Type 1 Diabetes EXercise Initiative: The Effect of Exercise on Glycemic Control in Type 1 Diabetes Study

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AID	Automated Insulin Delivery
CGM	Continuous Glucose Monitor
DKA	Diabetic Ketoacidosis
EDA	Electrodermal Activity
EKG	Electrocardiogram
GCP	Good Clinical Practice
MDI	Multiple Daily Injections
T1D	Type 1 Diabetes

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Type 1 Diabetes EXercise Initiative: The Effect of Exercise on Glycemic Control in Type 1 Diabetes Study
Précis	Understanding of the effects of different levels of exercise intensity and duration on glycemic control during and after exercise
Objectives	This study is designed to create an aggregated dataset including exercise, CGM and other relevant data inputs which can be used to better understand glucose response to exercise to assist in the development of management strategies.
Study Design	Observational study, conducted remotely outside of clinics, designed to create an aggregated dataset which includes exercise, CGM and other relevant data inputs that are thought to impact glycemia in those living with type 1 diabetes.
Number of Sites	N/A
Population	**Inclusion Criteria:** 1. Age ≥18 – <71 years 2. Clinical diagnosis of presumed autoimmune T1D 3. Duration of T1D ≥2 years 4. Following intensive insulin therapy regimen defined as basal-bolus delivery via an insulin pump or multiple daily injections (MDI) with no major changes in the past 3 months and no major changes (e.g., pump initiation) planned during the time of study participation. • *Users of commercially available (FDA approved) closed loop systems are eligible* • *Pump users who also regularly use insulin injections are not eligible* • *Animas pump users are not eligible* • *MDI users who administer insulin through a syringe and vial are eligible* • *MDI users must be willing to use a device provided by the study that records the injection dosages and/or enter insulin dosing information through an app* 5. Commercial Dexcom G6 CGM use on a regular basis (at least 21 out of the last 28 days) or willing to use a Dexcom G6 CGM. A blinded CGM will be provided, if not using a personal Dexcom CGM. 6. Uses either an Android or iOS smartphone that is compatible with app requirements 7. Access to a compatible computer with internet 8. Able to obtain medical clearance for exercise from a licensed health care provider, if required 9. Have had an eye exam in the last year if diabetes duration is 5 to less than 10 years and participant is ≥50 years old or if diabetes duration is 10 or more years. Have had an eye exam in the last 2 years if diabetes duration is 5 to less than 10 years and participant is <50 years old. 10. Willing to adhere to the protocol requirements, which include a minimum goal of 150 minutes of exercise per week, for the duration of the study 11. Participant is a resident of United States and plans to reside in the U.S. for the duration of the study • *This requirement is due to shipping limitations, U.S. use restrictions for some study software and devices, and GDPR regulations.* 12. Participant comprehends written and spoken English

PARTICIPANT AREA	DESCRIPTION
	• *This requirement is due to the fact that the study materials (app and exercise videos) will not be available in other languages* **Exclusion Criteria:** 1. Females: pregnant or intending to become pregnant during the study • *A urine pregnancy test is not required for the study.* 2. Uncontrolled hypertension, defined by blood pressure >160 systolic or >100 diastolic 3. Known stage 3 or higher chronic kidney disease (i.e., eGFR <45) 4. History of coronary artery disease, history of cardiovascular autonomic neuropathy, or abnormal electrocardiogram (EKG) considered to be a contraindication to increased exercise (EKG will be obtained if not available from the prior 12 months for all participants who are either ≥50 years old or have a ≥20-year duration of diabetes) 5. Use of a pacemaker or an electronic device that is implanted for a medical need 6. Two or more severe hypoglycemic events in the past 12 months (as defined by an episode that required third party assistance for treatment) 7. Known active, untreated proliferative diabetic retinopathy that could potentially be worsened by exercise protocol 8. Musculoskeletal injuries, foot ulcers, or peripheral neuropathy that would be considered a contraindication to exercise 9. Pain on exertion or physical exercise that would be considered a contraindication to exercise 10. Use of Afrezza or non-insulin anti-diabetic medications including SGLT2 inhibitors, GLP-1 agonists, and amylin (unless the drug will be discontinued during the time of study participation) • *Participants using a stable dose of metformin are eligible.* 11. Use of oral beta-blockers 12. Use of oral glucocorticoids 13. Use of atypical antipsychotic agents (i.e., Olanzapine, Aripiprazole) 14. Use of systemic progestin-only contraceptives 15. Regular use of agents that affect hepatic glucose production such as beta adrenergic agonists and xanthine derivatives; occasional use is not prohibited 16. Participation in other studies involving administration of an investigational drug or device within 30 days or 5 half-lives, whichever is longer, before screening for the current study or planning to participate in another such study during participation in the current study 17. Planning to make an extreme change in current diet during the study 18. Known allergy to nickel or other metal if contraindication to physical activity wearable use
Sample Size	Enrollment will proceed with the goal of at least 600 participants completing the study
Groups	Random assignment stratified by insulin administration method (current pump vs. closed loop vs. injection user), age group, and sex to one type of study exercise: aerobic exercise, resistance circuit exercise, or intermittent high-intensity interval exercise
Participant Duration	Approximately 4 weeks from the start of the exercise period
Protocol Overview/Synopsis	Participants will use physical activity wearable(s). The T1-DEXI app will be used to enter information related to an exercise event and data related to food intake. Food photos will be submitted through the app on the day of and day following study exercise. Information related to insulin use, sleep, stress and illness may also be collected through the app.

PARTICIPANT AREA	DESCRIPTION
	All participants will use the Dexcom G6 CGM for the study. Current Dexcom G6 users will continue to use their personal CGM throughout the study. If the participant is currently using a Dexcom CGM other than the Dexcom G6, they will be provided with a Dexcom G6 to use during the study and they may choose to use an unblinded device. All other participants, including those not currently using a CGM, will receive a blinded Dexcom G6 so that the participant is not able to see the sensor readings. Participants using an insulin pump will continue to use their personal pump during the study. MDI users may be given a device to use during the study that automatically logs insulin injection dose. Training and data collection for the study will be completed remotely. After initial training has been completed, data will be collected for approximately 4 weeks from start of the exercise period. Feedback will be provided to the participant during the data collection period and additional training will be provided as needed. During the data collection period, participants will be asked to complete at least 150 total minutes of exercise per week. Participants who do not meet their activity goals may be replaced. • Each participant will be assigned to a study exercise (aerobic exercise or resistance circuit exercise or intermittent high-intensity interval exercise). Participants will complete at least 6 total study exercise sessions consistent with their assigned type of exercise. Two study exercise sessions should be completed each of the first two weeks and one study exercise session should be completed each of the last two weeks of the data collection period. The study exercise videos include approximately 30 minutes of exercise. Study exercise session(s) will count toward the minimum 150-minute weekly exercise goal. • Participants will continue their typical forms of activity and exercise. Typical activity and exercise may include individual and group forms of exercise, in both competition and non-competition settings. There is no restriction on the other types of personal exercise which the participant may elect to complete. Optional saliva samples will be collected for genetic analyses.

SCHEDULE OF STUDY VISITS AND PROCEDURES

Remote study design; eligibility and other study questionnaires are self-reported by participant; all study visits and procedures are expected to be completed remotely with the exception of medical clearance/EKG. If required, these may require a health care provider visit.

	Enrollment	**Eligibility Confirmation**	**Baseline Data Collection/Study Preparation**	**Virtual Training Visit***	**4-Week At-Home Data Collection** ***(begins when 1st study exercise is completed)***	**Virtual Check-in Visit***	**Virtual Visit/Data Review***
Informed Consent	X						
Initial Eligibility Screening	X						
Questionnaires	X		X				X
Medical Clearance for Exercise, if required • Medical History Review • EKG *(if ≥50 years old or diabetes duration ≥20 years, if not available from prior 12 months)*		X					
Saliva Sample Collection for Genotyping *(optional)*			X				
Protocol Review**			X	X		X	
App Download and Device Setup • Physical activity wearable • HR monitor (chest strap)/App • T1-DEXI Study App • Exercise video access • CGM*** • Insulin log device†			X	X			
Device and App Training			X	X	X	X	
• Study Exercise • Data Collection through Apps and Devices					X		
Device Downloads††				X	X		X

*Additional virtual visits for training, follow up or data download may be scheduled as needed

**Protocol Review, App Download and Device Setup may be completed through video tutorials and/or virtual visits

***Required for all participants who do not currently use a Dexcom G6, including non-CGM users

†Clearance for participation by a health care provider will be required for those who are not currently active and/or do not meet screening criteria

††Injection users using compatible insulin pens may use an automated insulin tracking device

†††Device Downloads may be done at any time, but should be completed at training visit, virtual check-in (if needed), and must be completed at completion of follow-up

Chapter 1: Background Information

1.1 Introduction

A major area of focus is the many unmet needs and unanswered questions in type 1 diabetes (T1D). Exercise is at the cornerstone of T1D management.[1] It can improve cardiovascular fitness and insulin sensitivity and lower blood pressure and lipid levels.[2] Regular exercise is associated with reduced diabetes-related complications and can increase longevity in T1D, but it also makes diabetes management much more challenging.[3] Even with devices and metrics such as heart rate monitors, accelerometers and additional activity tracking data, there is a lack of knowledge on how to promote and sustain consistent physical activity amongst people with T1D.[4]

Moderate intensity exercise (walking, jogging, cycling) increases the risk of hypoglycemia, while more intense exercise (resistance training, sprinting, circuit training) often causes hyperglycemia.[5] All three types of physical activity, including moderate, high and resistance exercise generate distinguishably different responses which increases the risk of not maintaining euglycemia.[6] Glycemic response to exercise is highly variable, both within and among individuals, particularly after meals[7], but the reason(s) behind this variability is largely unknown. Any daily physical activity lasting ≥30 minutes markedly increases risk for nocturnal hypoglycemia.[8-11] Limited research has been done outside of a clinical setting, although some data shows the value of continuous glucose monitoring (CGM) in the prevention of exercise-associated hypoglycemia.[12] While CGM and automated insulin delivery (AID) systems hold promise for improved glycemic control around exercise, little research has been done demonstrating how existing AID algorithms may need to be altered for exercise[13], although emerging work looks promising.[14,15]

Existing clinical guidelines for exercise management[16] are based on a small number of clinical studies with ≤ 50 subjects.[17,18] More evidence is needed to inform recommendations for varying exercise intensities[19] and routine diabetes care along with the timing and composition of meals for individuals with T1D. Aggregation of data around a coordinated exercise event can assist in the development of translatable management strategies from the clinical setting to daily life. An understanding of the effect of different types, duration and intensities of exercise on glycemia and other hormones across a range of factors is critical for individuals with T1D.

1.2 Rationale

The primary objective of the project is to develop a better understanding of the effects of different levels of exercise intensity and duration on glycemic control during and after exercise across a wide range of patient characteristics. In order to accomplish this, study design will include collection and aggregation of data around exercise events in order to capture pertinent diabetes management information including insulin and glucose data, physical activity levels, stress levels and life-event data such as the timing and composition of meals. Creation of such a dataset will provide data that could be used to fulfill additional long-term objectives such as:

- Development of decision support tools and diabetes management strategies to minimize hypoglycemia and hyperglycemia during and after exercise, including hypoglycemia during the subsequent night.

- Development of algorithms for artificial pancreas systems that automate insulin delivery, and perhaps other hormones, to minimize hypoglycemia and hyperglycemia.

1.3 Potential Risks and Benefits

1.3.1 Known Potential Risks

Endurance exercise, as will be performed in this study, may be associated with generalized fatigue and hypoglycemia. In rare situations, exercise can promote myocardial infarction, sudden cardiac death or arrhythmias. In persons who have proliferative retinopathy, exercise that increases blood pressure significantly (>180 mmHg) can promote retinal bleeding. Participants will be screened through self-reported medical history and clearance for participation by a health care provider will be required for those who are not currently active and/or do not meet screening criteria. Participants are instructed to check blood glucose before and after study exercise. Therefore, the risk of serious exercise-associated adverse events are expected to be remote. Participants will be instructed that they should not complete study exercise if their medical condition changes.

The CGM sensor may produce pain when it is inserted into the skin. There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies.

Finger sticks for blood glucose measurements may produce pain and/or ecchymosis at the site.

Use of a physical activity wearable may cause redness, swelling, skin irritation, or discomfort. If participants experience redness, swelling, skin irritation, or discomfort while wearing a physical activity wearable, the device should be removed. An alternate physical activity wearable may be used for the remainder of the study follow up.

1.3.2 Known Potential Benefits

It is possible that participants will not directly benefit from being a part of this study. However, it is also possible that the study experience may have relevance for the participant with respect to determining his/her glycemic response to exercise.

1.3.3 Risk Assessment

The protocol risk assessment for this study has been categorized as no greater than minimal risk.

1.4 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Informed Consent

Study participants may be recruited from endocrinology centers as well as primary care networks in the United States. Information about the study may also be shared with participant community platforms, such as GLU, and with programs that offer diabetes workshops, such as JDRF PEAK. Potential participants may also become aware of the study by other means, such as another study participant. Eligible participants age ≥18 – <71 years will be included without regard to race, or ethnicity. Enrollment will proceed with the goal of at least 600 participants completing the study.

The study will utilize multiple recruitment pathways in order to include a population of participants expected to vary by:

- exercise history (baseline activity level)
- fitness level
- sex
- age
- HbA1c
- current CGM user vs. non-CGM user
- insulin administration method: current pump, current closed loop system and current injection user
  Note: Users of commercially available (FDA approved) closed loop systems may be included in study. Injection users will be capped at approximately 30%. The goal will be to include approximately equal groups of pump users, closed loop system users and injection users.
- primary diabetes care provider: endocrinologist or other

Overall recruitment goals will be to include approximately equal numbers of participants within three age bins (18 – <26, 26 – <45, 45 – <71 years). Participants will be randomly assigned to one of three exercise types: aerobic exercise, resistance circuit exercise, or intermittent high-intensity interval exercise. Assignment of exercise type will be stratified by insulin administration method (current pump vs. closed loop vs. injection user), age group and sex.

2.1.1 Informed Consent and Authorization Procedures

Individuals who indicate that they are interested will be directed to a website with information about the study. Interested individuals will be able to have a live chat or arrange for a phone call to answer questions about the study as part of the informed consent process. Individuals who want to participate in the study will sign the IRB-approved electronic consent form. As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information.

2.2 Participant Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Age ≥18 – <71 years
2. Clinical diagnosis of presumed autoimmune T1D
3. Duration of T1D ≥2 years
4. Following intensive insulin therapy defined as basal-bolus delivery via an insulin pump or multiple daily injections (MDI) with no major changes in the past 3 months and no major changes (e.g., pump initiation) planned during the time of study participation
   - *Users of commercially available (FDA approved) closed loop systems are eligible*
   - *Pump users who also regularly use insulin injections are not eligible*
   - *Animas pump users are not eligible*
   - *MDI users who administer insulin through a syringe and vial are eligible*
   - *MDI users must be willing to use a device provided by the study that records the injection dosages and/or enter insulin dosing information through an app*
5. Commercial Dexcom G6 CGM use on a regular basis (at least 21 out of the last 28 days) or willing to use a Dexcom G6 CGM. A blinded CGM will be provided, if not using a personal Dexcom CGM.
6. Uses either an Android or iOS smartphone that is compatible with app requirements
7. Access to a compatible computer with internet
8. Able to obtain medical clearance for exercise from a licensed health care provider, if required.
9. Have had an eye exam in the last year if diabetes duration is 5 to less than 10 years and participant is ≥50 years old or if diabetes duration is 10 or more years. Have had an eye exam in the last 2 years if diabetes duration is 5 to less than 10 years and participant is <50 years old.
10. Willing to adhere to the protocol requirements, which include a minimum goal of 150 minutes of exercise per week, for the duration of the study
11. Participant is a resident of United States and plans to reside in the U.S. for the duration of the study
    - *This requirement is due to shipping limitations, U.S. use restrictions for some study software and devices, and GDPR regulations.*
12. Participant comprehends written and spoken English
    - *This requirement is due to the fact that the study materials (apps and exercise videos) will not be available in other languages*

2.3 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1. Females: pregnant or intending to become pregnant during the study
   - *A urine pregnancy test is not required for the study.*
2. Uncontrolled hypertension, defined by blood pressure >160 systolic or >100 diastolic
3. Known stage 3 or higher chronic kidney disease (i.e., eGFR <45)
4. History of coronary artery disease, history of cardiovascular autonomic neuropathy, or abnormal electrocardiogram (EKG) considered to be a contraindication to increased exercise (EKG will be obtained if not available from the prior 12 months for all participants who are either ≥50 years old or have a ≥20-year duration of diabetes)
5. Use of a pacemaker or an electronic device that is implanted for a medical need

6. Two or more severe hypoglycemic events in the past 12 months (as defined by an episode that required third party assistance for treatment)
7. Known active, untreated proliferative diabetic retinopathy that could potentially be worsened by exercise protocol
8. Musculoskeletal injuries, foot ulcers, or peripheral neuropathy that would be considered a contraindication to exercise
9. Pain on exertion or physical exercise that would be considered a contraindication to exercise
10. Use of Afrezza or non-insulin anti-diabetic medications including SGLT2 inhibitors, GLP-1 agonists, and amylin (unless the drug will be discontinued during the time of study participation)
    - *Participants using a stable dose of metformin are eligible.*
11. Use of oral beta-blockers
12. Use of oral glucocorticoids
13. Use of atypical antipsychotic agents (i.e., Olanzapine, Aripiprazole)
14. Use of systemic progestin-only contraceptives
15. Regular use of agents that affect hepatic glucose production such as beta adrenergic agonists and xanthine derivatives; occasional use is not prohibited
16. Participation in other studies involving administration of an investigational drug or device within 30 days or 5 half-lives, whichever is longer, before screening for the current study or planning to participate in another such study during participation in the current study
17. Planning to make an extreme change in current diet during the study
18. Known allergy to nickel or other metal if contraindication to physical activity wearable use

2.4 Screening Procedures

Potential participants will be asked to confirm eligibility by completing an initial screening questionnaire. Based upon participant self-reported responses to screening questionnaire, participants who pass screening and are currently active will be approved for study participation. Those who are not currently active and/or do not meet screening criteria will be required to obtain medical clearance for exercise from a licensed health care provider to confirm eligibility. For those who require medical clearance from a licensed health care provider, it is recommended participants obtain clearance from the health care provider regularly seen for treatment of their diabetes (i.e. the health care provider that prescribes their insulin). The healthcare provider may complete clearance through review of records or may require a virtual or in-person exam.

- An EKG will be required as part of medical clearance for participants ≥50 years old or with diabetes duration ≥20 years, if not available from prior 12 months.
- A urine pregnancy test for females with child-bearing potential is not required for the study, but may be required at discretion of health care provider completing medical clearance.

Participants will be instructed that they should not complete study exercise if their medical condition changes.

2.5 Baseline Data Collection and Testing

After informed consent is signed, baseline data will be collected, including the following:

- Contact information
- Date of birth
- Demographics
- Socio-economic information (education, income, insurance)
- Height and weight
- Diabetes history, including diabetes duration, prior management, insulin delivery method, meal bolus determination method, prior severe hypoglycemia, prior diabetic ketoacidosis (DKA)
- Medical history may include medical conditions, nutrition, family history, hospitalization, and utilization of health care services
- Current diabetes management information including device use
- Medications including insulin use
- Current activity level
- Saliva collection for genetic analyses *(optional)*
- Questionnaires
    - Clarke Hypoglycemia Awareness Questionnaire to assess the glycemic threshold for and symptomatic response to hypoglycemia
    - International Physical Activity Questionnaire to assess usual activity level
    - Pittsburgh Sleep Quality Index to assess sleep quality and sleep disturbance

2.5.1 Saliva Sample for Genetic Analyses

Genotyping will be completed by a central laboratory at the Center for Public Health Genomics at the University of Virginia. The study coordinating center at the Jaeb Center for Health Research will send a saliva collection kit to the participant to obtain a saliva sample. The sample will be returned to the lab in a prepaid mailer.

The lab will extract DNA from the saliva sample. The DNA will be used for genotyping, which will allow us to look at specific places in the DNA that may help to understand how variations in DNA may be associated with exercise, diabetes, and glycemic response to exercise. The genetic analyses are not considered medical information and is not clinically actionable. No genetic information will be shared with the participant.

Chapter 3: Study Procedures and Data Collection

3.1 Overview

After initial training has been completed, data will be collected for approximately 4 weeks from start of the exercise period. Feedback will be provided to the participant during the data collection period and additional training will be provided as needed.

During the data collection period, participants will be asked to complete at least 150 total minutes of exercise per week. Participants who do not meet their activity goals may be replaced.

Each participant will be assigned to a study exercise (aerobic exercise or resistance circuit exercise or intermittent high-intensity interval exercise). Participants will complete at least 6 total study exercise sessions consistent with their assigned type of exercise. Two study exercise sessions should be completed each of the first two weeks and one study exercise session should be completed each of the last two weeks of the data collection period. The study exercise videos include approximately 30 minutes of exercise. Study exercise session(s) will count toward the minimum 150-minute weekly exercise goal.

Participants will continue their typical forms of activity and exercise. Typical activity and exercise may include individual and group forms of exercise, in both competition and non-competition settings. There is no restriction on the other types of personal exercise which the participant may elect to complete.

3.2 Study Training and Data Collection

Training and data collection for the study will be completed remotely. Study supplies will be sent to the participant by mail. Device user manuals will be provided along with study instructions, including the device download schedule. The study website will contain an online tutorial for setup and use of study devices such as the physical activity wearable and mobile applications. The online tutorial may include links to YouTube and other websites.

Throughout the study, members of the study staff will interact with the participant through texts, emails, phone calls and/or virtual training sessions. An initial virtual visit will be arranged to provide the participant with study instructions, training on use of devices and study apps as well as instructions for data download. The participant will be asked to complete the initial study exercise within 5 days of the virtual visit. The 4-week data collection period will begin after the participant completes the initial study exercise.

An additional virtual visit will occur 1 week after the initial study exercise has been completed. Thereafter, the participant or members of the study team may request additional virtual visits or phone calls as needed.

3.3 Physical Activity Wearables

All participants will be provided with a wrist-worn physical activity wearable to use consistently during the study.

One of the physical activity wearables that may be used in the study is the Verily Study Watch (Study Watch). Study Watch is a miniaturized data monitoring and data collection device for continuous recording of physiological and environmental data. It is worn on the wrist like a watch. Study Watch is not a medical device.

Study Watch collects information such as pulse rate, electrodermal activity (sweat measurement), bioimpedance, altitude, pressure, relative humidity, environment temperature, ambient light level, sound level, time zone information, wear time and battery level. Study Watch is intended for data collection purposes only, with minimal information communicated to the subject via the device.

Subject data are continuously recorded by Study Watch on its own by photoplethysmogram sensors. Encrypted data collected by Study Watch is transmitted securely via Study Hub to the secure Verily cloud server.

Study Hub is a fully automated, no-user-interface network access point for uploading data from medical devices to the Verily cloud server. Study Hub charges Study Watch via the charging cradle and syncs data from Study Watch to the secure Verily cloud server using a cellular connection.

Another commercially-available fitness tracker may be used in addition to or instead of the Study Watch.

A chest strap heart rate monitor may be provided for use during study and personal exercise. An app will be used to record the data from the chest strap heart rate monitor.

3.4 Mobile Apps

Apps needed for the study will be installed on the participant's personal smartphone. Participants will be asked to remove the apps once they have completed the data collection period. If participants enable sharing of GPS through an app that is used to collect data for the study, location data will be collected.

3.4.1 T1-DEXI App

The T1-DEXI study app will be used to enter information related to all exercise events, such as the type of activity, perceived intensity of activity, time of last meal prior to activity, and snack/carbohydrate intake during or post-exercise.

Data related to food intake, such as estimates of carbohydrate, protein and fat, size of meal and estimated calories will be routinely entered through the smartphone app. Food photos will also be submitted through the app on the day of and day following study exercise (see Section 3.8 Food Intake and Food Photos).

Insulin data may be entered through the app. Participants will also be asked to answer a series of daily questions related to sleep, stress, and illness.

Smartphone app alerts or text contacts may be used throughout the data collection period to remind participants to monitor their minimum activity goal, to check their blood glucose before and after study exercise, to enter relevant information related to an exercise event into the app or to submit missing data.

3.4.1.1 GPS Data

GPS data will be collected to determine if movement patterns are related to glycemic excursions. These data could be used as an added input for development of automated insulin delivery systems, if location is determined to be related to behavior (activity and food intake) which influence glycemic change. GPS data also will be valuable to align data using time zone

information from the devices used for data collection in the study (CGM, insulin pumps or automated insulin dose trackers, and physical activity monitors). When study participants move between time zones, there can be ambiguities with regards to when data was captured by each of these devices. The geolocation of the user will allow confirmation of the time zone to ensure that all data collected from the various devices are aligned properly.

At time of app setup, participants will be asked to enable GPS data collection. If participants do not disable location services for the T1-DEXI app, GPS data will be collected throughout the study. Ability to disable GPS data collection from other apps may be dependent on phone operating system or app requirements.

3.5 Continuous Glucose Monitoring

All participants will use the Dexcom G6 CGM for the study. Current Dexcom G6 users will continue to use their personal CGM throughout the study. If the participant is currently using a Dexcom CGM other than the Dexcom G6, they will be provided with a Dexcom G6 to use during the study and they may choose to use an unblinded device. All other participants, including those not currently using a CGM, will receive a blinded Dexcom G6 so that the participant is not able to see the sensor readings. For participants who use a blinded CGM, after completion of the data collection period, the participant will be able to review their glucose readings.

Those participants who are given a G6 CGM to use during the study will be provided with instructions on the sensor insertion, use and care of the CGM. The Dexcom sensor measures glucose concentrations every 5 minutes. The current approved sensor may last up to 10 days. A receiver shield will be used for study provided CGMs. The shield is a protective cover and will not alter how the device is used. The receiver shield is investigational and is classified as a Non-Signification Risk (NSR) device by the Sponsor.

3.6 Insulin Delivery and Insulin Data

Participants using an insulin pump will continue to use their personal pump during the study. If participants elect to remove their pump during activity, they will be instructed to suspend pump upon removal.

MDI users with a compatible insulin pen may be given a device to use during the study that automatically logs insulin dose. An app needed for the study to transfer data from the device used to log insulin dose will be installed on the participant's personal smartphone. Participants will be trained on use of the device and app as needed.

One of the devices that automatically logs inulin dose that may be used in the study is the Biocorp Mallya (Mallya) device. Mallya is a data collection device that automatically captures data such as date of injection, time of injection, insulin type and dose. Mallya attaches directly to the insulin pen and does not alter how the pen is used. Mallya is intended for data collection purposes only, with minimal information communicated to the participant via the app or device. Mallya is an investigational device, and it is classified as a Non-Significant Risk (NSR) device by the Sponsor.

Participants will use their own insulin during the study.

3.7 Study Exercise

Each participant will be assigned to a study exercise (aerobic exercise or resistance circuit exercise or intermittent high-intensity interval exercise). During the 4-week data collection period, participants will complete at least 6 total study exercise sessions consistent with their assigned type of exercise. Two study exercise sessions should be completed each of the first two weeks and one study exercise session should be completed each of the last two weeks of the data collection period. Study exercise should not be performed on consecutive days. Instructions for the exercise will be provided via video links.

The 4-week data collection begins at the time the participant completes their initial study exercise. Information about exercise will be entered via the T1-DEXI app on their personal smartphone prior to and after each exercise session to record information about most recent meal, snacks during exercise, type of exercise, intensity of exercise, and competition versus noncompetition.

Participants may receive reminders via phone or text to complete their exercise each week and to monitor adherence to protocol. Participants may also receive reminders to enter activity information through the study app.

Before and after study exercise completion, blood glucose concentration should be checked.

3.8 Food Intake and Food Photos

Participants will be asked to use the T1-DEXI app that runs on their personal smartphone to enter food intake estimation of carbohydrates, proteins, fats, total calories of meals and snacks. On the day of a study exercise session and on the day following a study exercise session, the participant will be asked to take photos of all meals and snacks before and after consumption. A reference card will be included in the photos to allow the photos to be scaled to similar sizes despite a variety of plate and bowl sizes and backgrounds. Details about the meal or snack that are not obvious in the picture can be added by including photo-specific text. Participants may receive text or email reminders to submit photos to minimize missing data.

3.9 Device Downloads

The device download schedule will be reviewed with each participant as part of their training. Study and personal CGMs, insulin pumps, automated insulin dose trackers and physical activity wearable(s) will be uploaded by the participant during the study.

The wrist-worn physical activity wearable(s) will be synced regularly to upload data.

3.10 Final Data Collection

At the end of the data collection period, the participant will be reminded, if necessary, to upload study data and return study devices. A final questionnaire will be administered, which will include adverse event reporting.

3.10.1 App Deletion and Device Return

The participant will be reminded to delete the T1-DEXI study app and apps for other study devices from their personal smartphone. Participants will be provided with postage-paid packaging to return study devices.

Chapter 4: Miscellaneous Considerations

4.1 Adverse Events

Participants will be asked to report the following events

- Severe hypoglycemia
  - Reportable events will be defined as hypoglycemia in which the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness.
- DKA
  - The participant will be asked if he/she was seen at a health care facility and/or hospitalized and what the ketone level was if known.
- Hospitalizations
- Exercise related injuries
  - Reportable events include an injury or fall as a result of the study exercise, development of signs or symptoms of a myocardial infarction, poor perfusion (pallor, cyanosis), angina, pathologic arrhythmia, or another medical condition not expected to occur during or following the exercise.
- Device-related events with potential impact on participant safety
  - Skin reactions from physical activity wearables or from sensor placement are reportable if severe and/or required treatment.

4.2 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study.

4.3 Study Costs

The study will pay for the costs of the research procedures that are part of the study, including a physical exam by a health care provider, if required, to provide clearance for study participation, an EKG, if required, to provide clearance for exercise, and pregnancy test if ordered by the health care provider providing medical clearance. The information regarding approved reimbursement rates will be included on the medical clearance form that is given to the health care provider.

The wrist-worn physical activity wearable and chest strap heart rate monitor will be provided. A set of resistance bands will be provided to participants assigned to resistance circuit exercise. CGM users not currently using a Dexcom G6 CGM will receive CGM supplies for use during the study. MDI users may receive automated insulin trackers to record insulin doses. Participants may keep the chest strap heart rate monitor after the study. Participants assigned to complete resistance study exercise may keep the set of resistance bands. All other devices will be returned.

Costs of standard medical care for diabetes, including insulin, that would occur even if the participant were not in this study, will be the participant's responsibility.

4.4 Participant Compensation

Participant compensation will be specified in the informed consent form.

4.5 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. For participants who withdraw, their data will be used up until the time of withdrawal.

Participants who do not complete baseline procedures in a timely fashion or are noncompliant with respect to the protocol may be withdrawn.

4.6 Contact Information

Contact information for each participant, including name, email address, mobile number, and mailing address will be provided to the coordinating center, the Jaeb Center for Health Research in Tampa, FL. Permission to obtain such information will be included in the Informed Consent Form. The contact information for the study will be maintained in a secure database and will be maintained separately from study data.

Contact information is necessary for shipment of study supplies, for set up of certain apps needed for the study on the participant's personal smartphone, and for participant payments. Contact information will be used by study staff for training and follow up. To minimize missing data, text, email or phone contacts may be used throughout the data collection period to remind participants of study protocol requirements related to data collection. Mobile number will be shared with parties involved in processing of data, if the mobile number is required to send automated text reminders to minimize missing data.

4.7 Confidentiality

For security purposes, participants will be assigned an identifier that will be used to identify study data instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL, participating institutions and investigators in the research study and parties involved in processing of data, in accordance with the terms of the study contracts. Saliva samples sent to the Center for Public Health Genomics (CPHG) at the University of Virginia for genotyping will be assigned a separate laboratory sample identifier. Additional participant data shared with the Center for Public Health Genomics (CPHG) at the University of Virginia will be limited to participant sex and race/ethnicity in order to validate integrity of the dataset.

The participant's personal diabetes care devices and the study diabetes care devices may be uploaded to Tidepool or Glooko/Diasend. Date of birth and email address may be required for creating an account in Dexcom Clarity. This information will be accessible to Dexcom. If participants do not want to provide their email or do not have an email address then an email account will be created for them.

A study provided Polar account will be used to share heart rate data. Participants may choose to customize their Polar Beat account to include their date of birth. Date of birth is used to calculate heart rate zones and other metrics visible to the participant in real-time via the app. This information will be accessible to Polar. Participants are not required to provide this information.

No identifiable health information of an enrolled participant will be released by the Coordinating Center, except as described above.

4.8 Future Use of Data

Data collected for this study, including data from questionnaires, apps and study devices will be analyzed and stored at coordinating center, the Jaeb Center for Health Research in Tampa, FL and by parties involved in processing of data. After the study is completed, these data will be transmitted to and stored at a data repository designated by the study sponsor, the Helmsley Charitable Trust for use by other researchers including those outside of the study. Permission to transmit data to this data repository will be included in the informed consent. Until the data are transferred to the data repository, these data will be retained by the coordinating center, the Jaeb Center for Health Research in Tampa, FL and the parties involved in processing of data.

GPS, or location data collected through apps used in the study will not be transferred to the designated data repository and will not be available for use by researchers outside of the study.

Specimens collected for the study to provide genotyping data will be destroyed and will not be made available for other research. The genotyping data will be transferred to the data repository.

4.9 Quality Assurance and Monitoring

Designated personnel from the coordinating center will be responsible for maintaining quality assurance and quality control systems to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Chapter 5: Questionnaires

5.1 Questionnaires

Questionnaires are completed by all participants. Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

MEASURE	CONSTRUCT MEASURED/RELEVANT POINTS
Clarke Hypoglycemia Awareness Questionnaire	8 question survey to assess the glycemic threshold for and symptomatic response to hypoglycemia
International Physical Activity Questionnaire	7 question survey to assess usual activity level
Pittsburgh Sleep Quality Index	19 item survey to assess sleep quality and sleep disturbance

Chapter 6: Statistical Considerations

6.1 Statistical and Analysis Plans

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

6.2 Statistical Hypotheses

There is no primary hypothesis test. All hypothesis tests for this study are considered exploratory.

6.3 Sample Size

Data from the initial DEXI pilot study was used to estimate the sample size needed for the main study. The estimated sample size is based on achieving a margin of error of 5.0 mg/dL for mean change in glucose during exercise in each target subgroup (3 exercise types and 2 insulin modalities). The study requires 60 subjects per subgroup, and the study is expected to enroll 30% MDI participants, 35% insulin pump, and 35% closed loop participants. Thus, a total of 600 subjects to complete the study is required to ensure each target subgroup has a margin of error of 5.0 mg/dL or less. This initial sample size was increased by 10% to account for dropouts.

The final sample size to achieve a mean change in glucose during study-related exercise subgroup-level margin of error of 5.0 mg/dL is 660 subjects.

6.4 Outcome Measures

Primary Outcome:

- Change in glucose (glucose at the end of exercise minus baseline, mg/dL) during exercise by exercise type (i.e. aerobic, intermitted high-intensity interval, or resistance circuit) and insulin modality

Secondary Outcomes:

CGM-measured outcomes in the 24 hours following study-assigned exercise and 24 hours on sedentary days:

- Mean glucose (mg/dL)
- Glucose SD (mg/dL)
- Glucose coefficient of variation (%)
- % time in range 70-180 mg/dL
- % time below 70 mg/dL
- % time above 180 mg/dL
- Frequency of CGM-measured hypoglycemic events

Heart rate outcomes during exercise

- Age-adjusted % heart rate reserve during exercise

6.5 Description of Statistical Methods

6.5.1 General Approach

This is a parallel group study where each participant is randomized to one exercise type (i.e. aerobic, interval, or resistance). Randomization will be stratified by insulin modality (current injections vs. closed loop vs. pump user), age group, and sex.

6.5.2 Analysis Cohorts

The analysis cohort for the primary and secondary outcomes will be detailed in the Statistical Analysis Plan (SAP). Safety outcomes will be reported for all randomized participants, irrespective of whether the subject completed the study.

6.6 Analysis of the Primary Outcome

Change in glucose during exercise will be calculated for each exercise event. Summary statistics appropriate to the distribution will be calculated separately by exercise group and insulin modality. A 95% confidence interval of change in glucose during exercise will be constructed for each subgroup from a mixed effect model adjusting for baseline glucose, age, and sex with a random participant effect. If residual values from the regression model have a skewed distribution then an appropriate transformation or a nonparametric analysis based on ranks will be performed.

There will be no imputation of missing CGM data.

6.7 Analysis of the Secondary Outcomes

Summary statistics appropriate to the distribution will be calculated for each of the secondary metrics in Section 6.4. Metric calculations and analyses comparing post-exercise vs. sedentary 24-hour periods will be detailed in the SAP.

6.8 Safety Analyses

The following safety outcomes will be tabulated by participant within the post-randomization period. The summary statistics will include available start dates, stop dates, severity, relationship, resolution, and duration.

- Severe hypoglycemia events in which the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness.
- DKA events in which the participant was seen at a health care facility and/or hospitalized.
- Hospitalizations
- Exercise related injuries or falls as a result of study exercise, development of signs or symptoms of a myocardial infarction, poor perfusion (pallor, cyanosis), angina, pathologic arrhythmia, or another medical condition not expected to occur during or following the exercise.

- Device-related events with potential impact on participant safety
- Skin reactions from the Study Watch, or from CGM sensor placement if severe and/or required treatment.
- All other reported adverse events.

6.9 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the study cohort will be tabulated. For continuous variables, summary statistics appropriate to the distribution will be given. For discrete variables, number and percentage will be reported for each category.

6.10 Multiple Comparisons/Multiplicity

The primary analysis does not involve a hypothesis test so no correction for multiple comparisons for this analysis will be performed.

For all other exploratory hypotheses tests, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure for multiple comparisons as detailed in the SAP. Note that this procedure can handle correlated outcome metrics and does not assume independent hypothesis tests.

6.11 Exploratory Analyses

The relationship between change in glucose during exercise with other pre-exercise factors will be explored. Variable selection techniques will be used to determine which pre-exercise factors can be used as covariates in a multivariate model.

The secondary CGM outcomes will be further explored within other time periods following study-assigned exercise. Additional exploratory analyses will be described in the SAP.

Chapter 7: Ethics/Protection of Human Participants

7.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

7.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

7.3 Informed Consent Process

7.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Individuals who indicate that they are interested in study participation will be directed to a website with information about the study. Interested individuals will be able to have a live chat or arrange for a phone call to answer questions about the study as part of the informed consent process. Participants who want to participate in the study will sign the IRB-approved electronic consent form.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participant may withdraw consent at any time throughout the course of the study. The participant will be able to print a copy of the informed consent document for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Chapter 8: References

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