Consent and Authorization Form for Research Study
Approved by Institutional Review Board

Study Title: Effects of hyperbaric oxygen therapy on glucose homeostasis in patients living with diabetes mellitus
Name of Investigator: Enoch Huang, MD
Phone Number: 503-413-3311
Study Sponsor: Dexcom Inc.

1. **Why have I been asked to take part in this research study?**
   You have been invited to take part in a research study (the "research study" or "study") being performed by Legacy Health. You have been invited because you are a healthy adult who has type 1 or type 2 diabetes and is willing to volunteer.

   The purpose of this Consent Form is to give you information about the research study; then you can decide whether you would like to take part.

2. **Who is doing the study?**
   The study is being performed by Legacy Research Institute and the Legacy Hyperbaric Medicine Department.

3. **Why is this study being done?**
   The purpose of this Research Study is:
   1. To determine the reliability and performance of the Dexcom G6® continuous glucose monitoring (CGM) system in patients with diabetes undergoing hyperbaric oxygen (HBO2) exposure. The study-specific blood glucose meter and CGM system are approved by the FDA (U.S. Food and Drug Administration) and available for sale.
   2. To determine whether HBO_2 exposure causes blood glucose to drop as a result of the treatment.
   3. To determine whether HBO_2 causes a change in blood glucagon (a hormone that raises blood glucose).

   The length of time you will be in the Study is 10 days. Approximately 24 people will be enrolled in this study at Legacy Health.

4. What will happen if I take part in this Study?

Before you start the study: You will be asked to read and sign this consent form.

Study Overview: We will be measuring your blood sugar using the CGM as well as measuring fingerstick blood glucose using our portable blood glucose meters. We will also be taking blood samples from a vein in your arm to compare the fingerstick and CGM blood glucose measurements against our hospital's laboratory blood sugar measurement, which will require placement of an intravenous (IV) catheter. We will be comparing a control day where you are not getting HBO_2 to a day where you are getting an HBO_2 treatment to see what the effect of HBO_2 is on your blood glucose. We will be asking you to check your blood glucose at home using one of our blood glucose meters at least 4 times a day during your study participation to confirm that the CGM is working properly. You will also be asked to complete a log of your meals and medications during the study period.

Day 1 of study: If you agree to participate in this study, one of the hyperbaric physicians (Dr. Huang or Dr. Savaser) will perform a screening history and physical examination. If you are a woman of child-bearing potential (who is not surgically sterile), you will be asked to submit to a urine pregnancy test. If the urine pregnancy test is positive you will not be allowed to participate in the study and will be referred to your physician for follow-up on your pregnancy.

Once the physician clears you for hyperbaric exposure, study staff will connect you to two versions of the Dexcom System – a Continuous Glucose Monitor (CGM) and a Continuous Glucose Logger (CGL). The Dexcom System consists of a sensor, transmitter, and a display device. A one-touch applicator easily inserts a small sensor just beneath the skin on your belly (CGM) and the back of the arm (CGL). It is secured to your skin by an adhesive patch (Figure 2). The sensor is water resistant and you can shower and exercise while it is in place. The sensor measures glucose levels just underneath your skin every 30 seconds (CGL) or every 5 minutes (CGM). A transmitter is fastened on top of the sensor and sends this information from the CGM wirelessly to a Dexcom-provided receiver, which must be carried with you to receive transmitted data. The CGM can store 3 hours of data between synchronizations with the receiver.

Figure 2. Insertion of CGM or CGL

The sensor will remain under your skin for at least 36 hours and then you will return to the Hyperbaric Medicine Clinic. The readings during this time may have increased variability – this is normal and readings will stabilize. If your blood glucose readings remain <70 mg/dL after 36 hours, you will not be allowed to participate in the study and will be referred to your primary care provider for evaluation and treatment.

Prior to returning to the clinic for your first study session and for each day of your study participation, you will be asked to:

- Check your blood glucose 4 times a day using a glucose meter that we provide you
- Keep a log of your meals and medications

Study Session 1 (Control): Beginning at midnight before your first study session, you will not be allowed to eat or drink anything except water. This is to ensure that your blood glucose is not affected by your meals. If you have eaten, your study day will be rescheduled.

Medication adjustments:

- If you take diabetes medication by mouth, you should not take anything until you have eaten after your study session.
- If you take an injection of short-acting insulin with your meals, you should not give yourself insulin until you have eaten after your study session.
- If your blood glucose is over 250 mg/dL, you should give yourself your prescribed amount of short-acting insulin and record it in your log
- If you take an injection of long-acting insulin, study investigators will customize your doses based on how many times a day you take the long-acting insulin
    - Patients who are on twice-daily long-acting insulin will take their normal dose in the morning, but 2/3 of their dose the night before
    - Patients who are only on night-time long-acting insulin will take 2/3 their normal dose the night before
    - Patients who are only on morning long-acting insulin will take 2/3 of their normal dose in the morning

At the Hyperbaric Medicine Clinic, study staff will check the CGM system to make sure it has been working properly. If the CGM has not been functioning and we cannot get it working, your study session will be rescheduled after we have resolved the technical issues.

The first control study session is designed to simulate a HBO_2 treatment without putting you into the hyperbaric chamber at all. You will be escorted to an observation room where you will be observed for the same amount of time that a HBO_2 treatment would take. You will be observed for 30 minutes before and for 30 minutes after your simulated HBO_2 exposure, so you will be in the observation room for about 3 hours. You will not be allowed to eat or drink anything other than water unless your blood glucose drops below 70mg/dl or you feel symptoms of low blood glucose regardless of your blood glucose.

A dedicated research associate will be in an observation room with you to monitor you and to check your blood glucose. We will check your blood glucose by using a lancet to pierce the skin of your fingertips ("fingerstick") to get a drop of blood. We will be checking blood glucose a total of 12 times during your simulated hyperbaric exposure, which means that you will have your finger stuck a minimum of 12 times.

We will also obtain 5 cc (1 teaspoon) of blood through the IV a total of 12 times for laboratory testing to see how those blood glucose measurements compare with the results we get from the fingerstick samples.

Study Session 2 (HBO_2 exposure): Beginning at midnight before your HBO_2 session, you will not be allowed to eat or drink anything except water. This is to ensure that your blood glucose is not affected by your meals. If you have eaten, your study day will be rescheduled.

Medication adjustments:

- If you take diabetes medication by mouth, you should not take anything until you have eaten after your study session.
- If you take an injection of short-acting insulin with your meals, you should not give yourself insulin until you have eaten after your study session.
- If your blood glucose is over 250 mg/dL, you should give yourself your prescribed amount of short-acting insulin and record it in your log
- If you take an injection of long-acting insulin, study investigators will customize your doses based on how many times a day you take the long-acting insulin
    - Patients who are on twice-daily long-acting insulin will take their normal dose in the morning, but 2/3 of their dose the night before
    - Patients who are only on night-time long-acting insulin will take 2/3 their normal dose the night before
    - Patients who are only on morning long-acting insulin will take 2/3 of their normal dose in the morning

At the Hyperbaric Medicine Clinic, study staff will check the CGM system to make sure it has been working properly. If the CGM has not been functioning and we cannot get it

working, your hyperbaric treatment will be rescheduled after we have resolved the technical issues. Once the CGM has been verified to be functioning properly, you will have an IV placed and be fitted for an oxygen hood to be used for your HBO_2 treatment. If you are unable to complete HBO_2 by the end of the sensor's lifetime, you will be given one additional opportunity at completing the study after having a second sensor implanted. If you cannot successfully complete the hyperbaric treatment, you will not be allowed a second chance at completing the study.

A clear plastic self-adhesive ring will be attached to your skin within 3 cm of your CGM. This will be connected to a transcutaneous oximeter, which measures the oxygen content of your skin. This will be left in place for the 30-minute period before starting hyperbaric oxygen, throughout your hyperbaric oxygen treatment, and for 30 minutes after your hyperbaric oxygen treatment.

The hyperbaric oxygen chamber can accommodate 8 patients at a time. You could be in the chamber along with regularly scheduled patients. In the chamber the pressure will increase to approximately 2-1/2 times normal atmospheric pressure (2.4 atmospheres absolute [ATA]). Once we reach the treatment pressure, you will breathe oxygen by placing the hood over your head and securing it in place. You will breathe oxygen for a 30-minute period, then take the hood off for 5 minutes for an "air break." You will have a total of three 30-minute oxygen periods and two 5-minute air breaks. After the third oxygen period is over, the pressure around you will be decreased until it is back to normal atmospheric pressure. You will be observed for 30 minutes before and for 30 minutes after your HBO_2 exposure, so you will be in the hyperbaric chamber for about 3 hours. You will not be allowed to eat or drink anything other than water unless your blood sugar drops below 70 mg/dL or you feel symptoms of low blood sugar regardless of your blood sugar.

A dedicated Inside Observer will be in the chamber with you to assist with your oxygen hood and to check your blood glucose. We will be checking your blood glucose the same way we did during the control session, obtaining a minimum of 12 fingersticks and 12 blood samples through the IV.

After you have completed the HBO_2 session, you will continue wearing the CGM for a total of 10 days to make sure that the CGM sensors and transmitters are functioning properly. During the remaining days of the study, you will be asked to:

- Check your blood glucose 4 times a day using a glucose meter that we provide you
- Keep a log of your meals and medications

Day 10 of study: On the tenth day of the study, you will be asked to return to the hyperbaric medicine clinic. Once staff has verified that the data was successfully recorded, the CGM sensor will be removed and the transmitter and display device collected by staff. The removed sensors will be placed in a specimen cup labeled with your study identification number. Sealed specimen cups will be sent to the manufacturer for examination and microscopic evaluation to determine if there has been any damage to the membrane as a result of HBO_2. Following evaluation, sensors will be destroyed.

If the data was not successfully recorded, you will have the opportunity to repeat the study with a new transmitter and sensor. You will still be paid for completing the study protocol.

5. What are the possible side effects and risks from being in the study?

Potential Risks/Discomforts with CGM Use
The following have been identified as possible risks of sensor insertion and wear:

- Excessive pain or discomfort, defined as 8 or greater on a 10-point scale (where 0 is no pain or discomfort and 10 is the worst pain or discomfort possible)
- Excessive bleeding or bruising
- Significant skin irritation or redness at the insertion site
- Significant skin irritation or redness at the adhesive area
- Local infection

Redness may occur where the sensor adhesive patch is placed. This will occur in most research participants and will clear up in about one day.

It is possible that an allergic reaction to one or more parts of the sensor and/or transmitter may develop. This is similar to allergies that occur due to medical tape or jewelry. Allergic reactions are typically mild and require only a topical cream to make them better.

Risks of Multiple Fingersticks
Risks associated with drawing blood from your finger multiple times include momentary discomfort and/or bruising. Infection or fainting are also possible, although unlikely.

Risks of Placement of Intravenous Catheter
Risks associated with placement of an IV include pain, bruising, and bleeding at the IV insertion site. Infection is possible, although unlikely.

Risks of HBO_2
In this study, you will receive your hyperbaric oxygen therapy in a multiplace hyperbaric chamber. Treatment pressure will be approximately 2.4 atmospheres absolute with 100% oxygen. Treatment will occur for three 30-minute oxygen breathing periods with 5-minute breaks in between for a total of 90 minutes of breathing oxygen.

Common risks include:

- Middle-ear sinus barotrauma (ear or sinus discomfort due to unequal pressure within middle ears or sinuses)
- Confinement anxiety

Very rare risks include:

- Oxygen related seizures
- Pneumothorax (chest pain and difficulty breathing due to collapsed lung)
- Arterial gas emboli (a bubble that becomes trapped in a blood vessel and blocks it)
- Decompression sickness (sickness caused by a decrease in pressure)

Unknown risks included:
There may be other risks in the study that are unknown at this time, as the study-specific blood glucose meter and CGM system are approved by the FDA (U.S. Food and Drug Administration) patients with diabetes, but it is unknown if there are additional risks to using the devices in patients undergoing hyperbaric oxygen (HBO2) exposure.

Fire hazard:
A risk unique to the hyperbaric chamber is the risk of injury due to fire as a result of elevated oxygen levels. Because of this, there are limits around what electronic devices are allowed in the hyperbaric chamber. Due to this inherent risk, our research team has taken measures to minimize risk of fire. Participants will not be allowed to take any electronic device (phone, computer, pager, etc.) into the chamber. The hyperbaric chamber has fire suppression equipment and the staff is trained how to respond in the event of this extremely rare event.

Reproductive Risks (Information on Pregnancy / Birth Control
The treatment in this study may have risks to a pregnant woman, an unborn human fetus or a breastfeeding child. If you are pregnant, planning to become pregnant or breastfeeding, you cannot take part in this study.

6. What are the possible benefits of this study?
You may not personally benefit from being in this study. By being a research participant, you may add to new information which helps other people in the future.

7. What are the costs of taking part in this study?
All costs associated with this research study will be paid by the study sponsor.

8. Will I be paid for being in this study?
The sponsor will pay you for taking part in the research study. You will be given up to $400.00 upon study completion and return of the CGM system. You will be given partial payment if you only complete part of the study. Payments will be made as follows:

Implantation of CGM loggers: $50.00
Completion of control study session: $100.00
Completion of HBO2 study session: $100.00
Completion of follow-up data collection: $200.00

9. What happens if I am injured or hurt because I took part in this study?
If you have an injury or illness, you should seek medical care for it and tell the study doctor. If you become sick or hurt while taking part in this research study, medical treatment will be available; this might be first aid, emergency treatment or follow-up care as needed. Legacy Health will bill your health insurance for the cost of such care. If your insurance does not pay for that care, or pays only a part of the cost, Legacy Health may bill you for any unpaid amounts. By providing or making available medical care for injuries or illness, Legacy Health and the people doing this research study are not admitting fault for injury or illness.

10. What are my rights in this study?

Taking part in this research study is voluntary; it is your choice. You are free to decide not to take part; and you can decide to stop taking part at any time. Your decision will not affect your relationship with or treatment at Legacy Health. It will also not lead to any penalty or loss of benefits that you would have outside of the research study.

You can decide to stop being in the study at any time. If you decide to stop for any reason, tell the study doctor as soon as possible. Also, you can decide whether the study doctor can continue to collect your medical information for the study.

New information learned during the research study could affect whether you still want to take part. New findings will be explained to you, and your written agreement to stay in the study may be needed.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available that suggests the study is not right for you
- If you are not able to meet the study requirements
- If the study is stopped by the sponsor

11. Who can answer my questions about this study?

Talk to the study doctor and staff about any questions or concerns you have about this study. You should also tell them about any side effects you have. Call the study doctor Enoch Huang, MD or Davut Savaser, MD at 503-413-3311.

You have a right to know about the risks, benefits, alternative procedures, and your rights as a research participant. If at any time you believe you have not been well informed, or if you feel pressure to take part in the study, even if you do not want to, you can talk to a Research Specialist. Legacy Health's Research Regulatory Specialist is available by phone during weekday working hours (8:30 a.m. to 5:00 p.m.) at (503) 413-5355.

12. Who will see my medical information?

For this research study, the study doctor and research staff will need information from your medical records. This information about you is called Protected Health Information (PHI). PHI includes any part of your health records that could be used to identify you, such as name, address, birth date, etc. With this Consent Form, you allow Legacy Health to use and share your PHI only for the purposes of this Research Study.

WHO: You authorize (give permission to) Legacy Health to provide your PHI to the investigators in this study.

FOR HOW LONG: You authorize (give permission to) Legacy Health to use and share your PHI indefinitely for the purposes of this research study.

We will keep your information as secure as we can. Once Legacy Health gives PHI to the people or agencies listed above, Legacy Health cannot guarantee they will keep it private.

They might give PHI to other people who are not limited by the terms of this Consent Form; and it might be used in ways that you did not intend.

You may change your mind and cancel this authorization at any time. To cancel this authorization, you must write to:

Enoch Huang, MD
Legacy Emanuel Chronic Wound and Outpatient Burn Clinic
Legacy Emanuel Specialty Center
3001 N. Gantenbein Avenue
Portland, OR 97227

If you cancel this authorization, you may no longer be able to take part in the study. The information already collected by Legacy Health and Dexcom may be used and shared as allowed by this authorization and consent form.

You will receive a copy of this consent form.

My signature agreeing to take part in this Research Study

I have read this Consent Form. I have talked about it with the study doctor, and my questions have been answered.

I agree to take part in this research study. I know I can change my mind and can stop being part of the study at any time.

I also give my permission to Legacy Health to use and share my Protected Health Information (PHI) for the purposes of this research study, as described in this consent form.

Signature of Research Participant Date

Printed Name of Research Participant

The research participant has been informed of the purpose and procedures of this research study. This includes the risks involved in the study and the use of Protected Health Information. The participant's questions have been answered to the best of our ability. A copy of this Consent and Authorization has been given to the participant.

Signature of Investigator or Designee Date