PROTOCOL TITLE: Evaluation of physician-based decision support in patients with type 1 diabetes on multiple daily injection therapy

STUDY SITE:	Oregon Health Science University 3181 SW Sam Jackson Park Rd Portland, OR 97639
FUNDING:	Dexcom
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Background:

The team at OHSU is developing a smartphone based application to provide decision support for patients with type 1 diabetes taking multiple daily injections and using continuous glucose monitoring (CGM). This smartphone application, DailyDose, will recommend changes to insulin doses to the user, such as adjusting the patient's insulin to carbohydrate ratio. The goals of this study are: 1) to assess the impact of physician-driven insulin setting changes. Data gathered from this study will inform how much improvement in time in range can be expected over a 7 day period after an appropriate insulin dose change. This information will be used to power a future study assessing DailyDose (a decision support tool that incorporates diabetes management strategies to minimize hypoglycemia and hyperglycemia, especially after exercise including hypoglycemia the night following exercise) and 2) the collection of paired multiple daily injection data and CGM data in the context of everyday life and with structured exercise sessions. Creation of such a dataset will be extremely valuable for the ongoing development of the recommendation algorithms that function within DailyDose.

The recent commercialization of Inpen, which captures short-acting insulin doses, and the availablility of GoCaps and Clipsulin, FDA-cleared devices, which capture multiple types of insulin doses including from a Lantus Solostar pen, has enabled the conduct of this type of study. The availability of devices such as a FitBit or Apple Watch allows for tracking of activity level. As a component of this study, subjects will wear the FDA-approved Dexcom G5 or G6 CGM system. The CGM values will be accessible via the Dexcom Clarity portal, which will allow study investigators to make insulin dose recommendations. Subjects will also wear an investigational Dexcom G6 sensor that includes a temperature logger that has been developed by Dexcom with the goal of assessing if sensor accuracy can be improved by correcting for changes in temperature. (See Appendix D for letter referencing IDE).

Primary Objective

- The primary objective is to assess if weekly insulin dose changes by the physician increases time in range (Dexcom G5 or G6 CGM 70-180 mg/dL) and decreases time in hypoglycemia (Dexcom G5 or G6 CGM <70 mg/dL).

Study Hypothesis:

- The study hypothesis is that weekly insulin dose changes by the physician will increase time in range and decrease time in hypoglycemia.

Endpoints

Because the main purpose of the study is to refine methods and inform a formal trial, we are interested in point estimates (as an indication of feasibility) and within- and between-subjects variability in the endpoints listed below.

Primary Endpoints:

- Time in range (70-180 mg/dl): measured on Days 1-7 as compared to Days 22-28 based on the Dexcom G5 or G6 CGM data.
- Time in hypoglycemia (<70 mg/dl): measured on Days 1-7 as compared to Days 22-28 based on the Dexcom G5 or G6 CGM data.

*Note that data from Day 1 and Day 28 will not contain 24 hrs of data. The hours will be matched such that if for example if data on Day 1 is available starting at 10 am, data from Day 22 will be taken starting at 10 am. Similarly, if data from Day 28 ends at 5 pm, the data from Day 7 after 5 pm will be excluded to allow for an equal comparison.

Secondary Endpoints:

- Time in significant hypoglycemia (<54 mg/dl): measured on Days 1-7 as compared to Days 22-28 based on the Dexcom G5 or G6 CGM data.
- Mean glucose measured on Days 1-7 as compared to Days 22-28 based on the Dexcom G5 or G6 CGM data.
- Standard deviation of glucose measured on Days 1-7 as compared to Days 22-28 based on the Dexcom G5 or G6 CGM data.
- Additional within-subject time effects in glucose control measures (time in range and time in hypoglycemia): daily variation over the 28 days of study; means for work compared to non-work days; means for days 15-21 vs 1-7; and in the four hours after initiation of exercise.
- Sensor accuracy of the investigational Dexcom G6 sensor: mean absolute difference when reference capillary blood glucose is ≤75 mg/dL and mean absolute relative difference when reference capillary blood glucose is >75 mg/dL.
- Completeness of the investigational Dexcom G6 sensor data: Number, length, and timing of intervals of missing data.
- Sequence effect: Evaluate for a trend in the intervention effect from the first to last subject.

Study Type
This is a single center randomized prospective study comparing time in range and time in hypoglycemia before insulin dosing changes as compared to after three weekly dose adjustments made by the study investigator.

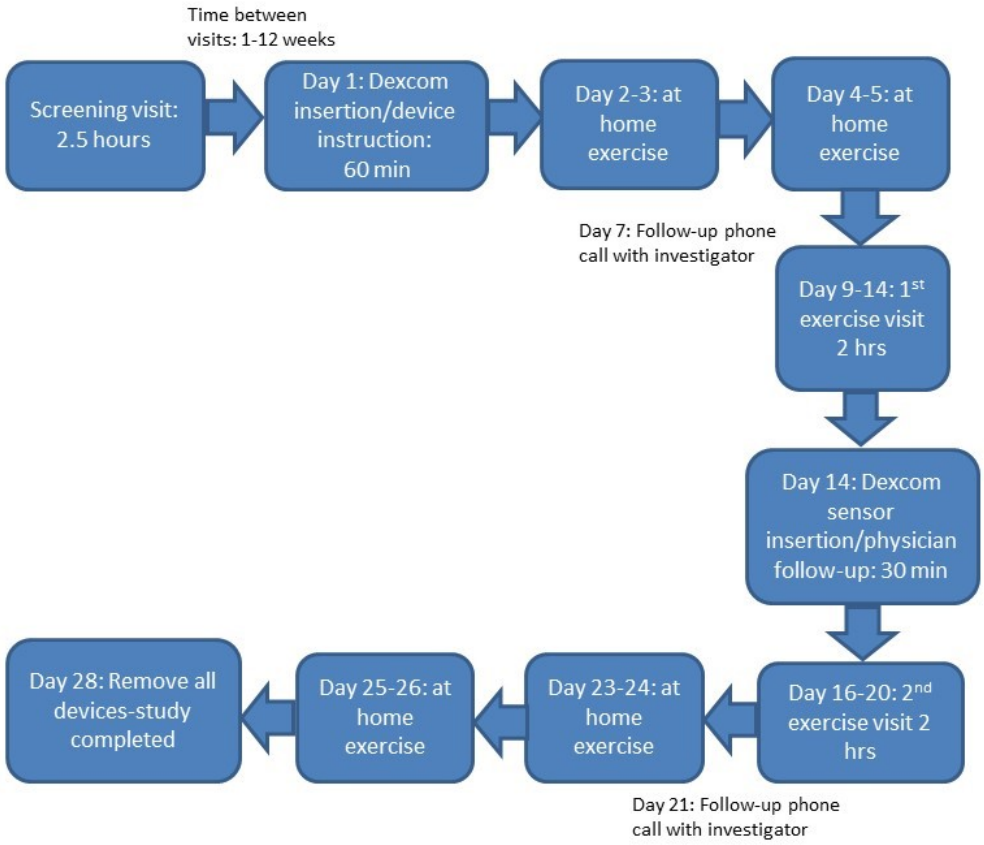
Study Population
Study population will be adults with type 1 diabetes, ages 18 – 50 years of age. Older subjects are excluded due to higher risk of unrecognized coronary artery disease. Younger subjects are excluded as it is appropriate to assess safety and efficacy first in the adult population. Twenty four subjects will be recruited to participate in studies.

Power Analysis
A formal power analysis was not conducted. The purpose of this study is to enable an accurate power analysis for a subsequent study using DailyDose.

Protocol Summary:
Subjects will be on study for 28 days. Sensor glucose, exercise, insulin and meal data will be collected during this time. Subjects will wear the Dexcom G5 or G6 and G6 with temperature logger CGM systems and a FitBit Ionic (or similar FitBit) or Apple Watch physical activity monitor for the entire 28 days. The Dexcom G6 with temperature logger CGM is an investigational device (See Appendix D for letter referencing IDE) and will be inserted on Days 1 and 14. Insulin data will be collected using the InPen for aspart insulin and GoCaps or Clipsulin for the long acting insulin. Subjects will complete 2 exercise visits in-clinic, on Days 9 (window of days 9-14) and 16 (window of days 16-20). Subjects will be asked to exercise an additional 4 times while an outpatient: 1) Days 2 or 3, 2) Days 4 or 5, 3) Days 23 or 24 and 4) Days 25 or 26. Subjects will use the T1 DEXI mobile app created by OHSU to capture photos of meals and document all hypoglycemia treatments over the 28 day period. These images may be fed in later to Bitesnap, an application for food analysis. Subjects will be randomized to aerobic, anaerobic or high intensity interval exercise sessions for 30 minutes each. During the in-clinic exercise visits, subjects will check capillary blood glucose (CBG) before exercise, every 10 minutes during exercise, at the end of exercise and every 15 min for an additional 30 min at the end of exercise. While at home, subjects will check CBG two times daily and before and after exercise, for symptoms of hypoglycemia, and for Dexcom G5 or G6 alarms for sensor <70 mg/dL and >300 mg/dL. Subjects will use the Inpen dose calculator using Dexcom G5/G6 or CBG values to determine aspart insulin doses for meals and correction of hyperglycemia. Physicians will review CGM and insulin data every 7 days and make insulin dose recommendations that the subject will adjust in the Inpen dose calculator. See **Figure 1** below for a diagram of the study flow.

A physician or nurse practitioner will be on campus for all in-clinic exercise sessions. The study investigators retain the authority to modify any aspects of the protocol at his/her discretion if he/she believes the subject's safety is a concern.

Figure 1: Study Flow Design



Subject Criteria

Inclusion Criteria:

1. Diagnosis of type 1 diabetes mellitus for at least 1 year.
2. Male or female subjects 18 to 50 years of age.
3. Physically willing and able to perform 30 min of exercise (as determined by the investigator after reviewing the subject's activity level).
4. Use of multiple daily insulin injections (MDI).
5. A1C ≥7.0% at the time of screening.
6. Willingness to follow all study procedures, including attending all clinic visits.
7. Willingness to sign informed consent and HIPAA documents.

Exclusion Criteria:

1. Female of childbearing potential who is pregnant or intending to become pregnant or breast-feeding, or is not using adequate contraceptive methods. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.

2. Any cardiovascular disease, defined as a clinically significant EKG abnormality at the time of screening or any history of: stroke, heart failure, myocardial infarction, angina pectoris, or coronary arterial bypass graft or angioplasty. Diagnosis of 2nd or 3rd degree heart block or any non-physiological arrhythmia judged by the investigator to be exclusionary.
3. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as reported by the OHSU laboratory).
4. Liver failure, cirrhosis, or any other liver disease that compromises liver function as determined by the investigator.
5. Hematocrit of less than 36% for men, less than 32% for women.
6. History of severe hypoglycemia during the past 12 months prior to screening visit or hypoglycemia unawareness as judged by the investigator. Subjects will complete a hypoglycemia awareness questionnaire. Subjects will be excluded for four or more R responses.
7. Adrenal insufficiency.
8. Any active infection.
9. Known or suspected abuse of alcohol, narcotics, or illicit drugs.
10. Seizure disorder.
11. Active foot ulceration.
12. Peripheral arterial disease.
13. Major surgical operation within 30 days prior to screening.
14. Use of an investigational drug within 30 days prior to screening.
15. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
16. Bleeding disorder or platelet count below 50,000.
17. Allergy to aspart or glargine insulin.
18. Need for uninterrupted treatment of acetaminophen.
19. Current administration of oral or parenteral corticosteroids.
20. Any life threatening disease, including malignant neoplasms and medical history of malignant neoplasms within the past 5 years prior to screening (except basal and squamous cell skin cancer).
21. Beta blockers or non-dihydropyridine calcium channel blockers.
22. Current use of any medication intended to lower glucose other than insulin (ex. use of liraglutide).
23. A positive response to any of the questions from the Physical Activity Readiness Questionnaire with one exception: subject will not be excluded if he/she takes a single blood pressure medication that doesn't impact heart rate and blood pressure is controlled on the medication (blood pressure is less than 140/90 mmHg).
24. Any chest discomfort with physical activity, including pain or pressure, or other types of discomfort.
25. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the subject's safety or compliance with the protocol.

Subject Recruiting:
Subjects will be recruited from OHSU clinics, from flyers to be posted in approved places at OHSU or posted on the web to the clinical trials page for the OHSU Schnitzer Diabetes Clinic, to the Clinic's facebook group, electronic newletter or from the OHSU Subject Recruitment website. Handouts will also be made available to faculty at Providence, Tuality, Kaiser and Legacy to pass along to patients/participants who show interest in the study. Records from OHSU Schnitzer Diabetes Clinic patients may be screened to find potential subjects. Subjects will also be recruited from a list of subjects who participated in past OHSU studies who have agreed to be contacted regarding future studies involving Drs. Castle or El Youssef, from the OHSU diabetes research registry and/or www.clinicaltrials.gov. Non-English speaking subjects will not be recruited since this protocol would require the use of medical devices and mobile software that do not have non-english versions available.

Up to 50 subjects may be screened in this study. Goal enrollment is 24 subjects. Up to four subjects will be replaced if needed, with a total enrollment of up to 28 subjects.

Withdrawal Criteria
The subject may withdraw at will at any time or at the discretion of the Investigator.

A subject must be withdrawn if the following applies:
1. Hypoglycemia during the treatment period posing a safety problem as judged by the investigator.
2. Hyperglycemia during the treatment period posing a safety problem as judged by the investigator.
3. Protocol deviation having influence on efficacy or safety data as judged by the Investigator.
4. Substantial and repeated non-compliance with trial procedures.
5. Pregnancy.
6. Intention of becoming pregnant.

Visit Procedures
Screening (Visit 1)
Screening will take place within 12 weeks prior to the Day 1 investigational Dexcom G6 sensor insertion/exercise visit (Visit 2). All screening visits will take place at OHSU's Oregon Clinical Translational Research Institute (OCTRI) outpatient clinic, the Biomedical Engineering Point of Care (BME POC) Laboratory or at the Harold Schnitzer Diabetes Health Center. The subject will be sent the consent form prior to the screening by email so that they can have time to read it fully at their leisure and prepare any questions they might have. Upon arrival at the clinic and prior to any procedures, study staff will explain the study, give the subject ample time to ask questions and consider participation, and ensure that subject voices understanding of the informed consent and study requirements. To minimize the possibility of coercion and to ensure that subject is signing the appropriate version of consent, an informed consent checklist will be used by study staff. After the subject has signed the consent, a copy of the consent/authorization form will be given to the subject. The original will be kept for the source document.

VO_{2max} testing will take place at the Human Performance Lab, which is located within OHSU and is attached to the main hospital. A code cart is on site within the Human Performance Lab and a code team is available by page at all times. Subjects will be asked to fast before the screening visit for 3 hours. A capillary blood glucose (CBG) will be obtained and measured by a Contour Next glucose meter and recorded after consenting. Prior to measurement of any blood samples, the meter will undergo quality control testing with two different glucose levels, one high and one low, and both values must fall within the accepted range for a meter to be used. After the CBG is obtained, the study investigator may adjust the subject's basal insulin rate as necessary in preparation for VO_{2max} testing to avoid hypoglycemia.

Study personnel will review medical history, and medications. Height, weight, pulse, and blood pressure will be obtained. A study investigator will perform a physical examination, excluding breast and pelvic exams. Females of child-bearing potential will take a urine pregnancy test, which must be negative to participate. A venous blood sample will be taken for the following tests: hemoglobin A1C, complete blood count, complete metabolic set (including creatinine, liver set, and electrolytes. If subjects have had any of the aforementioned labs performed within the 3 months prior to the screening visit and we can access the results, a venous blood sample will not be taken for that test. An EKG will be completed. A study investigator will assess inclusion/exclusion criteria and review the subject's medical record for clarification as needed. A three-digit subject ID number will be assigned to the subject.

Subjects will undergo VO_{2max} testing at the end of the screening visit if all inclusion criteria are met and no exclusion criteria are met, with the exception of blood test results which will not be immediately available. A study investigator will be present for the entire VO_{2max} testing procedure. Additional CBG samples will be taken immediately before and after completion of the VO_{2max} test. Subjects will be given juice and the VO_{2max} test will either be delayed by approximately 1 hour for CBG values of <80 mg/dL, or rescheduled for a different day. Subjects will be given 15-20 grams of carbohydrates for CBG values of <70 mg/dL at any point during the screening visit. CBG values will be reviewed by an investigator and subjects will be provided with a snack after VO_{2max} testing as needed to avoid post-testing hypoglycemia. Subjects that screen fail by meeting any of the exclusion criteria prior to proceeding to the VO_{2max} test will not complete the VO_{2max} test. The VO_{2max} test can be completed at a separate visit after the initial screening visit but before the Dexcom G6 sensor insertion if needed to accommodate the subject's schedule. This visit will take approximately 2.5 hours.

Dexcom G6 Sensor Insertion Visits:
Dexcom G6 sensor insertion visits will be on Days 1 and 14. After arrival at the OHSU OCTRI outpatient clinic, the Biomedical Engineering Point of Care (BME POC) Laboratory or Harold Schnitzer Diabetes Health Center clinic, women of childbearing potential will receive a urine pregnancy test if the last pregnancy test performed was more than 7 days prior. This test must be negative before further participation is allowed. This visit will take approximately 30 minutes.

Subjects will have two glucose sensors inserted at this visit, a commercial G5 or G6 glucose sensor and an investigational G6 with temperature logger sensor. Subjects will receive training on how to insert the commercial Dexcom G5 or G6 system according to the manufacturer's directions. Subjects will be instructed how to connect the transmitter to the Dexcom app on an

iPhone that will be returned at the end of the study. Subjects will be instructed how to calibrate and change out the sensor according to the manufacturer's directions. If subjects are given a Dexcom G5, they will be asked to calibrate the sensor every 12 hours and the change out the sensor at home every 7 days. If subjects are given a Dexcom G6, they will only enter two start-up calibrations and change out every 10 days while at home. Subjects will be asked to replace the commercial sensors if they fail or become dislodged. Trained study personnel or a Dexcom representative will insert the G6 with temperature logger after appropriate preparation of the abdominal skin as per the manufacturer's directions. An adhesive overlay may be placed over G5 and/or G6 sensors to prevent dislodgement. The subjects will not be able to view the Dexcom G6 with temperature logger sensor values. The wire glucose sensors are sterile and will be used for single use only as directed by the manufacturer.

The G5/G6 CGM alerts will be set at 70 mg/dL and 300 mg/dL. Subjects will be given a Contour Next meter for measuring their capillary blood glucose in order to calibrate the Dexcom CGM system. Subjects will be instructed to check a CBG for symptoms of hypoglycemia and for CGM alarms indicating sensed glucose is less than 70 mg/dL. Subjects will be instructed to discontinue the use of acetaminophen for all periods when wearing the Dexcom G5 sensor. Subjects will be asked to collect the time, date and location of all G6 sensor insertions while at home.

For the first sensor insertion visit on Day 1, subjects will be given a FitBit or Apple Watch to wear. Subjects will also be provided with Novolog cartridges for use in the Inpen and Lantus Solostar or Tresiba insulin pens for Days 1-28. Subjects will use the Inpen smartphone application to calculate insulin doses based on their usual insulin carbohydrate and correction factor ratios. These ratios will be entered in to the Inpen application by the study investigator at the time of the first study visit. If a subject was using Humalog or Apidra insulin prior to the study, the insulin doses will generally be kept the same given these short-acting insulin formulations are equivalent to Novolog. The investigator will review the patient's current long acting insulin and their medical history to determine if the subject should use Tresiba or Lantus during the study. Subjects will use GoCaps or Clipsulin to track their long acting insulin dose. If subjects are switching their long-acting insulin, the investigator will review the insulin dose with the subject and determine an appropriate dose of Lantus or Tresiba.

Subjects will be instructed on the use of these devices along with the mobile app T1 DEXI. Meals and exercise can be scheduled for specific times each week within the app. The app will alert the user with pre- and post meal reminders on the day of and the day after exercise. Subjects will be instructed to take a picture of their meals using the T1 DEXI app every day for the 28 days and to record all carbohydrate treatments for hypoglycemia. A dietician or dietetic student will review the meal photos to determine meal content. Study staff may contact subjects by phone, text, or email for clarification if the meal photo is difficult to interpret. User Guides for all devices will be sent home with subjects, including for the T1 DEXI app. Subjects will be able to contact study staff for any issues with the devices. This instruction on Day 1 should take an additional 30 minutes.

For the second sensor insertion visit on Day 14, study staff can insert the new G6 with temperature logger sensor before staff removes the previous G6 sensor to facilitate a quicker discharge. The sensor site will be inspected for signs of irritation or infection. In addition, the

sensor will be inspected for the possibility of breakage or fracture. If there is any evidence of sensor breakage, it will be recorded. If an area of inflammation of 1 cm or greater exists around the point of insertion, a de-identified photograph will be taken of the area and the subject will return 1-3 days later for a follow-up visit.

Data Collection

In this study, we will be collecting de-identified physiologic data from people with type 1 diabetes. The following data will be collected from participants in this study:

- Glucose sensor data (Dexcom G5/G6)
- Short-acting insulin injected into the body with an InPen wireless smart insulin pen.
- Long-acting insulin injected into the body with a GoCaps or Clipsulin wireless smart insulin pen.
- Physical activity data collected with a FitBit Ionic or Apple Watch watch. This fitness data will include the following:
    - Heart rate
    - Step count
    - Metabolic expenditure
    - Sleep
    - Activity types (e.g. running, jogging, etc).
- Self-report food and exercise data logged by the participant

To collect the data, each participant in the study will be given an Apple iPhone. The iPhone will have the following apps that will be used to collect data.

- A Dexcom commercial app will collect data from the Dexcom G5/G6 glucose sensor.
- A Companion InPen commercial app will collect data from the short-acting insulin InPen.
- A GoCaps commercial app will collect data from the GoCaps long-acting insulin pen.
- A Clipsulin commercial app will collect data from the Clipsulin insulin pen.
- The FitBit commercial app will collect data from the FitBit Ionic.
- The Apple Watch will collect data from Apple HealthKit.
- A custom app developed by OHSU called T1-Dexi will also be installed on the iPhone. The T1-Dexi app has undergone a security review by OHSU IT and the results of this can be provided upon request.

The T1-Dexi app will serve as the 'data aggregator' on the phone and will perform the following functions:

- T1-Dexi app will collect self-report meals and exercise data from the participants both as text / categorical selections and also as food photographs collected from the camera on the phone.
- T1-Dexi app will aggregate all of the data collected from the glucose sensor, insulin pens, activity tracker, and self-logged food and exercise data to be stored as de-identified data within the iCloud storage area of the phone. The data stored within iCloud is de-identified and does not contain any information from the 18 HIPAA designations of personally identifiable information. ITG has granted an Exception approval for using and storing data on the iCloud. Data stored on the iCloud will be deleted once the study is complete.

We plan to install the OHSU AirWatch Agent / Container on the iPhones. Upon enrollment, subjects will be assigned with a three-digit code that will be used instead of their name, medical record number or other personally identifying information. The key associating the code and the subjects personnal identifying information will be restricted to the PI and study staff. The key will be encrypted and kept secure on a restricted OHSU network drive in a limited access folder. The iPhones will be registered to the study participants' unique study ID number and all of the data stored on the iPhone will be associated with this ID.

Two In-Clinic Exercise Visits:

The in-clinic exercise visits will be conducted in the Harold Schnitzer Diabetes Health Center, the Biomedical Engineering Point of Care (BME POC) Laboratory or the OCTRI outpatient research unit. After arrival at the clinic, women of childbearing potential will receive a urine pregnancy test if the last pregnancy test performed was more than 7 days prior. This test must be negative before further participation is allowed. A code cart is on site at all locations and a code team is available by page at all times. The exercise visits will be on Days 9 (window of days 9-14) and 16 (window of days 16-20). The subject will be asked to check his/her CBG before driving to the clinic and to bring a snack in the car in case hypoglycemia does occur (in which case, the subject must park and treat the hypoglycemia).

Subjects will be randomized to either aerobic, anaerobic or high intensity interval exercise sessions. Exercise sessions will be approximately 2 hours. A 30 minute exercise video will be provided for the subjects to follow along with. A list of exercises to be performed is provided in Appendix E. Subjects will be given a Polar heart rate strap to wear during the in-clinic exercise. A capillary blood glucose (CBG) will be obtained and measured by the Contour Next glucose meter given to the subject. For subject safety, CBG must be 80 mg/dl or higher to begin exercise. Subjects will be given 15 grams of carbohydate (such as 4 oz of juice) for values <120 mg/dL at the start of exercise or for values of <70 mg/dL at any point after the start of exercise. For subjects who require carbohydrate treatment for values < 70 mg/dl, a CBG will be repeated in 15 minutes and exercise will be resumed once CBG is 70 mg/dL or higher. A study investigator will be contacted if CBG >250 mg/dL to determine if the subject requires a dose of short-acting insulin and serum ketones will be checked by the Precision Xtra blood ketone meter. The exercise visit will be cancelled if ketones are greater than 0.6 mmol/L. The subject will be discharged with a bottle of water along with instructions from the investigator for checking glucose at home. Subjects will be taken to the emergency room for ketone levels > 3.0 mmol/L. The PEAK recommendations, guidelines from a collaboration of researchers through the Juvenile Diabetes Research Foundation (JDRF) for exercising with Type 1 diabetes, specify that it is safe to exercise if ketones are below this threshold [1]. Oral temperature will be taken with a thermometer just before and at the end of exercise and recorded. During exercise visits, for comparison with the CGM readings, CBG will be checked before exercise, every 10 minutes during exercise, at the end of exercise and every 15 minutes for an additional 30 minutes at the end of exercise.

During the exercise period, there will be defined rules for stopping exercise, including:

1) If the subject feels unwell,

2) If the subject develops hypoglycemic symptoms, such as excessive sweating, shaking/tremors, palpitations, feelings of dread or panic, light-headedness, nausea, difficulty concentrating or the like,
3) If the subject develops chest pain/pressure,
4) If the subject develops undue shortness of breath (SOB),
5) Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin
6) For patient preference.

At-home Study Exercise Sessions:
Subjects will be asked to complete four at-home exercise sessions consistent with the assigned type of exercise, on Days 2 or 3, Days 4 or 5, Days 23 or 24 and Days 25 or 26. Instructions for the exercise will be provided via video links and will be the same set as instructions for the in-clinic visits (see Appendix E). Subjects will be instructed to check a CBG before initiating exercise to ensure safety. Subjects will be instructed to consume a snack if glucose is <120 mg/dL and delay exercise until glucose is >80 mg/dL. Also, if glucose is >250 mg/dL, subjects will be instructed to use the InPen app to calculate if a correction dose is needed and delay exercise until glucose is <250 mg/dL. Subjects will enter information about exercise into the T1 DEXI app. Subjects will receive reminders via phone or text to complete their exercise and to monitor adherence to protocol. Participants may also receive reminders to enter activity information through the T1DEXI app. Subjects will also be instructed to check a CBG after exercise and consume a snack if needed.

Study Investigator review of CGM data:
The study investigator will review the subject's insulin and CGM data online approximately every 7 days (Days 7, 14, and 21) and make insulin dose recommendations by phone. Subjects will confirm the settings were changed appropriately by taking a screen shot of the change and sending the picture to a study phone. The study investigator will make a note of why any changes were made.

Day 28 Study Completion visit:
At this visit, the insulin pens and other devices will be turned in for download. The subject's weight will be collected at this visit. The study investigator will consult with the subject regarding appropriate insulin dosing for the remainder of the day. The FitBit or Apple Watch and Dexcom sensor(s) will be removed from the subject. The sensor site will be inspected for signs of irritation or infection. In addition, the sensor will be inspected for the possibility of breakage or fracture. If there is any evidence of sensor breakage, it will be recorded. If an area of inflammation of 1 cm or greater exists around the point of insertion, a de-identified photograph will be taken of the area and the subject will return 1-3 days later for a follow-up visit. A capillary blood glucose value will be taken immediately prior to discharging the subject. Subjects will be given oral carbohydrate for values below 85 mg/dl, and will be instructed to give an injection of aspart insulin if deemed appropriate by the study investigator for values above 150 mg/dl.

If a study visit is stopped prematurely the subject will be asked if they can repeat the study visit that was terminated early with additional compensation provided. Repeating the study visit will be optional.

Cleaning and Disinfecting
All devices will be cleaned and disinfected between subjects. The smart phone, Dexcom G5 and G6 transmitters and FitBit or Apple Watch will be cleaned by study staff. Technicians who are disinfecting units will wash hands thoroughly and wear gloves. All items will undergo intermediate-level disinfection using SANI-CLOTH AF3 Germicidal disposable wipes. The disinfectant will be applied and allowed to air dry. After disinfection, when the units are completely dry, they will be placed in a sealed bag labeled with subject information.

Statistical methods
Data will be analyzed using generalized estimating equations, which takes into account correlated data and repeated measures. Data will be analyzed using an intention-to-treat analysis and missing sensed glucose values will be interpolated for up to 20 min segments.

Confidentiality and Protection of Human Subjects

RISKS and BENEFITS

Risks: The risks of the protocol procedures are considered minor. Subjects will be managing their own blood glucose as they normally would with recommendations for insulin dosing from the study investigator. A study investigator will be on campus during all exercise visits.

Risks from exercise include falls, sprains, bruises, very low risk of bone fractures and head trauma. The likelihood of significant harm is quite low.

Rarely, there can be allergic responses to insulin such as skin redness, hives, itching of the skin, swelling of the mouth, or breathing difficulties. These reactions are considered very unlikely.

There is a small risk of sensor fracture, and in such a case, a piece of the sensor could be left in the tissue after sensor removal. For this reason, the study investigator will inspect each removed sensor for the possibility of breakage or fracture. Any evidence of sensor breakage will be recorded and reported to FDA and the sensor company.

Benefits: The subject may not directly benefit from being in this study; however, their participation may help to advance automated insulin decision support software.

COSTS:
Subjects will receive $700 for completion of all study visits. If subjects withdraw early from the study, compensation will be given as follows: $175 per 7 study days in the study. If the subject completes a partial week, the subject will also receive $175 for the partial week. There is no compensation for the screening visit. If a subject is asked to repeat an in-clinic exercise study visit due to technical problems, he/she will receive an additional $75.

Monitoring Entity:

This investigation will be monitored by the principal investigators, Jessica Castle, MD and Peter Jacobs, PhD. Drs. Jacobs and Castle have no commercial interest in any of the companies which manufacture any of the devices used in this study.

Data Collection:

Subject privacy will be protected by using a three-digit identifying number to code study documents. Study staff will record data required by the protocol onto the Case Report Forms (CRF). Case report forms (CRF) for this study will be entered into REDCAP, a clinical research electronic data application designed to support traditional case report form data capture for research studies housed at Oregon Health Science University and administered by the Oregon Clinical and Translation Research Institute (OCTRI). Investigators and research coordinator will verify that the procedures are conducted according to the approved protocol. All paper source documents will be kept in a locked cabinet for a minimum of five years. Original, completed CRF's will be kept with the PI in a designated repository. All data from CRF's will subsequently be entered into the authorized electronic REDCAP database.

Recording of Data:

Investigators and staff will record data collected during the clinical trial on the CRF's. Case report forms (CRF) for this study will be entered into REDCAP, a clinical research electronic data repository housed at Oregon Health Science University and administered by the Oregon Clinical and Translation Research Institute (OCTRI). The REDCAP CRFs will include:

1. Screening form
2. G6 and Device Training visit
3. G6 Sensor Insertion visit
4. Exercise Visit
5. Physician Follow-up
6. Study Completion visit
7. Adverse Event form
8. Serious Adverse Event form
9. Concomitant Medications

The Principal Investigators may authorize other personnel to make entries in the CRF.

The de-identified data collected during this study will be used for analysis of the primary and secondary endpoints listed in this protocol. This data will also be stored in the OregonAPC repository according to IRB protocol 19858. During screening, participants may sign the consent form to store their study data in the data repository. The data to be collected includes: 1) glucose sensor data, 2) blood glucose data, 3) insulin and data, 4) physical activity data, and 5) food and exercise data. All data, except for blood glucose, is aggregated by the DEXI app. The blood glucose data is collected through downloading the Contour Next BG meters and exporting data as an excel file. There are no biological specimens collected during this study.

Monitoring Procedures:

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and amendments and clarifications adopted by the 29th (Tokyo, 1975), 35th (Venice, 1983), 41st (Hong Kong, 1989), 48th (Somerset West, South Africa, 1996), 52nd (Edinburgh, 2000), 53rd (Washington, 2002), 55th (Tokyo, 2004), 59th (Seoul, 2008), and 64th (Brazil, 2013) General Assemblies. The investigator will ensure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IEC requirements relative to clinical studies.

Should a conflict arise, the investigator will follow whichever law or guideline affords the greater protection to the individual subject. The investigator will also ensure thorough familiarity with the appropriate use and potential risks of use of the study device, as described in this protocol, prior to the initiation of the study.

Unanticipated problems will be detected by reviewing descriptions of known or foreseeable adverse events and risks in the IRB-approved research protocol and the current IRB approved consent form, any underlying disease or conditions of the subject experiencing the adverse event, a careful assessment of whether the adverse event is related or possibly related to the subject's participation in the study.

Triggers for reporting unanticipated problems are seizure, hospitalization, death or any other occurrence considered serious by the PI. If ongoing monitoring of the closed-loop studies reveals studies repeatedly being terminated because of unresponsive hyperglycemia or repeated serious hypoglycemia (resulting in altered mental status, loss of consciousness, or seizure) believed not amenable to revisions in control system parameter tuning, then the study will be discontinued immediately. If studies in two subjects are stopped for severe hypoglycemia or severe hyperglycemia, then the entire study will be halted. In addition, if there is any unexpected event such as death or patient hospitalization, the studies will be stopped until the root cause is evaluated.

Any adverse event (AE) and/or unanticipated problem (UP) will be reported to the investigator monitor immediately by one of the investigators. Hypo- and hyperglycemia will not be considered AEs unless subject has positive ketones or displays symptoms of hypoglycemia such as: loss of consciousness, slurred speech, hospitalization or EMS services called. One of the investigators will always be on-call during the closed-loop studies and will write up a description of the adverse event/unanticipated problem. All reportable new information (RNI) will be reported to the IRB within five calendar days after the PI learns of the event. RNI is any information that might meet the regulatory definition of an unanticipated problem involving risks to subjects or others or serious or continuing noncompliance that might impact the criteria for IRB approval. The report will be submitted to the IRB by the principal investigator or study coordinator. A summary of all UP's and adverse events, including those that do not meet the requirement for RNI, will be submitted with the continuing review.

Confidentiality Procedures:

To protect confidentiality, standard institutional practices will be followed as described in the OHSU Information Security and Research Data Resource Guide (http://ozone.ohsu.edu/cc/sec/isg/res_sec.pdf) to maintain the confidentiality and security of data collected in this study. Study staff will be trained regarding these procedures. See IRB protocol 19858 for a complete description of the confidentiality and security of the study data collected during this study to be stored in the OregonAPC repository. Paper files will be stored in locked filing cabinets in restricted access offices at OHSU. After the study, source documents will be maintained at the participating clinical center (or offsite record storage facilities) 2 years after a marketing application is approved for our group's decision support device or discontinuance of pursuit of marketing approval.

Appendix A: Physical Activity Readiness Questionnaire

Physical Activity Readiness Questionnaire (PAR-Q) and You

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly:

YES	NO		
☐	☐	1.	Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2.	Do you feel pain in your chest when you do physical activity?
☐	☐	3.	In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7.	Do you know of any other reason why you should not do physical activity?

If you answered:

YES to one or more questions

Talk to your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want – as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- Start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- Take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.

Delay becoming much more active:

- If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- If you are or may be pregnant – talk to your doctor before you start becoming more active.

Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

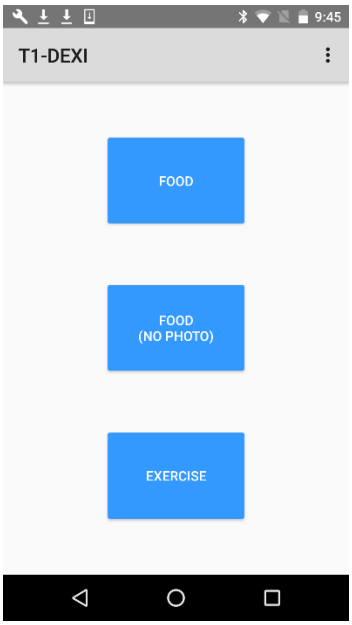
Informed use of the PAR-Q: Reprinted from ACSM's Health/Fitness Facility Standards and Guidelines, 1997 by American College of Sports Medicine

Appendix B: Devices
FitBit

Apple Watch

Dexcom G6 Continuous Glucose Monitoring System which includes Sensor and Sensor Transmitter

iPhone Smart phone with T1 DEXI app



Contour Next Blood Glucose Meter

Appendix C: Hypoglycemia Awareness questionnaire:This survey item will be used to categorize awareness or having reduced awareness of hypoglycemia.

1. Check the category that best describes you: (check one only)

- ☐ I always have symptoms when my blood sugar is low (A)
- ☐ I sometimes have symptoms when my blood sugar is low (R)
- ☐ I no longer have symptoms when my blood sugar is low (R)

2. Have you lost some of the symptoms that used to occur when your blood sugar was low?

- ☐ Yes (R)
- ☐ No (A)

3. In the past 6 months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself).

- ☐ Never (A)
- ☐ Once or twice (R)
- ☐ Every other month (R)
- ☐ Once a month (R)
- ☐ More than once a month (R)

4. In the past year, how often have you had severe hypoglycemia episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose?)

- ☐ Never (A)
- ☐ 1 time (R)
- ☐ 2 times (R)
- ☐ 3 times (R)
- ☐ 4 times (R)
- ☐ 5 times (R)
- ☐ 6 times (R)
- ☐ 7 times (R)
- ☐ 8 times (R)
- ☐ 9 times (R)
- ☐ 10 times (R)

- 11 times (R)
- 12 or more times (R)

5. How often in the last month have you had readings < 70 mg/dl with symptoms?

- Never
- 1 to 3 times
- 1 time/week
- 2 to 3 times/week
- 4 to 5 times/week
- Almost daily

6. How often in the last month have you had readings < 70 mgdl, without symptoms? R: 5<6, A: 6<5;

- Never
- 1 to 3 times
- 1 time/week
- 2 to 3 times/week
- 4 to 5 times/week
- Almost daily

7. How low does your blood sugar need to go before you feel symptoms?

- 60-69 mg/dl (A)
- 50-59 mg/dl (A)
- 40-49 mg/dl (R)
- < 40 mg/dl (R)

8. To what extent can you tell by your symptoms that your blood sugar is low?

- Never (R)
- Rarely (R)
- Sometimes (R)
- Often (A)

Appendix D: Letter of Authorization Dexcom

dexcom
One Step Ahead

6340 Sequence Drive
San Diego, CA 92121
1-858-203-6362
Fax 1-858-332-0204
www.dexcom.com

December 8, 2017

Jessica Castle MD
Oregon Health and Science University
3181 SW Sam Jackson Park Rd
MC: OP 05-DC
Portland, OR 97239
+1 (503) 494-7072
castleje@ohsu.edu

Subject: Evaluation of physician-based decision support in patients with type 1 diabetes on multiple daily injection therapy
Device(s): Dexcom G6 Continuous Glucose Monitoring System: G160069
Dexcom G5 Continuous Glucose Monitoring System: P120005/S033

To Whom It May Concern:

Dexcom, Inc. grants right of authorization for the Oregon Health and Science University to reference the following IDE and PMA supplement to serve as a master file for relevant documents. All information within the IDE is considered confidential.

Trade Name:	Dexcom G6 Continuous Glucose Monitoring System; Dexcom G5 Continuous glucose Monitoring System
Classification Name:	Sensor, Glucose, Invasive, Non-Adjunctive
Applicant:	Dexcom, Inc.
IDE/PMA Number:	G160069, P120005/S033
Product Code:	PQF

This authorization is in support of the Oregon Health and Science University's study, Evaluation of physician-based decision support in patients with type 1 diabetes on multiple daily injection therapy.

If you have any questions regarding this letter of authorization, please do not hesitate to contact me at 858.203.6362, or by e-mail at neeta.sharma@dexcom.com.

Respectfully,

Neeta Sharma
Vice President, Regulatory Affairs

Appendix E: Exercise Video Outlines

Aerobic Exercise Video Outline		
Segment	**Segment Time**	**Activities**
Warm-Up Intro (2 min)	**0:00 – 2:00**	**0:00: Welcome!** **0:15: Side to Side kick Back** **0:30: Side to Side Kick Back Pull Back** **0:45: Side to Side Reach Out** **1:00: Side to Side Reach Up** **1:15: Side to Side Reach Out** **1:30: Side to Side Pull Back** **1:45: Side to Side Kick Back**
Active Exercise **(30 min)**	**Each activity is performed for 45 seconds, followed by a 15 second instructional transition to the next activity**	**1. Low Kick** **2. Step back** **3. Heal Step** **4. Knee Raise** **5. Half Squat to Reach** **6. Side to Side Knee Raise Left (crunch)** **7. Side to Side Knee Raise Right (crunch)** **8. Knee to Elbow alternate** **9. Left Jab (left foot forward)** **10. Right Jab (left foot forward) Foundation** **11. Left Right Left Right Jab Side Roll Right (left foot forward) variation 1** **12. Left Right Left Right Jab Squat Squat (left foot forward) variation 2** **13. Left Right Left Right Jab Knee Knee (left foot forward) variation 3** **14. Left Right Left Right Jab Roll Knee (left foot forward) variation 4** **15. Right Left Right Left Jab (right foot forward) foundation** **16. Right Left Right Left Jab Roll Left (right foot forward) variation 1** **17. Right Left Right Left Jab Squat Squat (right foot forward) variation 2** **18. Right Left Right Left Jab Knee (right foot forward) variation 3**

		19. Right Left Right Left Jab Roll Knee (right foot forward) variation 4 **20. Hook, Hook, Upper Cut Upper Cut (left foot forward)** **21. Hook, Hook, Upper Cut Upper Cut (right foot forward)** **22. Squat to Upper Cut (left foot forward)** **23. Squat to Upper Cut (right foot forward)** **24. Left Right Left Right Knee Kick (left foot forward)** **25. Right Left Right Left Knee Kick (right foot forward)** **26. Forward Step Jab and Cross Step Back (left foot forward)** **27. Forward Step Jab and Cross Step Back (right foot forward)** **28. Horse Stance Overhead Reach Side Bend/ Standing Alternating Side Bend** **29. Cool Down (side to side kick back/pull back etc.)** **30. Cool Down (side to side kick back/reach up etc.)**

Intermittent High-Intensity Interval Exercise Video Outline		
Segment	**Segment Time**	**Activities**
Warm-Up Intro (2 min)	**0:00 – 2:00**	**0:00: Welcome!** **0:15: Side to Side Kick Back** **0:30: Side to Side Kick Back Pull Back** **0:45: Side to Side Reach Out** **1:00: Side to Side Reach Up** **1:15: Side to Side Reach Out** **1:30: Side to Side Pull Back** **1:45: Side to Side Kick Back**

Active Exercise (30 min)	**Each activity is performed for 40 seconds, followed by a 80 second cool down**	1. **Jumping Jacks – 40 secs high intensity** 2. **Jogging in place and then side-to-side kickbacks followed by pullbacks all at a light intensity -80 seconds** 3. **Forward Jumping Jacks – 40 sec high intensity** 4. **Jogging in place and then side-to-side kickbacks followed by pullbacks all at a light intensity -80 seconds** 5. **Squat to Upper Cut Fast – 40 sec high intensity** 6. **Jogging in place and then side-to-side kickbacks followed by pullbacks all at a light intensity -80 seconds** 7. **Power Jumping Jacks – 40 seconds high intensity** 8. **Jogging in place and then side-to-side kickbacks followed by pullbacks all at a light intensity- 80 seconds** 9. **Inchworm– 40 seconds** 10. **high intensity Jogging in place and then side-to-side kickbacks followed by pullbacks all at a light intensity- 80 seconds** 11. **High Knee Sprint – 40 seconds high intensity** 12. **Jogging in place and then side-to-side kickbacks followed by pullbacks all at a light intensity- 80 seconds** 13. **Quick Feet – 40 seconds high intensity** 14. **Jogging in place and then kick back/pull backs-all at a light intensity- 80 seconds** 15. **Mountain Climbers- 40 seconds high intensity** 16. **Stand up jog out and then kick back/pull backs all at a light intensity- 80 seconds** 17. **Bicycle Kicks – 40 seconds high intensity Jogging in place and then kick back/pull backs all at a light intensity -80 seconds** 18. **Push Ups – 40 seconds high intensity** 19. **Stand up jog out and then kick back/pull backs all at a light intensity- -80 seconds** 20. **Final cool down (2 min)**

Resistance Exercise Video Outline		
Segment	**Segment Time**	**Activities**
Warm-Up Intro (2 min)	**0:00 – 2:00**	**0:00: Welcome!** **0:15: Marching** **0:30: Marching arm circles** **0:45: Marching reach out** **1:00: Side to side reach out** **1:15: Butt kick reach out** **1:30: Heel dig** **1:45: Chest squeeze**
Active Exercise (28 min)	**Each activity is performed at a controlled pace in good form. Aiming for about 2 seconds to pull the weight the entire range, holding for 1 second, then controlling the return of the movement in about another 1 seconds.**	**Set 1: (approximately 8 min) Upper Body** **Resistance band bicep curl 3 x 8** **Resistance band high row 3 x 8** **Resistance band bent over row 3 x 8** **Resistance band side lateral shoulder raise 3 x 8** **Set 2: (approximately 10 min) Lower Body** **Resistance band calf raise 3 x 8** **Resistance band reverse lunge 3 x 8** **Resistance band squat 3 x 8** **Resistance band deadlift 3 x 8** **Set 3: (approximately 10 min) Total Body and Abs** **Resistance band side lunge to single arm side lateral raise 3 x 8/side** **Resistance band standing abdominal (ab) twist 3 x 8/side** **Resistance band bird dog 3 x 8** **Resistance band reverse crunch 3 x 8**

References

1. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, Kowalski A, Rabasa-Lhoret R, McCrimmon RJ, Hume C, Annan F. Exercise management in type 1 diabetes: a consensus statement. The lancet Diabetes & endocrinology. 2017 May 1;5(5):377-90.