Centre universitaire de santé McGill | McGill University Health Centre

INFORMATION AND CONSENT FORM

Research Study Title:	**A randomized, three-way, crossover study to assess the efficacy of fast-acting insulin-plus-pramlintide closed-loop co-administration, regular insulin-plus-pramlintide closed-loop co-administration, and fast-acting insulin-alone closed-loop infusion in regulating glucose levels over a 24-hour period in adults with type 1 diabetes in inpatient settings**
Principal investigator:	Laurent Legault, M.D., Montreal Children's Hospital
Co-Investigator(s)/sites:	Ahmad Haidar Eng., Ph.D., McGill University Jean-François Yale, M.D., Royal Victoria Hospital Michael Tsoukas, M.D., Royal Victoria Hospital
Sponsor:	McGill University Health Centre Research Institute
Funder	Juvenile Diabetes Research Fund (JDRF)
Protocol number:	MP-37-2017-2510 (MP)

INTRODUCTION

We are inviting you to take part in this research study because you have type 1 diabetes.
However, before you accept to take part in this study and sign this information and consent form, please take the time to read, understand and carefully examine the following information. You may also want to discuss this study with your family doctor, or a family member.
This form may contain words that you do not understand. We invite you to speak to the researcher responsible for this study (the "study doctor") or to other members of the research team, and ask them to explain to you any word or information that is unclear to you before you sign this form.

BACKGROUND

Despite current treatments, maintaining blood glucose levels within a good range is a difficult task for many people with type 1 diabetes, both during the day and overnight. Based on insulin pumps and glucose monitoring sensors currently available, we hope to develop an external artificial pancreas (a device that acts like a pancreas) that will be able to adjust the delivery of insulin according to the glucose profile. Amylin is another hormone that is co-secreted with insulin in response to food, and is deficient in patients with type 1 diabetes. Amylin, helps regulate glucose levels after meals. Pramlintide is a synthetic analog of the hormone amylin. Infusing pramlintide with fast-acting insulin or regular insulin might improve glucose levels, especially after meals.

The components of the artificial pancreas are:

- An insulin pump. A 2nd pump is necessary to infuse pramlintide.
- A continuous glucose monitoring system to measure glucose levels every 5 minutes.
- A computer program that calculates the insulin and/or pramlintide dose to infuse.

Pramlintide

This study uses a drug called pramlintide. Pramlintide is an experimental drug that has been approved in the United States by the Food and Drug Administration, but has not been approved for commercial use in Canada. Health Canada has approved pramlintide to be used only in research studies like this one.

Infusion of pramlintide might cause nausea. Mild nausea is more likely during the first days after starting pramlintide and usually does not last long. This is why the doctor will start pramlintide at a low dose and increase it gradually. Pramlintide may also cause decreased appetite, vomiting, stomach pain, tiredness, or dizziness.

The effects of pramlintide on an unborn baby have not been identified.

Should you suffer harm of any kind following administration of the study drug, or following any other procedure related to the research study, you will receive the appropriate care and services required by your state of health.

PURPOSE OF THE RESEARCH STUDY

The purpose of this study is to compare the effect of three strategies to control your day-and-night glucose levels:

1. artificial pancreas with fast-acting insulin;
2. artificial pancreas with fast-acting insulin and pramlintide;
3. artificial pancreas with regular insulin and pramlintide.

For this research study, we will recruit 28 participants, men and women with type 1 diabetes, over the age of 18 years. Participants will be recruited by the research staff.

DESCRIPTION OF THE RESEARCH PROCEDURES

This research study will take place at the Center of Innovative Medicine at McGill University Health Center (Glen).

1. Duration and number of visits

Your participation in this research project will last approximately 3 to 4 months and will include a total of 5 visits: one admission visit which will take about 2 hours, the optimization initiation visit which will take about 2 hours and three separate intervention visits, which will take 24 hours in a hospital setting.

2. Protocol Description

Visit 1: Admission Visit (2 hours)

If you agree to participate in this study, after the explanation of the consent form and the signature of it, the first visit (admission visit) will confirm your eligibility. You will meet the study coordinator or the nurse who will explain to you the different study procedures. You will meet with the study medical doctor for a

medical examination and he will explain to you the possible risks associated with this study, which are described further in this document. We will do a blood test to assess your diabetes control (HbA1c) as well as kidney function (creatinine and eGFR) if you have no recent (1 month or less) result available. For women of child bearing age, a pregnancy test will be performed. We will collect your height, weight and current insulin therapy (total daily dose, carbohydrate to insulin ratios, basal rates, insulin sensitivity, target blood glucose levels and active insulin time). You will be asked to complete a questionnaire on hypoglycemia awareness (5 minutes).

Visit 2: Optimization Initiation (2 hours)

You will meet a trained staff member who will explain to you how each device used in this study (pump and glucose sensor(s), artificial pancreas) work. Depending on the optimization schedule, you may be required to install the sensor(s), study pump(s) and additional infusion set as well as initiate the infusion of pramlintide during the visit. Otherwise, you will be required to do it at your own time, as per the optimization schedule. During the visit, the staff member will also explain and answer any questions related to the optimization period. Indications will be given for the pramlintide and regular insulin.

Before visits 3, 4 and 5, you will be randomized (like the flip of a coin) on the sequence of different treatments. The treatments are:

1. artificial pancreas with fast-acting insulin;
2. artificial pancreas with fast-acting insulin and pramlintide;
3. artificial pancreas with regular insulin and pramlintide.

Optimization Period (minimum 10 days)

During the optimization period, you may continue to use your personal insulin pump with your fast-acting insulin. If you don't own a Medtronic pump, you will also have an option to use a study pump for infusion of fast-acting insulin. For the delivery or regular insulin or pramlintide, the study staff will provide you with additional pumps as well as regular insulin (Humulin R) or pramlintide respectively. You will have to install a second catheter for the infusion of pramlintide.

You will also receive a continuous glucose sensor to monitor your blood sugar levels. The installation of the glucose sensor involves the insertion of a catheter in the abdominal region. The sensor needs to be worn at all times. You will have to calibrate the glucose sensor 2-3 times per day with a capillary blood glucose measurement. The study staff will contact you every few days to help you optimize your insulin basal rates and insulin-to-carbohydrate ratios according to your glucose sensor measurements. This optimization period will last for a minimum of 10 days with a target of less than 14 days. Gastrointestinal symptoms will also be collected during the optimization and intervention periods.

Optionally, you will receive a second sensor (FreeStyle Libre, Abbott) that will not require calibrations. This sensor has been recently approved by Health Canada. If you agree to wear the second sensor, the installation of FreeStyle Libre sensor will take place: **i)** 0-2 days **ii)** 6-8 days **iii)** 11-13 days prior to the interventions. The sensor installation schedule will be determined by a member of the research team and you will receive instructions on when to install the Freestyle Libre sensor. Training on the sensor use will be provided by a trained research member.

Visit 3, 4 and 5: Intervention visits (24 hours)

For your convenience, you will be given an option to sleep on site one night prior to the intervention, with research staff available on site. Study procedures, however, will start in the morning of the scheduled intervention.

The purpose of visits 3, 4 and 5 (intervention visits) is to compare three strategies to control glucose levels for 24 hours:

1. artificial pancreas with fast-acting insulin;
2. artificial pancreas with fast-acting insulin and pramlintide;
3. artificial pancreas with regular insulin and pramlintide.

If you do not use a Medtronic® pump for your personal insulin, a replacement pump will be given by the research team at visit 2 and you will be required to install it at least one day prior to the intervention visit.

On the day of the interventions, you will have to come to the Center of Innovative Medicine at 7:00. A nurse will revise the inclusion and exclusion criteria, ask if there are any changes in your medication and if you experienced an adverse event since the last visit. For women of child bearing potential, a pregnancy test will be performed before every intervention visit. A nurse will install a catheter in an arm vein to withdraw blood samples. From 8:00 till 8:00 the next morning, 2-ml blood samples will be taken every 10 to 30 minutes, for a total blood volume of 122 ml (approximately 25 teaspoons). For the intervention visit with regular insulin and pramlintide, the first blood sample will be taken at 7:40am and the second at 7:50am, afterwards the same schedule as the other intervention visits will be respected. Consequently, for the intervention visit of regular insulin and pramlintide, 3 extra blood samples will be taken, for a total of 128ml.

Every 10 minutes, glucose levels measured with the sensor will be manually transferred to a laptop on which a program will be installed that will control your glucose levels. This program will calculate the doses of insulin to maintain your glucose levels in the target range. This recommendation will be manually transferred by a study team member to the insulin pump as well as a dose adjustment to the pramlintide secondary pump.

At the inpatient intervention, you will be served three meals, at 8:00, 12:00, and 17:00. At 21:00, you will be served a bedtime snack. Throughout the 24-hour intervention, you will be allowed to perform light activities such as walking, play card, board, and video games. You will be encouraged to walk at least 30 min per day. You will sleep at our clinical research facility under the supervision of a nurse. A medical doctor will be on call.

You will leave our research facility the morning of the second day between 8:00 and 8:30.

3. Tests and procedures

During your participation in this research study, the study doctor or a member of the research team will conduct the following tests and procedures:

DESCRIPTION OF STUDY PROCEDURES	
Procedure	**Description**

Medical Exam	Medical examination by the study medical doctor to assess health risk factors. (Routine standard of care)
Glycosylated hemoglobin (HbA1c)	Blood test to assess your diabetes control. (Routine standard of care).
Pregnancy Test (hCG)	Urine test to detect pregnancy. (Routine standard of care).
Kidney Function (creatinine and eGFR)	Blood test to assess your kidney function. (Routine standard of care).
Questionnaires	Questionnaires to assess hypoglycemia awareness and quality of life. (Solely for study procedure)
Installation of glucose sensor	Installation of a continuous glucose sensor in the abdominal region to automatically measure glucose levels every 5 minutes. (Routine standard of care)
Installation of catheter for infusion of insulin and pramlintide	Installation of insulin and pramlintide pump catheters in the abdominal region. Infusion of insulin and pramlintide doses with two separate pumps. Doses are calculated by the study computer program recommendations based on the glucose measurements. (Solely for study procedure)
Blood samples	Insertion of a catheter in an arm vein to withdraw blood samples every 10 to 30 minutes. (Solely for study procedure)

The schedule of procedures for each visit is listed below:

SCHEDULE OF STUDY PROCEDURES					
Procedure	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Explanation of the study	X				
Consent form	X				
Medical exam	X				
Glycosylated hemoglobin (HbA1c)	X				
Pregnancy test (hCG)	X		X	X	X
Kidney function (creatinine, eGFR)	X				
Record weight (Kg)			X	X	X
Anthropometry (weight & height)	X				
Questionnaires	X				X
Stay at the research center for 24 hours			X	X	X
Installation of the glucose sensor		X	X	X	X
Installation of the catheter for the infusion of insulin and pramlintide		X	X	X	X
Blood samples			X	X	X

BENEFITS ASSOCIATED WITH THE RESEARCH STUDY

You should not expect any direct benefit from your participation in the study. However, we hope that the study results will contribute to the advancement of scientific knowledge in this field and help us find better treatments for patients.

RISKS ASSOCIATED WITH THE RESEARCH STUDY

A participation in the study involves the following risks and disadvantages.

1. **Blood sampling**

Blood sampling will be performed by qualified personnel. This procedure may still cause mild discomfort. Bruises or more rarely dizziness may occur.

2. **Glucose sensor, catheter for continuous infusion of insulin and pramlintide**

There is a risk of infection at the catheter's point of insertion as well as a possible irritation. These risks are very low. It is possible to feel a slight discomfort when the catheter is inserted. For the interventions for which we test the glucose control with two hormones, another catheter for pramlintide infusion similar to the one used for insulin infusion will be inserted.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research project is voluntary. Therefore, you may refuse to participate. You may also withdraw from the project at any time, without giving any reason, by informing the study doctor or a member of the research team.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the study doctor or clinical team.

The study doctor, the Research Ethics Board, the funding agency, or the Sponsor may put an end to your participation without your consent. This may happen if new findings or information indicate that participation is no longer in your interest, if you do not follow study instructions, or if there are administrative reasons to terminate the project.

If you withdraw or are withdrawn from the study, the information collected during the study will be stored as long as necessary to ensure your safety and the safety of the other participants, as well as to meet regulatory requirements. The Sponsor will continue to use any information collected from you prior to your withdrawal.

Any new findings that could influence your decision to stay in the research project will be shared with you as soon as possible.

CONFIDENTIALITY

During your participation in this study, the study doctor and their team will collect and record information about you in a study file. They will only collect information required to meet the scientific goals of the study.

The study file may include information from your medical chart, including your identity, concerning your past and present state of health, your lifestyle, as well as the results of the tests, exams, and procedures that you will undergo during this research project. Your research file could also contain other information, such as your name, address, gender, and date of birth. The data collected will be kept in a locked file cabinet in an area with limited access. In addition, documents on the computer will be protected by a password. Only the principal investigator and delegated staff will have access to the study data. For the inspection purposes, a person appointed by the Ethics Research Committee could access the participant's chart. The data collected will be stored for 25 years after the end of this study by the lead researcher and will be destroyed after,

according to the standards.

All the information collected during the research project will remain strictly confidential to the extent provided by law. You will only be identified by a code number. The key to the code linking your name to your study file will be kept by the study doctor.

To ensure your safety, a copy of this information and consent form will be placed in your medical chart. As a result, any person or company to whom you give access to your medical chart will have access to this information.

The study doctor will forward your coded data to the sponsor or their representatives.
The Sponsor may share the coded study data with their commercial partners.
The data may be published or shared during scientific meetings; however, it will not be possible to identify you.

For monitoring, control, safety, security, and marketing of a new study drug, your study file as well as your medical charts may be examined by a person mandated by Canadian or international regulatory authorities, such as Health Canada, as well as by representatives of the study sponsor, the institution, or the Research Ethics Board. All these individuals and organizations adhere to policies on confidentiality.
Thus, the data and results of this study will:

- Be published in journals and conferences, but it will not be possible to identify you;
- Be the subject of scientific debates;
- Serve for other analyzes related to the project to meet the research objectives in connection with this study;
- Serve for the development of future research projects on closed-loop systems that will have to be approved the Ethic Committee;
- Serve to make changes to the artificial pancreas to improve its efficacy;
- Be used by students of 1st, 2nd or 3rd university degree (bachelor, master or doctorate), supervised by the principal investigator, who participated in the data collection in order to write an internship report, thesis or dissertation.

You have the right to consult your study file in order to verify the information gathered, and to have it corrected if necessary. However, in order to protect the scientific integrity of the research project, accessing certain information before the project is ended may require that you be withdrawn from the study.

CONFLICT OF INTEREST / COMMERCIALISATION AND FINANCIAL BENEFITS

Professor Ahmad Haidar owns intellectual property (IP) in the field of artificial pancreas (mathematical dosing algorithm) with the intention to commercialize. Professor Ahmad Haidar developed this IP during his post-doc and plans to commercialize it through an entity in which he will own equity. If this occurs, research participants would not be offered financial benefits for this development.

TRANSFER OF DATA TO INDUSTRIAL PARTY

In exchange of material support, the research results will be shared anonymously to an industrial party for the purpose of researching, developing making, having made, marketing, distributing, using, selling, having sold, offering for sale, importing or exporting products for the treatment of human and human related diseases, (which may include research or activities performed with one or more Third Party collaborators) and to have any of the foregoing performed on the industrial party's behalf by a third party service provider.

INCIDENTAL FINDINGS

Material incidental findings are findings made in the course of the study that may have significant impacts on your current or future wellbeing or that of your family members. A material incidental finding concerning you in the course of this research will be communicated to you and to a health professional of your choice.

MARKETING POSSIBILITIES

The research results, including those following your participation in this study, could lead to the creation of commercial products. However, you will not receive any financial benefits.

FUNDING OF THE RESEARCH PROJECT

The researcher responsible of this study and McGill University received funding from the Juvenile Diabetes Research Foundation to conduct this research project.

COMPENSATION

You will receive an amount of 25$ compensation for the completion of the admissions visit (Visit 1) and an additional 325$ compensation for each completed 24-hour intervention visit (Visit 3, 4, 5), for a total of 3 intervention, for a total amount of 1000$ for costs and inconveniences incurred during this research study. If you withdraw from the study, or are withdrawn before it is completed, you will receive compensation proportional to the number of visits you have completed.

SHOULD YOU SUFFER ANY HARM

By agreeing to participate in this research project, you are not waiving any of your legal rights nor discharging the study doctor, the sponsor or the institution, of their civil and professional responsibilities.

CONTACT INFORMATION

If you have questions or if you have a problem you think may be related to your participation in this research study, or if you would like to withdraw, you may communicate with the study doctor or with someone on the research team at the following number: 514-398-4491 or 514-398-4354.

For any question concerning your rights as a research participant taking part in this study, or if you have comments, or wish to file a complaint, you may communicate with:

> The Patient Ombudsman of the Royal Victoria Hospital (MUHC) at the following phone number: 514-934-1934 extension 35655.

OVERVIEW OF ETHICAL ASPECTS OF THE RESEARCH

The McGill University Health Centre Research Ethics Board reviewed this study and is responsible for monitoring it at all participating institutions in the health and social services network in Quebec.

Research Study Title: **A randomized, three-way, crossover study to assess the efficacy of fast-acting insulin-plus-pramlintide closed-loop co-administration, regular insulin-plus-pramlintide closed-loop co-administration, and fast-acting insulin-alone closed-loop infusion in regulating glucose levels over a 24-hour period in adults with type 1 diabetes in inpatient settings**

SIGNATURES

Signature of the participant

I have reviewed the information and consent form. Both the research study and the information and consent form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above.

I authorize the principal investigator of this research study to communicate with me directly to ask if I am interested in participating in other research.

Yes ☐ No ☐

I authorize the study doctor to inform my regular doctor(s) that I am taking part in this study.

Yes ☐ No ☐

I wish to be informed about the incidental findings of this study.

Yes ☐ No ☐

I wish to wear a second sensor (FreeStyle Libre, Abbott) during the study.

Yes ☐ No ☐

I wish to be contacted for future studies related to type 1 diabetes.

Yes ☐ No ☐

Name of participant Signature Date

Signature of the person obtaining consent

I have explained the research study and the terms of this information and consent form to the research participant, and I answered all his/her questions.

Name of the person obtaining consent Signature Date

Commitment of the principal investigator

I certify that the nature and objectives as well as all the risks and benefits of this project were explained to the participant. I certify that we have clearly answered, to his satisfaction, all questions asked. I certify that we have clearly indicated that his participation is free and voluntary and that he may at any time terminate his participation to the project. A signed and dated copy of this form will be provided to the participant.

Name of the principal investigator	Signature	Date