Type 1 Diabetes EXercise Initiative Pediatric Study (T1DexiP): The Effect of Exercise on Glycemic Control in Youth with Type 1 Diabetes

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KEY ROLES

Protocol Chair/Director	
Name, degree	Michael Riddell, Ph.D.
Title	Professor, School of Kinesiology and Health Science, Senior Investigator
Institution Name	York University
Protocol Chair/Director	
Name, degree	Jennifer Sherr, M.D., Ph.D.
Title	Associate Professor in Pediatrics
Institution Name	Yale School of Medicine
JCHR Coordinating Center Director	
Name, degree	Robin L. Gal, M.S.P.H.
Title	Project Director
Institution Name	Jaeb Center for Health Research
Medical Monitor	
Name, degree	Roy Beck, M.D., Ph.D.
Title	Medical Director
Institution Name	Jaeb Center for Health Research

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
CGM	Continuous Glucose Monitor
DKA	Diabetic Ketoacidosis
DNA	Deoxyribonucleic acid
HbA1c	Hemoglobin A1c
IRB	Institutional Review Board
MDI	Multiple Daily Injections
SAP	Statistical Analyses Plan
T1D	Type 1 Diabetes

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Type 1 Diabetes EXercise Pediatrics Initiative (T1Dexi): The Effect of Exercise on Glycemic Control in Youth with Type 1 Diabetes
Précis	Understanding of the effects of different forms of physical activity on acute glycemia and on insulin and carbohydrate needs to better maintain euglycemia during and after exercise in youth with type 1 diabetes
Objectives	This study is designed to create an aggregated dataset including physical activity type and intensity, insulin therapy, nutrition, CGM and other relevant data inputs which can be used to better understand glucose responses to exercise in youth with type 1 diabetes to assist in the development of clinical management strategies and future automated insulin-delivery systems.
Study Design	Observational study, with data collected outside of clinic visits, designed to create an aggregated dataset which includes exercise, CGM and other relevant data inputs that are thought to impact glycemia in youth living with type 1 diabetes.
Population	**Inclusion Criteria:** 1. Age 12 – <18 years 2. Clinical diagnosis of presumed autoimmune T1D 3. Duration of T1D ≥3 months 4. Following intensive insulin therapy regimen defined as basal-bolus delivery via an insulin pump (including a closed-loop system) or multiple daily injections (MDI) with no major changes (e.g., pump initiation, pump discontinuation or transition from pump to closed-loop system) in the past month • Those using premix insulin or regular insulin as part of their current usual insulin regimen are not eligible. • Users of commercially available (FDA approved) closed loop systems are eligible if data from the system are able to be accessed. • MDI users who administer insulin through a syringe and vial or pen are eligible as long as they use a device that records the injection dosages and/or are willing to enter insulin dosages through a smart phone application. 5. Commercial Dexcom G6 CGM use on a regular basis (at least 21 out of the last 28 days) or willing to use a blinded Dexcom G6 CGM; a blinded CGM will be provided, if not using a personal Dexcom G6 CGM. 6. Use a smartphone that is compatible with app requirements 7. Access to a compatible computer with internet 8. At least moderately active on a regular basis as determined through questionnaire assessment 9. Willing to adhere to the protocol requirements, which includes the use of a wrist-worn physical activity monitor and use of required smart phone apps, for the duration of the study 10. 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.* 11. Participant and caregiver comprehend written and spoken English • *This requirement is due to the fact that the study materials will not be available in other languages*

PARTICIPANT AREA	DESCRIPTION
	Exclusion Criteria: 1. Females: pregnant or intending to become pregnant during the study *Note: A urine pregnancy test is not required for the study.* 2. Two or more severe hypoglycemic events in the past 12 months (as defined by an episode that required third party assistance for treatment) 3. Three or more overnight hospitalizations for blood sugar control in the past 12 months 4. Use of oral glucocorticoids during study 5. Cystic fibrosis 6. Physical or developmental impairment that would limit activity or impact ability to use devices and apps required in the study 7. 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
Sample Size	Enrollment will proceed with the goal of at least 250 participants completing the study; a minimum enrollment target of 30 and a maximum of 50 participants will be newly diagnosed T1D (≥3 months to <1 year)
Participant Duration	Approximately 10 days of data collection after enrollment questionnaires and initial training are complete.
Protocol Overview/Synopsis	Information about the study will be shared by endocrinology centers in the United States, through participant community platforms, programs that offer diabetes workshops and conferences, approved advertisements or may also become aware of the study by other means. Informed consent and assent will be obtained electronically. Eligibility will be assessed based on information provided by the participants. Training and data collection for the study will be completed remotely; there are no in-person visits. After training is completed, data will be collected for approximately 10 days. Feedback will be provided to the participant during the data collection period and additional training will be provided, as needed, to ensure that data collection is complete. Participants will use a physical activity wearable. The BANT app will be used to enter information daily related to exercise events. Participants also will be asked to take photos of all meals and snacks before and after consumption on at least three study days including weekdays and weekend days. 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. 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 will be asked to record their insulin injections via the BANT app or share their personal smart pen data. Participants will continue their typical forms of physical activity which may include individual and group forms of exercise in both competition and non-competition settings. 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 or parent; all study visits and procedures are completed remotely.

	Enrollment	Baseline Data Collection	Virtual Training Visit*	At Home Data Collection	Data Review*
Informed Consent	X				
Initial Eligibility Screening	X				
Questionnaires	X	X		X	X
Saliva Sample Collection for Genotyping** *(optional)*		X	X	X	X
App Download and Device Setup*** • Physical activity wearable • BANT App • CGM†			X		
Study Training			X		
Data Collection through Apps and Devices				X	
Device Downloads††			X	X	X

*Additional virtual training visits may be scheduled as needed.

**Saliva sample is optional for those who opt to provide sample and may be collected by participant at any time.

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

†Blinded CGM use required for all participants who do not currently use a Dexcom G6, including non-CGM users.

††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

Children and adolescents with type 1 diabetes are encouraged to participate regularly in physical activity and structured exercise for a variety of physical and mental health reasons (1). However, a number of barriers exist for youth with diabetes to participate in exercise, including a possible deterioration in glycemia (2) and a persistent fear of hypoglycemia (3; 4). The insulin dose and/or carbohydrate intake needs for exercise in the pediatric type 1 diabetes population has been largely ignored, and adolescents with the disease tend not to follow any evidence-informed guidelines (5). Only a handful of 'in clinic' pediatric exercise studies have been conducted to date (6-9), with evidence that the glycemic responses to an acute exercise session is highly variable and for unclear reasons (10). These studies, while important, have not done well in examining the complex relationships among food intake (i.e. macronutrient composition), insulin delivery method (i.e. pump vs multiple daily injections (MDI)) and exercise type on glycemia.

It has been speculated that wearable technologies could be used to monitor physical activity levels and sleep patterns in youth with diabetes (1; 11). The use of these technologies, along with continuous glucose monitoring (CGM), might also be helpful in improving insulin dosing strategies and nutritional needs for periods of increased physical activity (1). For example, wrist bands that measure heart rate, caloric expenditures and sleep duration and quality, along with glucose data from CGM could be used to lower (or increase) insulin delivery in an automated insulin delivery device, depending on the nature of the activity (e.g. intense activity vs. mild activity, vs. sustained activity vs. competitive activity, that is intermittent in nature). However, the relationships between activity type, nutritional intake and insulin dosing levels are largely unexplored outside of clinical settings, where only a small number of largely homogenous participants are examined.

Only with a large data set with the measurement of several potential variables on acute glycemia can these complex relationships be better appreciated and provide the foundation to tailor exercise guidelines and decision support for individual youth living with type 1 diabetes. Ideally, this research could make possible a type of precision medicine for glycemic management in youth with type 1 diabetes.

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 glycemia during and after exercise across a wide range of participant characteristics. In order to accomplish this, the 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, 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

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, and study participation will be discontinued.

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. On rare occasions, the sensor may break and leave a small portion under the skin that may cause redness, swelling, or pain at the insertion site.

There is a risk of breach of confidentiality. All data will be maintained in a secure database with restricted access to help assure confidentiality. Data downloaded from diabetes devices will be collected for the study. Some people may be uncomfortable with the researchers having such detailed information about their daily diabetes habits.

There is the possibility that completion of questionnaires could make the participant feel uncomfortable.

The study may include other risks that are unknown at this time.

1.3.2 Known Potential Benefits

It is possible that the participants will benefit from participating in this study by learning more about their own individual glucose responses to different forms of exercise that they routinely complete. Participants may become more aware of the impact of timing of insulin dosing and exercise type, such as post-meal exercise vs. pre-meal exercise, late day exercise vs. morning exercise, competitive vs. non-competitive activities, etc. However, it is possible that participants will not directly benefit from being a part of this study.

1.3.3 Risk Assessment

The protocol risk assessment for this study has been categorized as not 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.

Chapter 2: Study Enrollment and Baseline Data Collection

2.1 Participant Recruitment and Enrollment

Study participants may be recruited from endocrinology centers in the United States who will help identify and share information about the study with potential participants. Information about the study may also be shared with participant community platforms, with programs that offer diabetes workshops and conferences, such as JDRF and Children with Diabetes events, and through approved advertisements, if needed, for recruitment. Potential participants may also become aware of the study by other means, such as through another study participant.

Eligible participants age 12 – <18 years at time of enrollment will be included without regard to race, or ethnicity. Enrollment will proceed with the goal of at least 250 participants completing the study. Participants who have signed consent and started the screening process may be permitted to continue into the study, if eligible, even if the recruitment goal has been reached. Overall recruitment goals will be to include approximately equal numbers of participants within two age bins (12 – 14, 15 – 17 years). Within the enrollment goal of 250, there will be an enrollment target of a minimum of 30 and a maximum of 50 total participants with new onset diabetes, defined as diabetes diagnosis ≥3 months to <1 year.

After ~100 participants have enrolled into the study, the breakdown of certain demographics in the study cohort will be assessed to determine if demographic enrollment targets need to be re-assessed.

2.1.1 Informed Consent and Authorization Procedure

Individuals who indicate that they are interested will be directed to a website with information about the study. A parent or legal guardian (referred to subsequently as "parent") will be provided with the Informed Consent Form to read and will be given the opportunity to ask questions. Interested individuals and their parent 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. If the parent and child agree to participate, the parent will sign the Institutional Review Board (IRB)-approved electronic consent form. As part of the electronic consent, the parent will attest to assent of the minor to participate in the study. As part of the informed consent process, the consenting parent will be asked to sign an authorization for release of personal information. A copy of the consent form can be printed at time of consent.

Participants who turn 18 during the course of the study will need to re-consent.

2.2 Participant Inclusion Criteria

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

1. Age 12 – <18 years
2. Clinical diagnosis of presumed autoimmune T1D
3. Duration of T1D ≥3 months

4. Following intensive insulin therapy regimen defined as basal-bolus delivery via an insulin pump (including a closed-loop system) or MDI with no major changes (e.g., pump initiation, pump discontinuation or transition from pump to closed-loop system) in the past month
    - Those using premix insulin or regular insulin as part of their current usual insulin regimen are not eligible.
    - Users of commercially available (FDA approved) closed loop systems are eligible if data from the system are able to be accessed
    - MDI users who administer insulin through a syringe and vial or pen are eligible as long as they use a device that records the injection dosage and/or are willing to enter insulin dosages through a smart phone application.
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 blinded CGM. A blinded CGM will be provided, if not using a personal Dexcom G6 CGM.
6. Use a smartphone that is compatible with app requirements
7. Access to a compatible computer with internet
8. At least moderately active on a regular basis as determined through questionnaire assessment
9. Willing to adhere to the protocol requirements, which includes the use of a wrist-worn physical activity monitor and use of required smart phone apps, for the duration of the study
10. Participant is a resident of the 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.
11. Participant and caregiver comprehend written and spoken English
    - This requirement is due to the fact that the study materials 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
   Note: A urine pregnancy test is not required for the study.
2. Two or more severe hypoglycemic events in the past 12 months (as defined by an episode that required third party assistance for treatment)
3. Three or more overnight hospitalizations for blood sugar control in the past 12 months
4. Use of oral glucocorticoids during study
5. Cystic fibrosis
6. Physical or developmental impairment that would limit activity or impact ability to use devices and apps required in the study.

7. 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.

2.4 Screening Procedures

After informed consent is signed, potential participants and their parents will be asked to confirm eligibility by completing screening questionnaire(s) on the study website. Based upon self-reported responses to screening questionnaire(s), participants who pass screening will be approved for study participation.

2.4.1 Screening Activity Assessment

MEASURE	CONSTRUCT MEASURED/RELEVANT POINTS
Physical Activity Questionnaire for Children and Adolescents (PAQ)	A 7-day recall questionnaire to assess typical physical activity levels in persons 8-20 years old; questionnaire will be used to confirm that participant is at least moderately active on a regular basis.

2.5 Additional Baseline Data and Testing

Baseline data will be collected from eligible participants and parents after initial screening questionnaire(s) are completed.

Study questionnaires, which have been approved by the IRB, are completed on the study website. The responses to surveys may not be monitored in real-time. Parent may assist the participant with completion of questionnaires, if needed. Parent will also be asked to complete questionnaires. The procedures for administration are described in the study procedures manual.

Baseline data to be collected may include the following:

- Contact information
- Date of birth
- Demographics
- Socio-economic information (education, income, insurance)
- Height and weight
- Diabetes history and management information including diabetes duration, prior management, insulin use and delivery method, meal bolus determination method, prior severe hypoglycemia, prior diabetic ketoacidosis (DKA) and device use
- Medical history may include medical conditions, current medications, nutrition, family history, hospitalization, and utilization of health care services
- Medications other than insulin
- Usual activity habits for participants and parents
- Questionnaires, including standardized questionnaires, for participant and parent completion
- Saliva collection for genetic analyses *(optional)*

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 deoxyribonucleic acid (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 or their parent.

2.5.2 Participant Standardized Questionnaires

MEASURE	CONSTRUCT MEASURED/RELEVANT POINTS
Barriers to Physical Activity in Type 1 Diabetes (BAPAD)	11 question survey to assess barriers to physical activity
Hypoglycemia Fear Scale for Children (HFS-C)	25 question survey to assess worry about and behaviors to avoid hypoglycemia episodes
Pubertal Development Scale (PDS)	5 question minimally invasive self-rating Tanner Staging measure to assess pubertal status, without using pictorial representations, interviews or physical examinations
Clarke Hypoglycemia Awareness Questionnaire	8 question survey to assess the glycemic threshold for and symptomatic response to hypoglycemia

2.5.3 Parent Standardized Questionnaires

MEASURE	CONSTRUCT MEASURED/RELEVANT POINTS
International Physical Activity Questionnaire (IPAQ)	7 question survey to assess usual parental activity level
Hypoglycemia Fear Scale for Parents (HFS-P)	25 question survey to assess fear of hypoglycemia parents have for their child with type 1 diabetes

2.6 Randomization

This is a prospective observational study with no randomization.

2.7 Screen Failures

Individuals who do not meet study eligibility requirements will be dropped from the study.

Chapter 3: Study Procedures and Data Collection

3.1 Overview

After initial training has been completed, data will be collected for approximately 10 days. Participants may be asked to try to begin the study on a specific day to maximize the chance of complete data collection on both weekdays and weekend days.

Throughout the data collection period, 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.

Participants may be invited to repeat the study if key data, such as CGM data, are not available, but data are otherwise 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 may 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. 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 commercially available wrist-worn physical activity wearable. The physical activity wearable collects data such as physical activity levels via pulse rate, step count and energy expenditures. It can also collect and monitor sleep duration and sleep quality. Participants will be asked to use the physical activity wearable consistently throughout the study so that a representative profile of their activity can be determined.

3.4 Mobile Apps

Apps needed for the study will be installed on a smartphone that will be used during the study. If a participant does not have a smartphone that is compatible with the study apps, a loaner phone will be provided for use during the study.

3.4.1 BANT App

Participants will be asked to use the BANT app that runs on a smartphone to log information related to exercise, insulin and food intake. The participant will also be asked to take photos of all meals and snacks before and after consumption on at least three study days including

weekdays and weekend days. 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.

The app can collect exercise information which includes the type of activity, duration, subjective ratings of exercise intensity and mode. Insulin data captured includes the type of insulin and the route of administration. Meal and snacks can be logged with photos and carbohydrates consumed. Details that are not obvious in the photos can be added by including photo-specific text. All the data are captured with a date and time stamp. Weight may also be entered through the app.

The app may include messaging to encourage physical activity levels that are consistent with current activity guidelines for pediatrics and adolescents. Participants may receive reminder notifications to enter information into the app to minimize missing data.

3.4.2 Garmin App

The Garmin vivosmart uses the Garmin Connect phone application. The Garmin Connect app syncs with the wearable when in range (watches can store data for several days) and the app profiles metrics including step counts, continuous heart rate, pulse oximetry, stress level, number of active minutes per day (intensity minutes), calories expended per day, the number of floors climbed and any user-defined exercise events. Sleep details include metric such as sleep time, heart rate variability analytics, time awake, and duration in each of the 3 sleep stages (i.e. light, deep and REM). Participants may be provided with instructions related to fitness tracker settings that should be used during the study.

3.5 Continuous Glucose Monitoring

All participants will use the Dexcom G6 CGM for the study so that the sensor glucose analytics are standardized. The Dexcom sensor measures glucose concentrations every 5 minutes. The current approved sensor may last up to 10 days.

- Current Dexcom G6 users will continue to use their personal CGM throughout the study.
- All other participants, including non-Dexcom CGM users and those not currently using a CGM, will receive a Dexcom G6 Pro, which is blinded so that the participant is not able to see the sensor readings. Those participants who are given a Dexcom G6 Pro to use during the study will be provided with instructions on the sensor insertion, use and care of the CGM. An Android phone may be provided which is used as a receiver to collect data from the blinded Dexcom G6 Pro. Current non-Dexcom CGM users, including pump users with integrated CGM should continue to use their personal CGM for glucose management. For participants who use a blinded Dexcom G6 Pro CGM, after completion of the data collection period, the participant will be able to review their glucose readings.

Participants with missing CGM data may be asked to participate in the study again.

3.6 Insulin Delivery and Insulin Data

Participants will use their own insulin during the study.

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 and then resume their pump when they normally would put it back on to allow for accurate insulin delivery records.

MDI users may be asked to enter insulin dose information in the Bant app. MDI users who administer insulin through an FDA approved insulin smart pen may be asked to upload or share their insulin data through the Tidepool Mobile App. Tidepool Mobile is an iPhone companion app that allows you to connect to Apple Health for continuous, automatic syncing of insulin data.

3.7 Device Downloads

For participants using devices which require download, the device download schedule will be reviewed with each participant as part of their training. The participant will be reminded, if necessary, to upload study data.

3.8 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.

3.8.1 App Deletion

The participant will be reminded to delete any study apps from their personal smartphone.

3.8.2 Device Return

Participants will be provided with postage-paid packaging to return study devices, if applicable.

Chapter 4: Miscellaneous Considerations

4.1 Adverse Events

Participants will also 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 glucose and ketone levels were if known.
- Hospitalizations
- Device-related events with potential impact on participant safety
  - Skin reactions from physical activity wearables or from sensor placement for those using a blinded Dexcom G6 Pro provided for the study will be reported as adverse events if they are classified as severe and/or required treatment.

4.2 Participant Compensation

Participant compensation will be specified in the informed consent form.

4.3 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. The reason for withdrawal will be collected. Additionally, at the time of withdrawal, the participant will be asked to complete device downloads and questionnaires. For participants who withdraw, their data will be used up until the time of withdrawal.

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

4.3.1 Pregnancy

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

4.4 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. Contact information for the parent providing consent will also be provided to the coordinating center. 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, set up of certain apps needed for the study on the smartphone that is used during the study, questionnaire access and 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.

4.5 Confidentiality

For security purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the JCHR coordinating center 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 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 at the University of Virginia will be limited to participant sex and race/ethnicity in order to validate integrity of the dataset.

A study provided Garmin account will be used to share heart rate data. Participants may choose to customize their Garmin Connect 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. Participants are not required to provide exact date of birth, but if provided, this information will be accessible to Garmin.

The Bant application uses token authentication for users and all data are encrypted during transmission over HTTPS. The Application Server is hosted in a data center behind a firewall. By establishing the server within a data center, data is automatically backed up through the hosting organization's backup and restore procedures. It also acts as a safe repository for research data and also allows the user to recover their data if the smartphone is lost or reset.

The participant's personal diabetes care devices, health apps and the study diabetes care devices may be uploaded to Tidepool, Glooko/Diasend or through a connected app like Apple Health; device data exports may also be completed through device specific applications like Tandem t:connect. If accounts need to be created in order to upload or export device data, date of birth and email address may be required to create an account and this information would be accessible by the company. 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.

The informed consent form will specify entities that will have access to or receive data. No identifiable health information of an enrolled participant will be released by the coordinating center, except as described above.

4.6 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.

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.

4.7 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 that data are generated, documented and reported in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

Chapter 5: Statistical Considerations

5.1 Statistical and Analysis Plans

The approach to sample size and statistical analyses are summarized below. The analysis plan synopsis in this chapter contains the framework of the anticipated final analysis plan.

5.2 Statistical Hypotheses

This study has not been formally powered for statistical hypotheses. There is no primary statistical hypothesis. The purpose of this study is to collect an aggregated dataset to better understand glucose responses to exercise in youth with type 1 diabetes; all statistical analyses are considered exploratory.

5.3 Sample Size

Study targets enrollment of 250 participants, with 30 to 50 participants newly diagnosed with type 1 diabetes, defined as diabetes diagnosis ≥3 months to <1 year.

5.4 Outcome Measures

CGM-Measured Outcomes during Exercise

- Change in glucose (glucose at the end of exercise minus baseline, mg/dL)
- Change from baseline to nadir glucose

CGM-Measured Outcomes Post-Exercise

- Mean glucose
- Glucose standard deviation
- Glucose coefficient of variation
- % time in range 70-180 mg/dL
- % time <70 mg/dL
- % time <54 mg/dL
- CGM-measured hypoglycemic events <54 mg/dL
- CGM-measured hypoglycemic events <70 mg/dL
- % time >180 mg/dL
- % time >250 mg/dL
- Overnight nadir glucose

Heart Rate Outcomes during Exercise

- Age-adjusted % heart rate reserve during exercise

5.5 Description of Statistical Methods

5.5.1 Analysis Cohorts

The analysis cohort for the outcomes will be detailed in the Statistical Analysis Plan (SAP).

5.6 Analysis of the Outcomes

Summary statistics appropriate to the distribution will be calculated for each of the metrics in Section 5.4. The association between certain glycemic metrics and the following factors will be assessed:

Participant-Level Factors at Baseline

- Age
- Sex
- Diabetes duration
- Physical activity level
- Body Mass Index
- HbA1c
- Insulin modality
- Personal CGM use status

Event-Level Factors before or at Start of Exercise

- Exercise time of day
- Insulin on board
- Baseline heart rate prior to exercise
- Carbohydrates on board
- Baseline glucose prior to exercise
- Glucose rate of change (mg/dL/min) prior to exercise
- % time in range 70-180 mg/dL during 24 hours prior to exercise
- % time <70 mg/dL during 24 hours prior to exercise

The association between certain post-exercise glycemic metrics and the following factors will be explored:

- Exercise duration
- Perceived exercise intensity
- Age-adjusted % heart rate reserve during exercise

- Change in glucose during exercise

Metric calculations and analyses will be detailed in the SAP.

5.7 Safety Analyses

The following safety outcomes, as defined in Section 4.1, will be listed by participant:

- Severe hypoglycemia
- DKA
- Hospitalizations
- Device-related events with potential impact on participant safety

Analyses will be detailed in the SAP.

5.8 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the study cohort will be tabulated.

Chapter 6: Ethics/Protection of Human Participants

6.1 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.

6.2 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.

6.3 Informed Consent Process

6.3.1 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 and their parent 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. Parents of participants who want to participate in the study will sign the IRB-approved electronic consent form on behalf of the participant. The parent will confirm that the participant would like to participate in the study and will attest to the assent of the minor to participate in the study.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The parent 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 7: References

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11. Kordonouri O, Riddell MC: Use of apps for physical activity in type 1 diabetes: current status and requirements for future development. Therapeutic advances in endocrinology and metabolism 2019;10:2042018819839298