviewed by the IRB:

- ☐ The Revision to IRB approved study has been reviewed and approved by the fully convened IRB.
- ☑ This Revision was determined to meet the criteria for Expedited Review.
  - ☐ A minor change to a previously approved project, which does not adversely change the risks to the subjects enrolled.
  - ☐ Initial Review of this project was conducted under the Expedited Review process.
- ☐ This Revision was reviewed to assess if the information changed would impact the subjects' willingness to continue participating in the research study.
  - ☑ The information changed would not impact the subject's willingness to continue participation, or
  - ☐ The information changed would impact the subject's willingness to continue participation and an appropriate mechanism is in place to provide information to the research subject.
- ☐ The revised Consent Form has been reviewed and approved by the IRB.
- ☐ Subjects currently enrolled in study must sign the new consent.
- ☐ Approval of this amendment does not alter the expiration date of the protocol.
- ☐ This study continues to meet the regulatory criteria as outlined in 45CFR46.111.

Lawrence R. Schiller, MD, IRB Chair (or designee) — Date: 9/22/09

**IF FULL BOARD REVIEW IS REQUIRED:**

| **Date Received:** | **IRB Meeting Assignment:** |
|---|---|
| **Primary Reviewer #1:** | **Primary Reviewer #2:** |

Proposed Revisions:

# Sub-study for 008-095: Pancreatic Cell Isle: Transplantation- A Novel Approach to Improve Islet Quality and Engraftment

In an experimental treatment like allogenic pancreatic islet cell transplantation, there are many complex issues to take into consideration. When a patient consents to this treatment he/she receives a large quantity of complicated material prior to and during the informed consent process that shapes their decision making process. Many factors must be taken into consideration because this is a long-term study that may affect the subject for the rest of his/her life. Possible issues under consideration include immunosuppressant medications, regularity of clinic visits and lab tests, the likelihood of transplant rejection or inefficiency, the possibility of re-transplantation multiple times, and the side affects of immunosuppressants.

The proposed sub-study aims to analyze issues related to the pancreatic islet cells transplantation informed consent process; to compare and contrast the informed consent process in the pancreatic islet cell study to other transplant studies and long-term and short-term experimental studies; to propose suggestions for improvement to the informed consent process with respect to the islet cell transplant protocol and other study protocols.

To compare islet cell transplantation's informed consent process to that of others, the project will examine the informed consent process from various perspectives including those of islet cell transplantation patients, BAS and BUMC research nurses and coordinators, and BRI IRB members. Patients will be assessed through an interview about their consenting process, their treatment experience, the issues they considered prior to consent and still consider, and changes they would like to see made to the process. Research nurses and coordinators will be interviewed about issues that may arise during the informed consent process and the differences between long-term and short-term protocols and other transplant protocols. IRB members will be interviewed about ethical and risk-benefit considerations concerning this type of study and other long-term studies.

The sub-study will examine the perspectives of 3-5 islet cell transplant subjects, 5-10 research nurses or coordinators, and 3-5 IRB members. No identifiers will be collected that link the collected data to the subject's identity. Those consenting to the sub-study will answer questions in an interview. Each interview will be conducted using a script of questions. Each interviewee will have the option of not choosing to answer any question they feel uncomfortable answering. Transplant patient subjects will answer the student researcher's questions in the presence of a research nurse. The interview should take about 15-30 minutes. This is a project being done by a student researcher. The interview will occur in an enclosed office, in the clinic, over the phone, or by e-mail depending on the subjects' availability. The student researcher will use the results of this project to write a research paper in fulfillment of the student's graduate thesis requirements.

IRB Project Number: 008-095

# Transplant Research

## Baylor All Saints Medical Center at Fort Worth

I am a student researcher in Transplant Research and I am conducting a research sub-study related to Pancreatic Islet Cell Transplantation- A Novel Approach to Improve Islet Quality and Engraftment. This research project is intended to gather information on the informed consent process from various perspectives. You have been selected to be in this study because you are an islet cell transplant patient, a research nurse, a coordinator, or an IRB member.

To take part in this study, you will need to answer some questions as part of an interview regarding the informed consent process. The questions will vary depending on your role in the islet cell transplantation process. Examples of these questions include:

1. Who talked you through the informed consent process? (patients)
2. Did you feel overwhelmed by the material you were given about this study or the procedure? (patients)
3. What things did you consider prior to consenting to this process? (patients)
4. What are the similarities and differences between consenting patients in long-term studies vs. short-term studies? (research nurses and coordinators)
5. What are the similarities and differences between consenting patients in long-term studies like islet cell transplants vs. short-term studies? (IRB members)

This interview should take about 15 -30 minutes. This is a project being done by a student researcher. The interview will occur in an enclosed office, in the clinic, by phone, or by e-mail. The student researcher will use the results of this project to write a research paper. If you are a patient or employee of the Baylor University Health Care System your participation (or non-participation) will in no way affect your medical treatment or employment status. By agreeing to answer these interview questions, you are saying that you are willing to take part in this sub-study.

There are no risks or benefits to you for being in this study. You have the option to not participate in the interview and therefore not be in the study. By participating in this study, you are saying that you are willing to take part in this study. Your participation will in no way affect your treatment or employment status.

If you have any questions about this project, please contact Sonia Kakade at 817-922-7689. If you have any questions about your rights as a research subject, please contact Lawrence Schiller, MD at 214-820-2687.

Thank you for your interest in this project. I hope you will take a few minutes to participate in the survey. Without the help of people like your important research would not be conducted.

BAYLOR
Research Institute
Affiliated with Baylor Health Care System

3310 Live Oak
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Dallas, Texas 75204
(214) 820-2687
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## IRB APPROVAL - Revisions to Previously Approved Projects

September 17, 2009

Marlon F. Levy, MD
Transplant Svc-Surgical Director, Transplantation
Baylor All Saints Hospital
1400 Eighth Avenue
Fort Worth, TX 76104

Re: Pancreatic Islet Cell Transplantation - A Novel Approach to Immunosuppression
Project#: 006-069 Protocol#: N/A Protocol Dt: 01/12/2009

The following items received expedited review:

- Request for Revisions - IRB007 (07/27/2009)
- Questionnaire / Survey (08/26/2009; 1)
- Proposed Revision Summary
- Survey Cover Letter

On behalf of the Institutional Review Board, I have reviewed the above referenced research project in accordance with 45 CFR 46 & 164 and 21 CFR 50 & 56. This review was conducted in accordance with the expedited review process as outlined in 45 CFR 46.110(b). Based on the information presented, I have determined that the study meets the criteria specified below.

45 CFR 46.110(b)(2):
(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized

Based on this review, the above referenced items are approved for implementation.

The Board reminds you that Baylor Policy requires that that unless waived, fully documented informed consent must be obtained in accordance with 45 CFR 46.116 and 21 CFR50.20 from all human subjects involved in this research study. Informed consent must be obtained by the principal investigator or other key personnel as listed in this submission. Documentation of informed consent must be kept on file for a period of three years past completion or discontinuation of the study and will no doubt be subject to inspection in the future.

In addition, 45 CFR 164 requires that, unless waived by the IRB, authorization must be obtained for use and disclosure of Protected Health Information. If this project is currently open to new enrollment, the approved version of the consent form(s) is listed above. The document(s) reviewed in this submission has been determined to satisfy the requirements as outlined in 45 CFR 164.508.

DHHS and FDA regulations require you to submit periodic and terminal progress reports to Baylor's Institutional Review Board and to receive at least annual approval of your activity from this Committee.

You are also required to report to this Committee immediately any death, unanticipated problems invoving risks to subjects or others, or serious adverse incidents resulting from your study. These events must be reported in accordance with current BRI Policies 830 and 838.

Federal regulations and institutional policies require that the IRB review any and all changes in your research activity. This includes amendments, revisions, administrative changes, advertisements, or ANY other change in the information as presented at initial review. In other words, should your project change, another review by the Board is required. Failure to comply with any of the above requirements, federal regulations, or institutional policy may result in severe sanctions being placed on the Medical Center and on you as the Principal Investigator. These sanctions could result in your research being permanently terminated for non-compliance.

Receipt of approval does not convey institutional authority to gain additional patient information. It is your responsibility as Principal Investigator to abide by institutional and/or departmental policies regarding confidentiality, access, and release of patient data.

Please be advised: there may be additional administrative requirements from Baylor Research Institute that must be met before the study may begin enrolling subjects.

Sincerely,

Lawrence R. Schiller, MD, Chair
Institutional Review Board – Blue

**BAYLOR RESEARCH INSTITUTE**
***INSTITUTIONAL REVIEW BOARD***
**Application for Revision to IRB Approved Study– IRB Form 7**
**This form must by TYPED – Handwritten copies not accepted**

RECEIVED
SEP 16 2009

**Revisions to research projects may not be instituted until written approval from the IRB has been given.**

IRB Project # 006-069 Date Submitted: 07/27/09

Project Title: Pancreatic Islet Cell Transplantation- A Novel Approach to Immunosuppresion

Principal Investigator: Dr. Marlon Levy, MD Department: Transplant Research

Telephone Extension: 4649 FAX: 817-922-4655

Mailing Address: 1400 Eighth Ave., Fort Worth, TX 76104 E-Mail Address: MarlonL@baylorhealth.edu

Contact Person (if different from PI): Kerri Purcell, RN Department: Transplant Research

Telephone Extension: 4640 E-Mail Address: KerriP@BaylorHealth.edu

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***Materials Revised in this submission:***

a. ☐ **Protocol**
If checked, list below the date, version, and title of the modification (i.e. Amendment, Revision, Administration Change).

b. ☐ **Consent Form**
If checked, attach a copy of the revised Consent Form with changes highlighted. In addition, list the version date of the attached document **and** outline the plan to provide this new information to subjects who are currently participating, but who have already given informed consent.

c. ☒ **Questionnaire/Survey *****
If checked, attach a copy with changes highlighted and provide the version date of the new document.
See attached patient, research nurse/coordinator, and IRB member scripts all of which are dated August 26, 2009, Version 1.

d. ☐ **Advertisement**
If checked, attach materials and specify where, when and how advertisement is going to be used. These should include a version date on all materials. The IRB can review a draft advertisement, but approval of a draft does not constitute final approval to use the advertisement. The IRB must also review the final layout for newspaper or tape (audio/video) for radio or television.

e. ☐ **Change in PI or addition/removal of other study staff**

f. ☐ **Other Change (list specifics below)**

**BAYLOR RESEARCH INSTITUTE**
***INSTITUTIONAL REVIEW BOARD***
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Describe the proposed revision(s). Attach any documentation associated with this revision. If this revision is a protocol amendment or consent form revision with extensive changes, please **summarize** below, be specific but brief ***(do not just state "See Attached").*** If this project is sponsored by an outside agency, we require that you also provide us with a copy of the cover letter or other supporting documentation from the sponsor regarding this revision. This allows us to confirm that this change is indeed supported by the sponsor.

A sub-study will investigate the pancreatic islet cell transplantation informed consent process. Data will be collected through interviews with patients, research nurses, coordinators, and IRB members. Interviews will be conducted in person, by phone, or by e-mail.

3. Provide the rationale for the proposed revision. Be brief but specific *(i.e. protocol and consent revised due to DSMB identification of new risks, protocol revised due to administrative changes at company, etc., change in study staff or addition of investigator).*

In accordance with UNTHSC graduate school requirements, the student researcher will conduct a sub-study to collect data for her thesis.

4. This revision includes the following:

a. ☐ Significant change in the scope or research objectives of the project.
b. ☐ Change in the overall risk/benefit ratio.
c. ☐ Increase in dosage of investigational drug (larger dose or longer treatment period)
d. ☐ Newly identified risk or an increase in the occurrence of risk since last approval.
e. ☐ Addition of vulnerable population to study
f. ☐ Addition of study procedures which involve greater than minimal risk
g. ☐ Reopening the study to enrollment (study was closed to enrollment prior to this amendment)
h. ☐ Some increases in number of subjects being enrolled (some increases - contact IRB office for determination)
i. ☒ None of the above

**If this study was originally reviewed by the Full IRB and A,B,C,D,E,F or G is checked, this revision must be reviewed by the Full IRB. If H is checked, contact the IRB office to determine if Full Board review is required. If Full Board review is required, submit original and three copies, at least three working days prior to the packet deadline for the IRB that manages this project. Other changes could also require review by the Full IRB, if in the opinion of the IRB Chair/Vice Chair they are considered more than minor or constitute greater than minimal risk. If this is the case, you will be contacted.**

**CERTIFICATION OF PRINCIPAL INVESTIGATOR:**

I certify that the information in this application is complete and correct.

I understand that as Principal Investigator, I have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the IRB.

The requested changes will not be implemented until approval has been received and I have received confirmation of such in writing from the IRB.

PI Signature

10 OCT 09 1533
Date

**BAYLOR RESEARCH INSTITUTE**
***INSTITUTIONAL REVIEW BOARD***
**Application for Revision to IRB Approved Study– IRB Form 7**

| **DO NOT WRITE BELOW THIS LINE – FOR IRB USE ONLY** | |
|---|---|
| This submission has received administrative review: | |
| Elizabeth Cothran, M.S., CIP, Director ORSP (or designee) | Date: 9/21/09 |
| This submission has been reviewed by the IRB: | |
| ☐ The Revision to IRB approved study has been reviewed and approved by the fully convened IRB. | |
| ☑ This Revision was determined to meet the criteria for Expedited Review. | |
| ☑ A minor change to a previously approved project, which does not adversely change the risks to the subjects enrolled. | |
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| ☐ The revised Consent Form has been reviewed and approved by the IRB. | |
| ☐ Subjects currently enrolled in study must sign the new consent. | |
| ☑ Approval of this amendment does not alter the expiration date of the protocol. | |
| ☑ This study continues to meet the regulatory criteria as outlined in 45CFR46.111. | |
| Lawrence R. Schiller, MD, IRB Chair (or designee) | Date 9/22/09 |
| **IF FULL BOARD REVIEW IS REQUIRED:** | |
| **Date Received:** | **IRB Meeting Assignment:** |
| **Primary Reviewer #1:** | **Primary Reviewer #2:** |

# Proposed Revisions:
# Sub-study for 006-069: Pancreatic Cell Islet Transplantation- A Novel Approach to Immunosuppression

In an experimental treatment like allogeneic pancreatic islet cell transplantation, there are many complex issues to take into consideration. When a patient consents to this treatment he/she receives a large quantity of complicated material prior to and during the informed consent process that shapes their decision making process. Many factors must be taken into consideration because this is a long-term study that may affect the subject for the rest of his/her life. Possible issues under consideration include immunosuppressant medications, regularity of clinic visits and lab tests, the likelihood of transplant rejection or inefficiency, the possibility of re-transplantation multiple times, and the side effects of immunosuppressants.

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IRB Project Number: 006-069

# Transplant Research

## Baylor All Saints Medical Center at Fort Worth

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There are no risks or benefits to you for being in this study. You have the option to not participate in the interview and therefore not be in the study. By participating in this study, you are saying that you are willing to take part in this study. Your participation will in no way affect your treatment or employment status.

If you have any questions about this project, please contact Sonia Kakade at 817-922-7689. If you have any questions about your rights as a research subject, please contact Lawrence Schiller, MD at 214-820-2687.

Thank you for your interest in this project. I hope you will take a few minutes to participate in the survey. Without the help of people like your important research would not be conducted.

## References


1. Dale M, Rang H. *Pharmacology*. 6th ed. Philadelphia, PA: Elsevier/Churchill Livingston; 2007.

2. Diabetes Overview. National Diabetes Information Clearinghouse (NDIC). National Institute of Diabetes and Digestive Kidney Disease (NIDDK). Available at: http://diabetes.niddk.nih.gov/dm/pubs/overview/index.htm. Accessed 7/3/2009.

3. Pancreatic Islet Transplantation. National Diabetes Information Clearinghouse (NDIC). National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). March 2007. Available at: http://diabetes.niddk.nih.gov/dm/pubs/pancreaticislet/. Accessed 6/1/2009.

4. Diagnosis of Diabetes. National Diabetes Information Clearinghouse (NDIC). Available at: http://diabetes.niddk.nih.gov/dm/pubs/diagnosis/index.htm. Accessed 7/3/2009.

5. National Diabetes Statistics, 2007. National Diabetes Information Clearinghouse (NDIC). June 2008. Available at: http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/. Accessed 7/3/2009.

6. Clinical Islet Transplantation Consortium. National Institute of Diabetes and Digestive Kidney Disease (NIDDK). Available at: http://www.citisletstudy.org/. Accessed 7/3/2009.

7. Ellis H. Anatomy of the pancreas. *Surgery (Oxford)*. 2007;25:72-73.

8. Nussey K, Whitehead M. *Endocrinology: An Integrated Approach*. London, UK: Taylor & Francis; 2001.

9. Koeppen BM, Stanton B. *Berne & Levy Physiology*. 6th ed. Philadelphia, PA: Elsevier/Churchill Livingston; 2008.

10. Elayat AA, el-Naggar MM, Tahir M. An immunocytochemical and morphometric study of the rat pancreatic islets. *J Anat*. 1995;186 ( Pt 3):629-637.

11. 2006 Scientific Summary of the Collaborative Islet Transplant Registry (CITR). Available at: https://web.emmes.com/study/isl/reports/2006%20Scientific%20Summary%20Final.pdf. Accessed 6/2/2009.

12. Ikemoto T, Noguchi H, Shimoda M, et al. Islet cell transplantation for the treatment of type 1 diabetes in the USA. *J Hepatobiliary Pancreat Surg*. 2009;16:118-123.

13. Noguchi H, Matsumoto S. Islet transplantation at the diabetes research institute japan. *J Hepatobiliary Pancreat Surg*. 2008;15:278-283.

14. Noguchi H, Matsumoto S, Matsushita M, et al. Immunosuppression for islet transplantation. *Acta Med Okayama*. 2006;60:71-76.

15. Onaca N, Naziruddin B, Matsumoto S, Noguchi H, Klintmalm GB, Levy MF. Pancreatic islet cell transplantation: Update and new developments. *Nutr Clin Pract*. 2007;22:485-493.

16. Berman A, Pawelec K, Fiedor P. Allogeneic transplantation of isolated islet cells in clinical practice. *Pol Arch Med Wewn*. 2009;119:326-332.

17. Onaca N, Klintmalm GB, Levy MF. Pancreatic islet cell transplantation: A treatment strategy for type I diabetes mellitus. *Nutr Clin Pract*. 2004;19:154-164.

18. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet*. 2009;373:1808-1817.

19. Sahu S, Tosh D, Hardikar AA. New sources of beta-cells for treating diabetes. *J Endocrinol*. 2009;202:13-16.

20. Jackson AM, Connolly JE, Matsumoto S, et al. Evidence for induced expression of HLA class II on human islets: Possible mechanism for HLA sensitization in transplant recipients. *Transplantation*. 2009;87:500-506.

21. Murphy K, Travers P, Walport M. *Immunobiology*. 7th ed. Garland Science; 2007.

22. Zenapaz (Daclizumab). Roche Pharmaceuticals. Hoffmann-La Roche Inc. September 2005. Available at: http://www.rocheusa.com/products/zenapax/pi.pdf. Accessed 6/7/2009.

23. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol*. 2009;27:519-550.

24. Mackay F, Loetscher H, Stueber D, Gehr G, Lesslauer W. Tumor necrosis factor alpha (TNF-alpha)-induced cell adhesion to human endothelial cells is under dominant control of one TNF receptor type, TNF-R55. *J Exp Med*. 1993;177:1277-1286.

25. Schroder K, Hertzog PJ, Ravasi T, Hume DA. Interferon-gamma: An overview of signals, mechanisms and functions. *J Leukoc Biol*. 2004;75:163-189.

26. New Targeted Immunosuppressant Drug. National Institute of Arthritis and Musculoskeletal and Skin Diseases. National Institutes of Health Department of Human and Health Services. October 2003. Available at: http://www.niams.nih.gov/News_and_Events/Press_Releases/2003/10_30.asp. Accessed 6/6/2009.

27. Islet Transplantation. American Diabetes Association. Published 2007. Available at: http://www.diabetes.org/type-1-diabetes/islet-transplants.jsp. Accessed 6/1/2009.

28. Dumont FJ, Su Q. Mechanism of action of the immunosuppressant rapamycin. *Life Sci*. 1996;58:373-395.

29. Prograf Tacrolimus Capsules and Injection. Astellas Pharma US, Inc. 2007. Available at: http://www.astellas.us/docs/prograf.pdf. Accessed 6/7/2009.

30. Cernea S, Pozzilli P. New potential treatments for protection of pancreatic B-cell function in type 1 diabetes. *Diabet Med*. 2008;25:1259-1267.

31. Chanaud CM. Determination of required content of the informed consent process for human participants in biomedical research conducted in the U.S. A practical tool to assist clinical investigators. *Contemp Clin Trials*. 2008;29:501-506.

32. Bankert EA, Amdur RJ. *Institutional Review Board: Management and Function*. 2nd ed. Sudbury, MA: Jones & Bartlett; 2006.

33. CFR – Code of Federal Regulations Title 21. Subpart B- Informed Consent of Human Subjects. Sec. 50.25 Elements of Iinformed Consent. US Food and Drug Administration.

US Department of Health and Human Services. April 21, 2008. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=50.25. Accessed 6/27/ 2009.

34. Title 45: Public Welfare Part 46—Protection of Human Subjects. Electronic Code of Federal Regulations. National Achieves and Records Administration. June 20, 2009. Available at: http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr;sid=6757c6ecfbef0ce6bb45bb2b5874075c;rgn=div5;view=text;node=45%3A1.0.1.1.25;idno=45;cc=ecfr. Accessed 6/21/2009.

35. *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Council for International Organizations of Medical Sciences (CIOMS), World Health Organization (WHO). 2002. Available at: http://www.cioms.ch/guidelines_nov_2002_blurb.htm. Accessed 6/15/2009.

36. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6 (R1). Available at: http://www.ich.org/LOB/media/MEDIA482.pdf. Accessed 6/15/2009.

37. Glaser, BG, Strauss, AL. *The Discovery of Grounded Theory: Strategies for Qualitative Research.* Chicago, IL: Aldine; 1967.

38. Corbin JM, Strauss A. Grounded Theory Research: Procedures, Canons, and Evaluative Criteria. *Qualitative Sociology.* 1990:13:3-21.

39. Daly KJ. Analytical Strategies. *Qualitative Methods for Family Studies and Human Development*. London, UK: Sage Publications; 2007:209-241.

40. McKneally MF, Martin DK, Ignagni E, D'Cruz J. Responding to trust: Surgeons' perspective on informed consent. *World J Surg*. 2009;33:1341-1347.

41. Meloche RM. Transplantation for the treatment of type 1 diabetes. *World J Gastroenterol*. 2007;13:6347-6355.