UNIVERSITY OF PENNSYLVANIA COMBINED RESEARCH SUBJECT HIPAA AUTHORIZATION AND INFORMED CONSENT FORM

Protocol Title: Effect of Hybrid Closed-Loop Insulin Delivery on Glucose Counterregulation in Long Standing Type 1 Diabetes: A Proof of Concept, Mechanistic, Single-Arm Clinical Trial

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Why am I being asked to volunteer?

You are being invited to participate in a research study because **you have type 1 diabetes and you have hypoglycemia unawareness.** Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the principal investigator and/or the research team about this form. If you decide to participate, you will be asked to sign this form. Your doctor may be the principal investigator in this research study. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may want to ask for a second opinion about your care from another doctor who is not an investigator in this study. You do not have to participate in any research study offered by your doctor.

IRB Approved from: 1-8-2021 to 1-7-2022

What is the purpose of this research study?

The study described in this document is designed to improve the frequency of when you become aware of hypoglycemia unawareness. We hope to find out whether the use of a hybrid closed loop insulin delivery pump system can help patients like you with hypoglycemia unawareness avoid low blood sugars and regain awareness.

Hypoglycemia is a condition that occurs when your blood sugar is too low. Unawareness means you are unable to recognize that your blood sugar is low, so you don't feel any different than when your blood sugar is at a normal level.

In order to understand the significance of any improvement you might have, we will compare any improvement in your hypoglycemia awareness by having you undergo metabolic testing at different times during your participation.

- Baseline (before you start to use the device and after you have completed the screening phase).
- 6 months (after you have been using the device for six months).
- Final (after you have been using the device for 18 months).

The metabolic testing you will have is called a Hyperinsulinemic Euglycemic - Hypoglycemic clamp. The clamp test got its name because during the test, your glucose is "clamped", or "held", at a certain level so that we can see how your body responds to insulin. These clamp visits are described in detail under each individual visit on pages 3-7 of this consent form.

How long will I be in the study? How many other people will be in the study?

This study is expected to go on for approximately 3 years. The University of Pennsylvania is the only site performing this research. We expect to screen up to a total of 30 people in order to enroll 15 to 18 participants in this study.

If you agree to participate in this research, your involvement will last approximately 22 months (10-13 visits). This includes a Screening phase that will last 4 weeks and an Intervention phase that will last 18 months.

Participant Schedule of Events

	SCREENING PHASE				INTERVENTION PHASE									
	Screening	Run-in (+ 4 wks)	Baseline (+ 2 wks)	Medtronic Training	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12	Month 15	Month 18
Contact Type Phone or Visit	V	V	V	Classroom V or P	V or P X4	V or P	V	V or P	V or P	V	V	V	V	V
Visits by #	Visit 0	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Informed Consent	X													
[1] History and Physical	X	X	X		X	X	X	X	X	X	X	X	X	X
Provide 4-week Glucose Diary	X								X					
Download & Review Participant's own Pump	X	X												
Collect & Assess Glucose Diaries		X								X				
ECG	X													

	Screening	Run-in (+4 wks)	Baseline (+ 2 wks)	Medtronic Training	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12	Month 15	Month 18
Visits by #	**Visit 0**	**Visit 1**	**Visit 2**	**Classroom V or P**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Hypoglycemia Severity Questionnaire (HypoA-Q)	X									X		X		X
Clarke Score Questionnaire	X									X		X		X
Hypo Score Questionnaire	X									X		X		X
[2] Blood Tests	X									X		X		X
Hba1c test	X						X			X		X		X
[3] Pregnancy Test	X		X							X				X
Provide Actigraph watch	X					X			X	X[4]	X[4]	X[4]	X[4]	X[4]
Collect prior 3 weeks of Actiwatch data information		X					X			X	X	X	X	X
[7] Insomnia Severity Index Epworth Sleepiness Scale		X					X			X	X	X	X	X
[7]Composite Scale of Morningnes Pittsburgh Sleep Quality Index	X													
Training 670 Hybrid Closed Loop System and Carelink upload				X										
[5]Follow up Tel. contact with 670G specialist					X	X		X	X					
[5] 670G download and review					X	X	X	X	X	X	X	X	X	X
Glucometer download & review (linked to pump)	X	X			X	X	X	X	X	X	X	X	X	X
[6] Hyperinsulinemic Eu – Hypo clamp			X							X				X

1 May be repeated at next visit if it is done later than 30 days

2 Blood tests may include: BMP (basic metabolic panel), CBC (complete blood count), LFTs (liver function test), TSH (thyroid stimulating hormone) and Cpeptide (verifies your inability to make insulin). If certain values already exist in your electronic medical record, we will not need to repeat the test. The HbA1c (3-month blood glucose average) will be done on a more frequent basis and is a separate line-item.

3 If female HCG (test can be done by serum or urine)

4 Actigraph will be mailed to participants' home prior to when they need to wear. Participants return Actigraph watch at their next visit.

5 Follow-up phone calls will be made one day and one week after primary insertion and will be mentioned at each visit in case participant would like them to continue. Additionally, all visits that do not mark major time points (months 1, 2, 4, & 5) may be done over the phone if participant is comfortable uploading their insulin pump device to the Medtronic Carelink online platform for review with the team NP.

6 This visit is an overnight visit. You will check-in to the overnight research center between 4:00 and 6:00pm the day prior to the clamp test.

7 May be administered on paper or in Redcap. Done at the same timepoints as when you wear the Acti-watch

What am I being asked to do?

SCREENING PHASE

Visit 0 (Screening visit)

The first visit is a screening visit to be sure that you are eligible for the study.

The study team will:

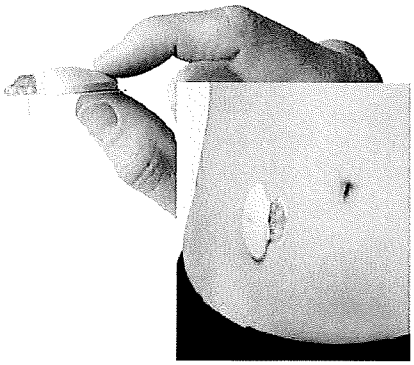
- Ask you questions about your health, including any medical conditions you have and

medications you take, and any other information that is needed to determine if you are eligible for the study.

- A physical exam will be performed, including a retina eye exam and the determination of height, weight and blood pressure.
- An electrocardiogram ("ECG"/ EKG"), a test that checks the electrical activity of your heart, will be done.
- We will ask you to complete three short questionnaires about your Hypoglycemia.
- We will download and review your own glucometer and pump devices.
- We will insert a continuous glucose monitor called an iPro2 (It is a sensor placed just under the skin that measures your tissue glucose levels continuously for up to 7 days). See full description below.
- We will provide you the Actigraph watch that you will wear fulltime for 7 days. (This information will help us establish a night-time resting period for you). See full description below.
- You will also be given an activity diary to complete during the time your wear the watch.
- We will ask you to complete 4 short questionnaires about your Sleep. You may complete these on a paper or using our study iPad electronically.
- We will show you what a Hybrid Closed Loop System looks like and will give you a user guide to take home.
- We will give you a diary where you will keep record of what you eat and any symptoms of low blood sugar you experience. You will fill out this log every day for 4 weeks and bring it with you at your next visit which will be visit 1 (run-in visit).
- If you are female and could become pregnant, a urine or blood pregnancy test will be done.
- We will draw your blood to test your organ function and your ability to make insulin.

About (10.5mL) 3 teaspoons of blood will be obtained at this visit. You should expect this visit to last about two hours.

Continuous Glucose Monitor (CGM)



At the end of the screening visit, you will have a continuous glucose monitor (CGM) placed on your belly and you will wear it for up to a week. The CGM is a small continuous glucose sensor (about the size of a quarter) that will be attached with a tiny needle under your skin and will be worn home and remain in place for 7 days. The CGM will be inserted by a member of the study team who will instruct you on how to care for it at home. Wearing this monitor will help define your body's glucose patterns.

The CGM that you will use is called iPro®2 Professional Continuous Glucose Monitor. This device is approved by the Food and Drug Administration (FDA).

The CGM kit has a sensor and a transmitter. The sensor has a plastic body and contains a thin, small needle and sensor wire about the size of a human hair. The sensor will be placed under the skin on your belly. Once inserted, the needle is removed and the sensor wire remains. The transmitter is about the size of a thumbprint and snaps on top of the sensor. Special tape is used to keep the sensor in place. The sensor wire continuously measures the glucose level in the fluid beneath the skin every 5 minutes. The glucose information is stored by the transmitter using radio waves. Once you return the transmitter to us we can retrieve your continuous glucose readings by sitting the transmitter in a docking station that is connected to a computer with a USB cord.

During the time you are using the CGM (7 days), you will need to check your blood sugar at least 3

times per day with your home blood glucose meter. We will provide you with instructions about when to check. If you do not have enough test strips for your own glucose meter we will provide you with a study glucose meter and enough test strips to cover the 7 days. You will also be given a box and label to ship the CGM system back to us.

You may be asked to wear the CGM for an additional 7 days to collect additional glucose readings if we were unable to retrieve enough readings.

The iPro®2 CGM can be worn during routine activities such as running and you can bathe or swim in 1 meter of water for up to 30 minutes.

Accelerometer

You will be able to choose one of two accelerometer watches for this study. The first is called an Actigraph monitor WGT3X-BT. It ismade by Actigraph, LLC. The second is called an Actigraph2. Both are small in size, comfortable and easy to wear. Both watches can be worn during routine activities such as running and you can bathe or swim in 1 meter of water for up to 30 minutes.

When you wear these devices we are collecting your activity, sleep, wake, and light exposure data in order to pinpoint a nocturnal pattern for you. You will be asked to wear these actigraph monitors a few times throughout the study, but the first time will be after your screening visit (visit 0). We will ask you to wear it non-stop for seven days and to return it at your run-in visit (visit 1).

You will return it after each use and when your study visits are 3 months apart, we will mail it to your home a few days before you are to begin to wear it.

Hybrid Closed Loop System (Medtronic 670G)

This system is FDA approved and intended for continuous delivery of basal insulin and boluses at rates that you select. This system includes SmartGuard® technology which can be programmed to automatically adjust your delivery of basal insulin based on your continuous glucose sensor values and can suspend delivery of your insulin when the sensor glucose value falls below or is anticipated to fall below predefined threshold (max / min) numbers.

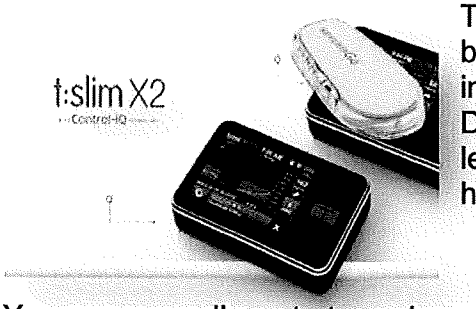
You can manually restart your basal insulin delivery at any time, and basal insulin delivery is automatically restarted after 2 hours of suspension regardless of the sensor glucose.

The system you will receive will contain the following:

- MiniMed 670G insulin pump.
- The Guardian Link Transmitter.
- The Guardian Sensor.
- A one-press Serter (push-like device to insert the sensor)
- Contour Next Link 2.4 glucose meter.
- Carelink software and computer connection cables.

You will receive standard training on this system once the study team has verified that you meet all the criteria for participation. This can be confirmed when you return for your run-in visit (visit 1below) and your iPro2 CGM download confirms your % of nocturnal hypoglycemia.

Tandem Hybrid Closed Loop t:slimX2 insulin pump with Control IQ



This system is FDA approved and intended for continuous delivery of basal insulin and boluses at rates that you select. This system includes a t:slimX2 insulin delivery pump that when used with the Dexcom G6 continuous glucose monitor (CGM) can predict glucose levels up to 30 minutes ahead and can correct boluses to help prevent highs and lows and increase time in range. (70-180mg/dL)

You can manually restart your basal insulin delivery at any time, and basal insulin delivery is automatically restarted after 2 hours of suspension regardless of the sensor glucose. If you don't already own a Tandem pump, we will work with your insurance to cover the cost of an upgrade.

The Tandem hybrid closed loop system will include the following:

- t:slimX2 Insulin Pump.
- Dexcom G6 Transmitter (sends glucose readings to a smart device or the Dexcom receiver every 5 minutes
- Dexcom G6 display device (receiver/smart phone)
- Dexcom Sensor (10-day wear)
- A one-touch applicator (push-like device to insert the sensor)
- t:connect software and computer connection cables
- Dexcom software and computer connection cables.

You will receive standard training on this system once the study team has verified that you meet all the criteria for participation. This can be confirmed when you return for your run-in visit (visit 1below) and your iPro2 CGM download confirms your % of nocturnal hypoglycemia.

Visit 1 (Run-in visit)

This visit will take place approximately 4 weeks after your screening visit. At this visit we will collect and review your completed glucose diaries and download your iPro2 to confirm your existing hypoglycemia; the final criterion to ensure you meet the requirements to participate in this study.

If you are eligible, we will give you an overview of MiniMed 670G system or the t:slimX2 with Basal-IQ and Control-IQ system and we will schedule a training visit with the Medtronic or the Tandem representative. This visit will take place as close as possible to the date of your baseline visit. If you are already familiar with the insulin pump, a training session via web and telephone is available. We will show you how to wear this system without using any automated features so we can make sure that you completely understand how the device works. We will also show you how to upload your system onto the Medtronic Care Link or the t-Connect electronic platforms. By doing this; when you have any follow-up phone calls with a study team member you can both interactively review your blood sugar patterns while having a conversation.

At this visit, if you have chosen the 670G closed loop system we will also give you a study glucometer. The Bayer Contour Next Link 2.4 and testing strips. We will provide you with enough pump and glucometer supplies to last you one month. Both devices are approved for use by the FDA. If you have chosen the t:slimX2 with Basal-IQ and Control-IQ system you will use your own blood glucose meter as

this system does not require a linking glucometer. The Dexcom G6 CGM is factory-calibrated—so no fingersticks are required.

Visit 2 (Baseline visit):

This visit is an overnight visit and will take place approximately 2 weeks after your Run-in visit. You will check-in to the research clinic / Center for Human Phenomic Science (CHPS) at the Hospital of the University of Pennsylvania the evening before the test between 4pm and 6pm.

The day of your arrival the following will occur:

- The research nurse will check you in, take your vital signs and make you comfortable.
- You will be served dinner.
- You will fast after 8pm.
- At approximately 9pm you will have two IVs placed (one in each arm). One IV is for a low-dose continuous insulin infusion and the other is for overnight hourly blood glucose monitoring which is a requirement of the Hospital of the University of Pennsylvania. (HUP) These IVs will remain in your arms overnight for use during the clamp test and will not be removed until the test is completed the next day.
- You will receive instructions from the nurses to turn your pump off and remove it before starting your overnight drip insulin infusion.

The next day the following will occur:

- At approximately 6:15am you will be taken in a wheel chair by your overnight research nurse to our testing research center located in the Perelman Center on the 4th floor of the South pavilion.
- We will take your vital signs (blood pressure, heart rate and breathing) get your weight and perform a brief physical exam.
- We will ask you about any problems you have experienced and any unusual or unpleasant feelings you may have had since your last visit.
- If you are female and could become pregnant, a urine or blood pregnancy test will be done.
- We will perform the clamp test: This test measures how your body responds to hypoglycemia (low blood glucose).

During the Clamp Test

- During this clamp test, you will receive a chemically modified glucose called a stable isotope through the IV; and we will gradually lower your blood glucose level to 45 mg/dl and keep it there for the last hour. We do this by adjusting the levels of both the insulin and glucose you are receiving to meet the desired blood glucose goal.
- During the clamp test, your blood glucose level will be checked frequently (every 5 minutes) and blood samples will be drawn regularly (every 20 minutes).
- You will be given lunch after the test is over. The study team will help you with your insulin dosing, if needed.

The clamp procedure itself will take approximately 6 hours to complete, and about (168mL) less than 1 cup of blood will be drawn. Not including the overnight part of the study, you should expect this visit to last 7 or 8 hours.

- We will download and review your study glucometer (if applicable) and your 670G or t:slimX2 with Basal-IQ and Control-IQ pump discuss any issues regarding the device and make any necessary insulin and/ or device adjustments.
- You will undergo further training on the MiniMed 670G or t:slimX2 with Basal-IQ and Control-IQ system so you will be able to use the automated features.
- We will schedule a phone call to take place in 1 week to review your use and comfort level of the automated pump system features.
- We will provide you with one month + of supplies to last through your next visit.

- We will schedule your next visit.

You will now be entering the 18-month intervention phase of the study.

Follow-up Telephone Calls:
You will be scheduled for two mandatory follow-up telephone calls with the study nurse practitioner specialized in the management of diabetes, insulin pumps and glucose sensors. One call will take place the morning after your training class and the 2nd call will take place one week after your training class. During these calls we can answer any questions and troubleshoot any issues you might be having with your new system. After these calls, at each study visit you will be given the option to continue having the calls if you so desire. Additionally, at months 1, 2, 4 and 5 you will have the option of uploading your insulin pump onto the Carelink or t-Connect online platform and doing your one-on-one required protocol visits over the telephone instead of coming in to the clinic.

INTERVENTION PHASE

Visit 3-7 (Months 1- 5):

For these five non-overnight visits you will meet with the study coordinator and nurse practitioner specialized in the management of diabetes, insulin pumps and glucose sensors. At months 1, 2, 4 and 5 you will have the option of uploading your insulin pump onto the Carelink or t-Connect online platform and doing one-on-one visits over the telephone instead of coming in to the clinic.
At these visits the following will occur:

- We will take your vital signs (blood pressure, heart rate and breathing) get your weight and perform a brief physical exam. (if you come in to the clinic only)
- We will ask you about any problems you have experienced and any unusual or unpleasant feelings you may have had since your last visit. (via phone or in person)
- We will download and review your study glucometer (if applicable) and your 670G or t:slimX2 with Basal-IQ and Control-IQ pump, discuss any issues regarding the device and make any necessary insulin and/ or device adjustments. (if via phone, you will download pump yourself and you will converse with the team NP as you both look at the screen with your downloads)
- We will make a decision on whether to continue the weekly phone calls.
- At month 2 we will give you (or mail to you) the Actigraph monitor and remind you to wear it fulltime for 3 weeks prior to your next visit. You will also be given an activity diary to complete during the time your wear the watch.
- At month 3 will do a blood test to get your Hba1c value.
- At month 3 we will download and review information collected from your Actigraph monitor which you will have worn for the prior 3 consecutive weeks.
- At month 3 we will ask you to complete two short questionnaires about your Sleep. You may complete these on a paper or using our study iPad electronically.
- At month 5 we will give you (or mail you) a diary where you will keep record of what you eat, when and how much you exercise, and any symptoms of low blood sugar you experience. You will fill out this log every day for 4 weeks and bring it with you at your next visit.
- At month 5 we will give you (or mail to you) the Actigraph monitor and remind you to wear it fulltime for 3 weeks prior to your next visit. You will also be given an activity diary to complete during the time your wear the watch.
- You will continue to wear the 670G or t:slimX2 with Basal-IQ and Control-IQ system and use the study glucometer (if applicable) and will be provided with enough supplies to last through your

next visit (+1 week).
- We will schedule your next visit.

Visit 8 (Month 6 visit):

This visit will be another overnight visit and is exactly like your last overnight visit. You will check-in to the research clinic / Center for Human Phenomic Science (CHPS) at the Hospital of the University of Pennsylvania the evening before the study test between 4pm and 6pm.

The day of your arrival the following will occur:

- The research nurse will check you in, take your vital signs and make you comfortable.
- You will be served dinner.
- You will fast after 8pm.
- At approximately 9pm you will have two IVs placed (one in each arm). One IV is for a low-dose continuous insulin infusion and the other is for overnight hourly blood glucose monitoring which is a requirement of the Hospital of the University of Pennsylvania. (HUP) These IVs will remain in your arms overnight for use during the clamp test and will not be removed until the test is completed the next day.
- You will receive instructions from the nurses to turn your pump off and remove it before starting your overnight drip insulin infusion.

The next day the following will occur:

- At approximately 6:15am you will be taken in a wheel chair by your overnight research nurse to our testing research center located in the Perelman Center on the 4th floor of the South pavilion.
- We will take your vital signs (blood pressure, heart rate, and breathing) get your weight and perform a brief physical exam.
- We will ask you about any problems you have experienced and any unusual or unpleasant feelings you may have had since your last visit.
- If you are female and could become pregnant, a urine or blood pregnancy test will be done.
- We will draw blood from your IV for an Hba1c test.
- We will perform the same clamp test that we did at your baseline visit: The test measures how your body responds to hypoglycemia (low blood glucose).

During the Clamp Test

- During this clamp test, you will receive a chemically modified glucose called a stable isotope through the IV and we will gradually lower your blood glucose level to 45 mg/dl and keep it there for the last hour. We do this by adjusting the levels of both the insulin and glucose you are receiving to meet the desired blood glucose goal.
- During the clamp test, your blood glucose level will be checked frequently (every 5 minutes) and blood samples will be drawn regularly (every 20 minutes).
- You will be given lunch after the test is over. The study team will help you with your insulin dosing, if needed.

The clamp procedure itself will take approximately 6 hours to complete, and about (168mL) less than 1 cup of blood will be drawn. Not including the overnight part of the study, you should expect this visit to last 7 or 8 hours.

- We will download and review your study glucometer (if applicable) and your 670G or t:slimX2 with Basal-IQ and Control-IQ pump, discuss any issues regarding the device and make any necessary insulin and/ or device adjustments.
- We will ask you to complete three short questionnaires about your Hypoglycemia
- We will collect and review your completed 4-week glucose diary.
- We will download and review information collected from your Actigraph monitor which you will have worn for the prior 3 consecutive weeks.

- We will ask you to complete two short questionnaires about your Sleep. You may complete these on a paper or using our study iPad electronically.
- We will make a decision on whether to continue the weekly phone calls and let you know we will be contacting you 4 weeks prior to your 9 month visit to remind you to wear the Actigraph monitor for 3 consecutive weeks prior to your visit.
- You will continue to wear the 670G system or t:slimX2 with Basal-IQ and Control-IQ and use the study glucometer (if applicable) and will be provided with one month of supplies to last through your next visit (+1 week).
- We will schedule your next visit.

Visit 9 (Month 9 visit):

At this visit the following will occur:

- We will take your vital signs (blood pressure, heart rate, and breathing) get your weight and perform a brief physical exam.
- We will take your vital signs (blood pressure, heart rate, and breathing) get your weight and perform a brief physical exam.
- We will ask you about any problems you have experienced and any unusual or unpleasant feelings you may have had since your last visit.
- We will download and review your study glucometer (if applicable) and your 670G pump or t:slimX2 with Basal-IQ and Control-IQ, discuss any issues regarding the device and make any necessary insulin and/ or device adjustments.
- We will download and review information collected from your Actigraph monitor which you will have worn for the prior 3 consecutive weeks.
- We will ask you to complete two short questionnaires about your Sleep. You may complete these on a paper or using our study iPad electronically.
- We will make a decision on whether to continue the weekly phone calls and let you know we will be contacting you 4 weeks prior to your 12 month visit to remind you to wear the Actigraph monitor for 3 consecutive weeks prior to your visit. We will also remind you to complete your activity log during the 3 weeks that you wear the actigraph.
- You will continue to wear the 670G system or t:slimX2 with Basal-IQ and Control-IQ and use the study glucometer (if applicable) and will be provided with enough supplies to last through your next visit (+1 week)
- We will schedule your next visit.

Visit 10 (Month 12 visit):

At this visit the following will occur:

- We will take your vital signs (blood pressure, heart rate, and breathing) get your weight and perform a brief physical exam.
- We will do a blood test to get your Hba1c value.
- We will ask you about any problems you have experienced and any unusual or unpleasant feelings you may have had since your last visit.
- We will download and review your study glucometer (if applicable) and your 670G or t:slimX2 with Basal-IQ and Control-IQ pump, discuss any issues regarding the device and make any necessary insulin and/ or device adjustments.
- We will ask you to complete three short questionnaires about your Hypoglycemia.
- We will make a decision on whether to continue any phone calls and let you know we will be contacting you 5 weeks prior to your 18 month and final visit to remind you:
    - to wear the Actiwatch2 for 3 consecutive weeks prior to your final visit.

- to complete the glucose diary 4 weeks prior to your final visit.
- to bring all of your own pre-study participation insulin delivery supplies (pump or injections or pen) for use after your final visit.

- We will give you a glucose diary where you will keep record of what you eat, and any symptoms of low blood sugar you experience. You will fill out this diary / log every day for 4 weeks prior to your final clamp and bring it with you at your final visit.
- We will ask you to complete two short questionnaires about your Sleep. You may complete these on a paper or using our study iPad electronically
- You will continue to wear the 670G system or t:slimX2 with Basal-IQ and Control-IQ and use the study glucometer (if applicable) and will be provided with enough supplies to last through your next visit (+1 week).
- We will schedule your next visit.

Visit 11 (Month 15 visit):

At this visit the following will occur:

- We will take your vital signs (blood pressure, heart rate, and breathing) get your weight and perform a brief physical exam.
- We will ask you about any problems you have experienced and any unusual or unpleasant feelings you may have had since your last visit.
- We will download and review your study glucometer (if applicable) and your 670G or t:slimX2 with Basal-IQ and Control-IQ pump, discuss any issues regarding the device and make any necessary insulin and/ or device adjustments.
- We will make a decision on whether to continue any phone calls and let you know we will be contacting you 5 weeks prior to your 18 month and final visit to remind you:
  - to wear the Actiwatch2 for 3 consecutive weeks prior to your final visit.
  - to complete the glucose diary 4 weeks prior to your final visit.
  - to bring all of your own pre-study participation insulin delivery supplies (pump or injections or pen) for use after your final visit.
- We will give you a glucose diary where you will keep record of what you eat, and any symptoms of low blood sugar you experience. You will fill out this diary / log every day for 4 weeks prior to your final clamp and bring it with you at your final visit.
- We will ask you to complete two short questionnaires about your Sleep. You may complete these on a paper or using our study iPad electronically
- You will continue to wear the 670G system or t:slimX2 with Basal-IQ and Control-IQ and use the study glucometer (if applicable) and will be provided with enough supplies to last through your next visit (+1 week).
- We will schedule your next and final visit.

Visit 12 (Month 18 Final visit):

This visit will be another overnight visit and is exactly like your last overnight visit. You will check-in to the research clinic / Center for Human Phenomic Science (CHPS) at the Hospital of the University of Pennsylvania the evening before the study test between 4pm and 6:00pm.

The day of your arrival the following will occur:

- The research nurse will check you in, take your vital signs and make you comfortable.
- You will be served dinner.
- You will fast after 8pm.
- At approximately 9pm you will have two IVs placed (one in each arm). One IV is for a low-dose continuous insulin infusion and the other is for overnight hourly blood glucose monitoring which is

a requirement of the Hospital of the University of Pennsylvania. (HUP) These IVs will remain in your arms overnight for use during the clamp test and will not be removed until the test is completed the next day.

- You will receive instructions from the nurses to turn your pump off and remove it before starting your overnight drip insulin infusion.

The next day the following will occur:

- At approximately 6:15am you will be taken in a wheel chair by your overnight research nurse to our testing research center located in the Perelman Center on the 4th floor of the South pavilion.
- We will take your vital signs (blood pressure, heart rate and breathing) check your weight and perform a brief physical exam.
- We will ask you about any problems you have experienced and any unusual or unpleasant feelings you may have had since your last visit.
- If you are female and could become pregnant, a urine or blood pregnancy test will be done.
- We will draw blood from your IV for an Hba1c test.
- We will perform the same clamp test that we did at your baseline visit: This test measures how your body responds to hypoglycemia (low blood glucose).

During the Clamp Test

- During this clamp test, you will receive a chemically modified glucose called a stable isotope through an IV and we will gradually lower your blood glucose level to 45 mg/dl and keep it there for the last hour. We do this by adjusting the levels of both the insulin and glucose you are receiving to meet the desired blood glucose goal.
- During the clamp test, your blood glucose level will be checked frequently (every 5 minutes) and blood samples will be drawn regularly (every 20 minutes).
- You will be given lunch after the test is over. The study team will help you with your insulin dosing, if needed.

The clamp procedure itself will take approximately 6 hours to complete, and about (168mL) less than 1 cup of blood will be drawn. Not including the overnight part of the study, you should expect this visit to last 7 or 8 hours.

- We will download and review your study glucometer (if applicable) and your 670G or t:slimX2 with Basal-IQ and Control-IQ pump, discuss any issues regarding the device and make any necessary insulin adjustments.
- We will ask you to complete three short questionnaires about your Hypoglycemia.
- You will return to your own insulin delivery system.
- We may collect your 670G system and Contour Link glucose meter. Because you obtained it through using your insurance upgrade, the t:slimX2 with Basal-IQ and Control-IQ system is yours to keep.
- We will collect and review your completed 4-week glucose diaries.
- We will collect and review your 3-week activity log.
- We will collect and review your Actigraph monitor and the data retrieved form it for the past 3 weeks.
- We will ask you to complete two short questionnaires about your sleep. You may complete these on a paper or using our study iPad electronically

What are the possible risks or discomforts?

There are known possible risks and discomforts associated with studies of this kind. As with any medication or testing procedure; there is a risk that a rare or previously unknown side effect, drug interaction, or allergy can occur. These unknown risks may affect you during your participation in the

research and/or at some point in the future.

Risks from the Hybrid closed-loop insulin delivery:
The risks of the hybrid closed-loop insulin delivery include local discomfort, skin irritation, bruising, bleeding, or rarely infection at the site of insulin infusion cannula or glucose sensor insertion.

These risks are minimized through proper instruction in insertion technique, including sterile procedures, by our diabetes research nurse practitioner.

While the use of a hybrid "closed-loop" system has been shown to reduce time spent in the hypoglycemic range, there is a risk of severe hypoglycemia if an incorrect "sensor glucose" number is used to make dosing adjustments to insulin delivery. This risk is minimized with the intensive education this study provides. We will not allow you to make insulin dosing decisions based solely on a sensor glucose recording. Medtronic and Tandem havebuilt safety measures into the closed-loop "process" during auto or closed loop mode that monitors for extreme sensor discord and will automatically exit the "closed- loop" function.

Another risk includes hyperglycemia (abnormally high blood sugar). Diabetic ketoacidosis could develop if an insulin infusion set becomes blocked or when inaccurate sensor glucose causes the insulin delivery to stop. Diabetic ketoacidosis is a serious complication of diabetes that occurs when your body produces high levels of blood acids called ketones. The condition develops when your body can't receive enough insulin. In this study this risk is minimized through intensive education that includes recognizing faulty insulin cannulas, rotating insertion sites every 2-3 days, and properly calibrating your glucose sensor at least 3 times daily. Also; the automated suspension of insulin delivery is programmed to last a maximum of 2 hours and even less if you take over the insulin delivery yourself.

Risks from the Blood Draw:
The risks of having blood drawn include temporary discomfort or pain, bruising at the site of puncture, fainting, and infection or a small blood clot or swelling to the vein and area surrounding where the blood is drawn. Also, when a large amount of blood is taken, your iron levels may become low. These conditions may cause you to feel tired or weak. If that happens, other medications may be required to help reduce these side effects.

It is important for you to know that the amount of blood that will be drawn for research purposes during your screening visit and 3 clamps will not exceed 550mLs (about 2.5 cups) in an 18-month period.

IV Risks
The risks of having IVs placed include discomfort, bruising, infection, fainting, blood clots, or infiltration of the IV solution, which could cause skin burning or tissue damage. However, these risks are very small and will be minimized by having experienced nurses and doctors continuously monitor the IV sites during the studies.

Risks from the Hyperinsulinemic Clamps:
The second part of the clamp study is designed to lower your blood glucose level to 45 mg/dl. You may feel lightheaded, dizzy, nauseous, sweaty, jittery, tired, or experience blurred vision from having your blood glucose changed. There is a small risk that your blood glucose becomes extremely low for a prolonged period. If this happens, it could cause a seizure. To minimize this risk, blood glucose will be monitored throughout the test. We will rapidly correct any lower than expected blood glucose by giving you glucose through your IV or by mouth to return blood glucose levels to normal.

Risks from the Stable Glucose Isotope:
During the clamp test you will be given a stable glucose isotope through an IV. These substances are

normally present in low amounts in food and in the environment. The isotopes are germ-free solutions mixed especially for research. There is a very small risk that giving you this solution may cause you to have an infection or fever. This risk is reduced by special testing of the isotopes prior to giving them in the IV.

Risks from the iPro2 Continuous Glucose Monitor (CGM):
You may feel skin irritation at the site where the needle is placed. You may also have one or more of the following: bruising, discomfort, pain, bleeding, redness, raised bumps, local infection, and appearance of a small "freckle-like" dot where the needle was inserted. You may get an infection where the sensor was inserted. If there is pain, redness, irritation, or rash at insertion site, the sensor will be removed and re-inserted in a different site. Any infection, or sign of infection, will be treated immediately.

Reproductive risks:
You cannot participate in this study if you are currently pregnant or become pregnant at any time during the study. It is possible that effects from the study procedures could cause harm to unborn children or children who are breast-feeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child.

If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you are able to become pregnant, you will be given a urine pregnancy test before entry into the study and at each clamp visit.

If you are sexually active, you must use medically accepted methods of birth control while you are on this study. Birth control methods which may be considered as highly effective include:

- Combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
- Barrier method of birth control to include: the diaphragm, cervical cap, male condom, or female condom/sheath plus spermicidal foam, sponges, or film.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Vasectomised partner.
- Sexual abstinence.

If you should become pregnant while participating in this study, or if you suspect that you have become pregnant, you must contact the Principal Investigator Dr. Michael Rickels immediately and consult an obstetrician or maternal-fetal specialist. It is important that you inform the study doctor or study coordinators because you will not be able to continue to participate in the study.

Privacy Risks
There is the unlikely chance that your information is viewed by someone outside the research team who is not authorized to see your health information. However, we make special efforts to make sure that this does not happen.

Unknown Other Risks
There also may be side effects or risks that are not known at this time. If we become aware of any new risks, you will be told about them. You will be able to decide if you want to continue participation in this study.
Risks related to your normal medical care are not listed in this form. We encourage you to discuss these

with your study doctor, your primary care provider, or another health care professional.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

The results of this study may help you and other people with type 1 diabetes in the future.

Although it is not guaranteed that you will benefit from being in this research study, it is likely you will benefit from close follow-up, and may also benefit from the guaranteed access to a hybrid closed- loop system and the intensive education and support required that is not presently fully reimbursed by your insurance.

We will provide you with access to your device download numbers (iPro2, Actigraph monitor, Tandem t:slim system & 670G system) as well as your lab results obtained during your participation in the study. You and your doctor will be able to review this information after you have completed the study. This information may be helpful for making changes that could help your diabetes management.

Even though we cannot guarantee or promise any benefits from using either the MiniMed 670G or t:slimX2 with Basal-IQ and Control-IQ system; if either's use combined with the intensive education does indeed offer more stable blood glucoses, then participants like you may experience fewer severe episodes of hypoglycemia.

What other choices do I have if I do not participate?

Your alternative is not to participate in this study. Participation in this study is your choice. By participating in this study you are not receiving any treatment for your condition.

If you choose not to participate in this study the alternative is to continue with your standard management of type 1 diabetes with available insulin delivery and glucose monitoring technologies.

Will I be paid for being in this study?

As you are completing this study, you will be compensated for your time using a visa gift card called a Greenphire ClinCard.

For each of the visits where a clamp was completed you will receive $150.00. You will also receive $50.00 for the completion of the remaining 10 visits, whether you complete them via phone or in the clinic. There will be no compensation for any xtra training visits you might require besides the initially scheduled visits

In addition, if you came to UPenn, at each visit (including any overnights), your parking ticket will be stamped. . . In summary; you will receive a total of $1,083.00. If your transportation was public, you will be compensated at the end of the study for your travel.

You will be paid in an ongoing manner as you complete each visit. The study coordinator will assign a visa card to you at the screening visit and will load it within 4 hours of your visit completion. .

If you do not complete the study, you will be compensated for the number of visits you have completed. If you have questions about your compensation for taking part in the study, please contact Ginger or Amy at the telephone number listed on page 1 of this consent document.

Please note: In order to be compensated for your participation in this study, you must provide your Social Security Number. The University of Pennsylvania is required to report to the IRS any cumulative

payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I have to pay for anything?

The study will pay for the costs of the study office visits and all research supplies and procedures that are being used or done specifically for the study. This includes the 670G closed hybrid loop system, the upgrade to the t:slimX2 with Basal-IQ and Control-IQ system, the CGM iPro2, the Actigraph monitor and the Contour Link blood glucose meter and test strips.

As with the t:slimX2 with Basal-IQ and Control-IQ system; if your insurance will allow you to "upgrade" to the 670G system and will cover the test strips needed for the Contour Link meter, then the study will cover the cost of your co-pay.

You and your health insurance may be billed for the costs of medical care (any deductibles or applicable co-pays for routine office visits, scans and blood work) during this study if these expenses would have happened even if you were not in the study. An example of these routine costs billed to insurance would be some screening labs such as an HbA1c or liver/ kidney function tests.

Co-pays and deductibles are highly variable depending on your type of insurance so please talk to your study team if you need help in determining exactly what the amount of your payment would be if it was required.

What happens if I am injured from being in the study?

If you are injured in this study, we will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, please tell Dr. Rickels who is in charge of the research study as soon as possible. Dr. Rickels' phone number is listed on the front page of this consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. Your participation in this study may be stopped at any time by your physician, the Principal Investigator, or the University of Pennsylvania Institutional Review Board (IRB) or the Food and Drug Administration (FDA) without your consent because:

- Your physician or the Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Principal Investigator or the University of Pennsylvania Institutional Review Board (IRB), or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

Who, outside the School of Medicine, might receive my information? How will my personal information be protected?

Results of laboratory tests and clinical procedures will be placed in your medical record and may be accessible to employees of the health system that are not part of the research team. This information

may also be viewed by your insurance company during routine audits.

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is audited by The Office of Clinical Research they may review your research records. The study data and safety monitoring board (DSMB) may also review your records.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

In addition, Medtronic Mini Med, Inc. and your Medtronic trainer will know your name, your address and the serial number to your new device. This way your device can be linked in the Medtronic system and the Medtronic "help desk" can keep a log of your after-hour calls for trouble-shooting purposes. Medtronic will also replace any faulty sensors or transmitters if the call was logged.

The school of nursing will also have access to your study binder as a school of nursing scholar is assisting with the analysis of your sleep / wake data and will be administering the sleep questionnaires. Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

Who may use and share information about me?

The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the investigator's study team.
- Authorized members of the workforce of the UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.).

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire. Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization.
- The University of Pennsylvania's Institutional Review Board grants permission.
- As permitted by law.

Electronic Medical Records and Research Results

What is an Electronic Medical Record and/or a Clinical Trial Management System?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a

study and to allow for your research data to be entered / stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.
If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. Laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

What information about me may be collected, used or shared with others?

The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, email address, date of birth, social security number
- Demographic information (e.g., age, sex, race/ ethnicity)
- Socioeconomic information (e.g., education, number in household income, employment status)
- Psychosocial and quality of life information
- Medical conditions including complications of T1D, surgeries, and pregnancies
- Medications
- Family history
- Laboratory Test Results
- Physical examination findings (e.g., blood pressure reading, heart rate, breathing rate and temperature, weight/BMI)
- Information related to the onset & diagnosis of T1D
- Treatment/management of T1D
- Problems encountered in self-management of T1D
- Results of tests, procedures and medical conditions you have had during your history of diabetes
- Participation in other studies

Why is my information being used?

Your information is important so the research team may contact you during the study. Your personal health information and results of tests and procedures are being collected as part of this research study. It is necessary in order to do the research, oversee the research and to see if the research was done right. In some situations, your personal health information might be used to help guide your medical treatment.

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study. You will be given a copy of this Research Subject combined Consent and HIPAA Authorization document describing your consent confidentiality and privacy rights for this study.

By signing this document, you are not only agreeing to participate in this research study but also permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

Name of Subject (Please Print)	Signature of Subject	Date

I certify that to the best of my knowledge the participant understands the nature, demands, risks, and benefits involved in his/her participation in this study.

Name of Person Obtaining Consent (Please Print)	Signature	Date

Future Research Participation

In the future, our team or other investigators at Penn may wish to contact you regarding new studies that you may be eligible to participate in. Do you want to be contacted regarding research participation in the future? (Regardless of your choice, you may still participate in the study and your future care will not be affected in any way).

☐ **Yes,** *I give permission to be contacted regarding future research participation.* _____ ***Initials***

☐ **No,** *I do not give permission to be contacted regarding future research participation.* _____ ***Initials***