EFFECTS OF PHYSICAL ACTIVITY AND EXERCISE ON GLYCAEMIC CONTROL IN CYSTIC FIBROSIS

Protocol Number	**X21-0429 & 2021/ETH12172**
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Protocol Version Number	**4**
Protocol Date	**February 3rd, 2022**
Sponsor (if applicable)	**N/A**
Proprietary Notice (if applicable)	**N/A**

Ethics Statement:

The study will be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (2007) (Link to National Statement) , the *CPMP/ICH Note for Guidance on Good Clinical Practice* (Link to CPMP/ICH) and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

CONTENTS

Protocol Title	**EFFECTS OF PHYSICAL ACTIVITY AND EXERCISE ON GLYCAEMIC CONTROL IN CYSTIC FIBROSIS**
Protocol version	4
Objectives	The primary objectives of this study (Effects of Physical Activity and Exercise on Glycaemic Control in Cystic Fibrosis) are: To perform continuous glucose monitoring in adult CF patients with and without CFRD and in healthy controls during supervised moderate intensity exercise and unsupervised habitual physical activity and home exercise routines to determine the prevalence of hypoglycaemia. The secondary objectives are: To repeat the aim above 4 weeks after eligible CF patients commence Elexacaftor/Tezacaftor/Ivafactor (Trikafta™), when it becomes available on the Pharmaceutical Benefits Scheme.
Study design	10-day Prospective Controlled Pilot Study
Planned sample size	CF participants: 45 Healthy volunteers: 15
Selection criteria	• Inclusion criteria - CF participants: a. RPAH CF clinic patients, aged ≥17 years, who are clinically stable. b. CF Patients with CFRD (n=15), impaired fasting glucose tolerance (n=15) and those with normal glycaemic control (n=15), according to their most recent oral glucose tolerance test (within 3 years, where applicable). c. Clinically-stable at time of data collection, as assessed by the patient's treating respiratory physician, including no non-routine antibiotics in the previous 14 days.

	d. Provides informed consent. e. Eligible for Elexacaftor/Tezacaftor/ Ivacaftor (Trikafta™) • Healthy control participants: a. Healthy clinically stable participants, aged ≥17 years b. No history of cardiovascular, neuromuscular, endocrine, respiratory disease • Exclusion criteria a. Unable to perform moderate intensity exercise or use continuous glucose monitoring device. b. Colonisation with Tier 3 organisms (*Burkholderia cepacia*, non-tuberculous mycobacteria) c. Previous lung transplant. d. Pregnant or lactating females. e. Known hypoglycaemia unawareness f. Mobile phone not compatible with the continuous glucose monitoring device
Study Procedure	Participants who meet the inclusion criteria will be invited to participate in a 10 day research study when they attend a routine RPA CF clinic appointment. If they provide consent to participate in the study, they will be provided with a continuous flash glucose monitor (CGM, FreeStyle Libre™ 2 Abbott Diabetes Care) and an activity monitor (activPAL™, PAL Technologies) either at CF clinic or by mail. The FreeStyle Libre™ 2 is a standard device used for glucose monitoring in diabetes clinics worldwide (Oskarsson et al 2018). Instructions on how to use the CGM will be provided by the CF Clinic diabetes educator either in person or via telehealth at the start of the trial. The activPAL™ is a validated device used for activity monitoring, including analyses of physical activity and sedentary behaviour (Edwardson, Winkler et al. 2017). Instructions on how to use the activPAL™ device will be provided by one of the Physiotherapists involved in the trial. The first day of CGM and activity monitoring will be Day 1 of the trial. Participants will be instructed to maintain their usual physical activity and exercise routines, as well as continue their usual diet and medication regimens for the study period. CF participants will be asked to complete four questionnaires at study entry: Clarkes hypoglycaemia awareness survey (Geddes, Wright et al. 2007); participant hypoglycaemia questionnaire; Edinburgh hypoglycaemia symptom scale and the CFQ-

	R, a CF-specific health-related quality of life questionnaire (Sole, Olveira et al. 2018). The questionnaires will be completed securely online via REDCap. Healthy control participants will be invited to complete the same questionnaires, except for the CFQ-R (for a total of three questionnaires). Participants will be provided with a one page activity, food and insulin diary to record sleeping and waking times, details of any exercise, timing and carbohydrate content of meals, and if prescribed, timing and dosage of insulin. Patients will be advised to use usual prandial insulin before exercise as per their usual routine. The participants will then be booked to have one 20-minute moderate intensity exercise session at the Queen Elizabeth II Pulmonary Rehabilitation, Royal Prince Alfred Hospital, Camperdown, NSW, between Day 4 and Day 8. The exercise will be performed on a stationary cycle (Ergoselect 5, ergoline GmbH, Germany) and participants will be monitored according to standard protocols for the Exercise Lab (ECG, oxygen saturation, blood pressure and metabolic measures). This session will be supervised and tailored for each patient by one of the physiotherapists involved in the study, who all have expertise in exercise testing and training. The workload on the cycle will be titrated to achieve 60-70% of estimated peak heart rate and a reported breathlessness score of moderate-somewhat severe, as per pulmonary rehabilitation guidelines. A physician will also be available to provide supervision if needed (SS, HJ, SV). Participants will be observed for one hour after completion of the exercise session and provided with a hypoglycaemia kit (fast and long acting carbohydrate) if they show any sign of hypoglycaemia. They are then able to return home and will be advised to perform their regular activity and exercise routines at any time convenient to them until trial completion at Day 10. After completion of the study (Day 11), the participants can discard the CGM in a biohazard sharps bin in their own home. This will be provided to them. Glucose monitoring results will be remotely downloaded using Libreview™ as per current standard of care, a cloud platform allowing access to glucose data with established security protocols. This secure, protected cloud-based diabetes management system allows glucose readings to be uploaded from LibreLink systems and reviewed. For both patients and healthcare professionals to access Libreview™ they must have an account which is password protected. Healthcare professionals must also be approved by admin of the 'Practice' so that they can access patient's glucose readings. For this study, the diabetic educator (MC) and Endocrinologist (KKJ) will access this data. Patients will also use a pre-paid Australia Post envelope to return the activPAL™ device to the RPAH CF Service along with the activity, food and insulin diary. The activPAL™ data will be downloaded to a local computer and analysed with the inbuilt software (PALanalysis). The data is then deleted from the monitor and prepared for the next participant.

	In the event of a COVID-19 outbreak where face to face visits are not permitted, the food diary, ActivPAL device and CGM will be mailed out to the patient with similar instructions. No supervised exercise testing will be performed. **Post-Trikafta™ study** If Trikafta™ becomes available on the PBS between 2021 and 2023, participants who completed the pre-Trikafta component of the study will be invited to complete this study a second time, after 4 weeks post Trikafta initiation. There will be no changes for the previously described protocol except that they will now be on a new medication. **Healthy Control Participants** Healthy control (HC) participants without CF will be recruited via advertisement placed in the clinic waiting room. Body Composition Substudy: Participants will also be invited to undergo a body composition scan at the RPAH Endocrine department prior to their exercise study at the QEII gym.
Statistical considerations	This is a pilot observational study evaluating the impact of physical activity and exercise on glycaemic control in patients with CF. Descriptive data will be expressed as mean ± SD, unless otherwise stated. Pair-wise comparisons will be tested by paired t-test or Wilcoxon signed-rank test depending on the normality of data distribution. Unpaired t-tests and Mann-Whitney U tests will be used for between group comparisons where appropriate. Associations will be tested by either Pearson or Spearman tests also based on normality of distribution. The ActivPal data will be used to identify “exercise days” and “sedentary days”. For exercise days, we will divide time into 4hr blocks for the 24hr post exercise and assess the association with the standard CGM output as previously outlined (both

	supervised and unsupervised exercise). Secondarily, we will compare CGM data averaged over the whole 24 hours comparing exercise to sedentary days (00:00-24:00).
Time Period of Data Collection	Commencement of recruitment will occur after RGO approval. Data collection will begin shortly after. The study will last 3 years or less depending on when proposed sample size is met.
Duration of the Study	3 years.
Funding (if applicable)	University of Sydney research account, held by Dr. Tiffany Dwyer, funded by a philanthropic donation from PS Davis Holdings. This account will pay for the CGM devices, consumables for the activPAL monitor, postage and hypoglycaemia kits.
Sponsor (if applicable)	N/A

Protocol Version Control box

Protocol Version Number	Date	Summary of Changes
1	November 12, 2021	Switched to preferred template
2	November 20, 2021	Current
3	December 23, 2021	Clarifications and corrections as requested by the RPAH Human Research Ethics Committee
4	February 3, 2022	Inclusion of DEXA scan substudy

1. BACKGROUND AND INTRODUCTION

1.1. DISEASE/PROPOSED INTERVENTION BACKGROUND

- Cystic fibrosis related diabetes (CFRD) is a disease complication that is present in about 40-50 % of adult patients with cystic fibrosis (Moran, Dunitz et al. 2009). Patients with CFRD are at risk of hypoglycaemia related to insulin therapy (Cryer 2008). Post-prandial and reactive hypoglycaemia in the absence of established diabetes and glucose lowering therapies has also been described in CF (Armaghanian, Brand-Miller et al. 2016). Reactive hypoglycaemia, or low blood glucose levels within 4 hours of a meal, has been demonstrated in the setting of oral glucose tolerance testing in CF (Mannik, Chang et al. 2018). Patients have also described symptoms suggestive of hypoglycaemia with exercise (Goulet-Gelinas, Saade et al. 2020) however no studies been performed in the CF population. With

exercise encouraged as a means of airway clearance in this population with suppurative lung disease, detection and prevention of hypoglycaemia is important (Ward, Morrow et al. 2020).

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Highly effective Cystic Fibrosis Transmembrane Receptor (CFTR) modulator therapy (Elexacaftor/Tezacaftor/Ivacaftor) is anticipated to be introduced to >85% of the CF population in Australia from 2022, once it is formally approved on the pharmaceutical benefits scheme. While it is associated with significant gains in lung function and improved quality of life, it can result in hypoglycaemia in some individuals (Heijerman, McKone et al. 2019, Middleton, Mall et al. 2019, Rang, Keating et al. 2020). Large phase 3 studies are underway to further assess the effect of highly effective CFTR modulator therapy on glucose tolerance (clinicaltrials.gov; NCT04599465). There are however no studies evaluating the impact of physical activity and exercise on glucose levels. This study aims to evaluate the effects of physical activity and exercise on glucose levels.

2. HYPOTHESIS

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a) Patients with and without CFRD will demonstrate hypoglycaemia during and/or after periods of moderate intensity exercise.
b) More frequent episodes of hypoglycaemia associated with exercise will occur after initiation of Trikafta in patients with and without CFRD.

3. STUDY OBJECTIVES / AIMS

3.1. PRIMARY OBJECTIVES

a. To perform continuous glucose monitoring in adult CF patients with and without CFRD and in healthy controls during supervised moderate intensity exercise and unsupervised habitual physical activity and home exercise routines to determine the prevalence of hypoglycaemia.

3.2. SECONDARY OBJECTIVES

a. To repeat the aim above 4 weeks after eligible CF patients commence Elexacaftor/Tezacaftor/Ivafactor (Trikafta™), when it becomes available on the Pharmaceutical Benefits Scheme.

b. Body composition substudy: Body composition via Dual Energy X-ray Absorptiometry before and after commencement of Trikafta.

4. STUDY DESIGN

4.1. DESIGN / STUDY TYPE

This will be a prospective controlled pilot study of patients with and without CFRD, who attend the Adult CF Clinic at Royal Prince Alfred Hospital, compared with healthy volunteers. The pre-Trikafta™ component of the study will commence in 2022 after ethical approval is granted.

4.2. EXPECTED PARTICIPANT NUMBERS

a. CF Patients with CFRD (n=15), impaired fasting glucose tolerance (n=15) and those with normal glycaemic control (n=15), according to their most recent oral glucose tolerance test (within 3 years, where applicable).
b. Healthy volunteers (control) = 15

4.3. TIME PERIOD OF THE STUDY

Task	Start Date	End Date
Ethics Submission	November 2021	December 2021
Ethics Review and Approval	Mid February 2022	Mid March 2022
Advertising	March 2022	June 2022
Recruitment	March 2022	March 2024
Conduction of surveys/groups etc.	N/A	N/A
Collection of data	April 2022	March 2025
Analysis of Data	March 2025	May 2025
Preparations of Reports	See below	See below.
Publication Draft	June 2025	July 2025

Submission of Publications and Final Reports	August 2025	October 2025

4.4. ENDPOINTS

PRIMARY ENDPOINTS

- Frequency of hypoglycaemia in the 48 hours after supervised exercise session (% time below 3.9 mM).

SECONDARY ENDPOINTS

- Frequency of hypoglycaemia during the 4-10 day trial period (% time below 3.9 mM).
- Frequency of any severe hypoglycaemia events
- CGM time in range, glucose variability, time above range, mean glucose (Chan, Vigers et al. 2018)
- Percent of time in normal glucose range time in range BGL 4-10 mmol/L
- Frequency of hyperglycaemia during the 10 day trial period (time above range BGL>7.2 mmol fasting or >10 mmol/L 2-3 hours postprandially)
- Timing of meals prior to exercise
- Physical activity (measured from activPAL)
- Time spent in moderate-vigorous physical activity
- Time spent sedentary (sitting or lying down when awake)
- Daily step count
- Edinburgh hypoglycaemia symptoms scale within 48 hours after observed exercise, if hypoglycaemia is observed (Deary, Hepburn et al. 1993)
- Clarkes hypoglycaemia awareness questionnaire
- Cystic Fibrosis hypoglycaemia questionnaire
- Body mass index, presence of liver disease, pancreatic insufficiency and lung function (FEV1) and association with glucose levels during exercise
- Total body weight, %Fat, bone and lean muscle
- Fat mass (g), Lean Mass (g) and total mass (g) measured in arms, legs and trunk

4.5. CENTRES

Site Name/s	Royal Prince Alfred Hospital (includes the RPAH pulmonary rehab department located at the Queen Elizabeth II building on Missenden Road, Camperdown)
Site Contact/Investigator	Dr. Sheila Sivam Secondary contact: Dr. Tiffany Dwyer
Study Procedures	Participants who meet the inclusion and exclusion criteria will be invited to participate in a 10 day research study when they attend a routine RPA CF clinic appointment. In addition, all CF patients with one Phe508del mutation (90% of our clinic cohort as per our clinic records – this record of mutations is used for CF specific medication orders ,which we submit for patients), will be sent an email invitation, which will include a copy of the patient information sheet and consent to review ahead of their next clinic appointment either face to face or via telehealth, or a discussion at a mutually convenient time either face to face or over the phone, where they can ask questions about the study. They will have 24 hours at a minimum to review the documents. Participants who are keen to enrol in the study after this discussion will need to return the consent form to the research team either in person or by mail. Our clinic staff email patients regularly and inform them of updates including trials. Choosing not to participate will not affect their clinical care. If they provide consent to participate in the study, they will be screened over the phone by CF physician members of the research team, to confirm that they meet in inclusion an exclusion criteria. They will be then provided with a continuous flash glucose monitor (CGM, FreeStyle Libre™ 2 Abbott Diabetes Care) and an activity monitor (activPAL™, PAL Technologies) either at CF clinic or by mail. The FreeStyle Libre™ is a standard device used for glucose monitoring in diabetes clinics worldwide (Oskarsson et al 2018). Instructions on how to use the CGM will be provided by the CF Clinic diabetes educator either in person or via telehealth at the start of the trial. The activPAL™ is a validated device used for activity monitoring, including analyses of physical activity and sedentary behaviour (Edwardson, Winkler et al. 2017). Instructions on how to use the activPAL™ device will be provided by one of the Physiotherapists involved in the trial. The first day of CGM and activity monitoring will be Day 1 of the trial. Participants will be instructed to maintain their usual physical activity and exercise routines, as well as continue their usual diet and medication regimens for the study period. CF participants will be asked to complete four questionnaires at study entry: Clarkes hypoglycaemia awareness survey (Geddes, Wright et al. 2007); participant hypoglycaemia questionnaire; Edinburgh hypoglycaemia questionnaire and the CFQ-R, a CF-specific health-related quality of life questionnaire (Sole, Olveira et al. 2018). The questionnaires will be completed securely online via REDCap. Healthy control participants will be invited to complete the same questionnaires, except for the CFQ-R (for a total of three questionnaires).

Participants will be provided with a one page activity, food and insulin diary to record sleeping and waking times, details of any exercise, timing and carbohydrate content of meals, and if prescribed, timing and dosage of insulin. Patients will be advised to use usual prandial insulin before exercise as per their usual routine.

The participants will then be booked to have one 20-minute moderate intensity exercise session at the Queen Elizabeth II Pulmonary Rehabilitation, Royal Prince Alfred Hospital, Camperdown, NSW, between Day 4 and Day 8. The exercise will be performed on a stationary cycle (Ergoselect 5, ergoline GmbH, Germany) and participants will be monitored according to standard protocols for the Exercise Lab (ECG, oxygen saturation, blood pressure and metabolic measures). This session will be supervised and tailored for each patient by one of the physiotherapists involved in the study, who all have expertise in exercise testing and training. The workload on the cycle will be titrated to achieve 60-70% of estimated peak heart rate and a reported breathlessness score of moderate-somewhat severe, as per pulmonary rehabilitation guidelines. A physician will also be available to provide supervision if needed (SS, HJ, SV). Participants will be observed for one hour after completion of the exercise session and provided with a hypoglycaemia kit (fast and long acting carbohydrate) if they show any sign of hypoglycaemia. They are then able to return home and will be advised to perform their regular activity and exercise routines at any time convenient to them until trial completion at Day 10.

After completion of the study (Day 11), the participants can discard the CGM in a biohazard sharps bin in their own home. This will be provided to them. Glucose monitoring results will be remotely downloaded using Libreview™ as per current standard of care, a cloud platform allowing access to glucose data with established security protocols. This secure, protected cloud-based diabetes management system allows glucose readings to be uploaded from LibreLink systems and reviewed. For both patients and healthcare professionals to access Libreview™ they must have an account which is password protected. Healthcare professionals must also be approved by admin of the 'Practice' so that they can access patient's glucose readings. For this study, the diabetic educator (MC) and Endocrinologist (KKJ) will access this data.

Patients will also use a pre-paid Australia Post envelope to return the activPAL™ device to the RPAH CF Service along with the activity, food and insulin diary. The activPAL™ data will be downloaded to a local computer and analysed with the inbuilt software (PALanalysis). The data is then deleted from the monitor and prepared for the next participant.

In the event of a COVID-19 outbreak where face to face visits are not permitted, the food diary, ActivPAL device and CGM will be mailed out to the patient with similar instructions. No supervised exercise testing will be performed.

4.3.1 Post-Trikafta™ study

If Trikafta™ becomes available on the PBS between 2021 and 2023, participants who completed the pre-Trikafta component of the study will be invited to complete this study a second time, after 4 weeks post Trikafta initiation. There will be no changes for the previously described protocol except that they now be on a new medication.

4.3.2 Healthy Control Participants

Healthy control (HC) participants without CF will be recruited via advertisement placed in the clinic waiting room.

4.3.3.Body Composition Substudy:

Participants will also be invited to undergo a body composition scan at the RPAH Endocrine department prior to their exercise study at the QEII gym. Often weight improves on treatment with gene modulators. Gained weight can be due to increases in fat free mass or fat mass (King et al Nutrition 2021). Components of body composition have different metabolic impact (Bellissimo et al J Cyst Fib 2019). Correlating changes in body composition with changes in glucose response could be achieved by assessing body composition via Dual Energy X-ray Absorptiometry before and after commencement of Trikafta.

5. STUDY PARTICIPANTS

5.1. INCLUSION CRITERIA

- CF participants

1. RPAH CF clinic patients, aged ≥17 years, who are clinically stable.
2. CF Patients with CFRD (n=15), impaired fasting glucose tolerance (n=15) and those with normal glycaemic control (n=15), according to their most recent oral glucose tolerance test (within 3 years, where applicable).

3. Clinically-stable at time of data collection, as assessed by the patient's treating respiratory physician, including no non-routine antibiotics in the previous 14 days.
4. Provides informed consent.
5. Eligible for Elexacaftor/Tezacaftor/ Ivacaftor (Trikafta™) – at least one Phe508del mutation.

- Healthy control participants

1. Healthy clinically stable participants, aged ≥17 years
2. No history of cardiovascular, neuromuscular, endocrine, respiratory disease.
3. Gender and age matched to enrolled CF participant

5.2. EXCLUSION CRITERIA

1. Unable to perform moderate intensity exercise or use continuous glucose monitoring device.
2. Colonisation with Tier 3 organisms (*Burkholderia cepacia*, non-tuberculous mycobacteria)
3. Previous lung transplant.
4. Pregnant or lactating females.
5. Known hypoglycaemia unawareness.
6. Mobile phone not compatible with the continuous glucose monitoring device.

6. STUDY PROCEDURES

Please see study procedures in section 4.5

6.1. STUDY PROCEDURE RISKS

All medical procedures - whether for diagnosis or treatment, routine or experimental – involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown and unforeseeable. In spite of all precautions, you might develop medical complications from participating in this study.

There is a slight possibility of a side effect during the supervised exercise session, although it is extremely unlikely that any unforeseen cardiac events (such as a heart attack, irregular heartbeat or rhythm or unstable blood pressure) would occur. Your heart rate and oxygen levels will be monitored. The test will be stopped if you request it or if the researchers decide this is necessary for your well-being. You will also be monitored for any signs of low blood sugar levels and if they occur, will be provided with the appropriate hypoglycaemia kit (fast and long-acting carbohydrate).

Flash glucose monitor insertion should cause no more than minimal discomfort, if pain is experienced, the monitor should be removed. There is a theoretical risk of infection at insertion site. The sensor needs to be removed if this occurs, and advice by a health care professional needs to be sought immediately. All parts of the sensor are considered biohazard, and need to be discarded into a sharps container provided by the investigators. The sensor cannot be shared with other persons due to infection risk. Reaction to the adhesive can occur, and if this is significant, the sensor needs to be removed.

There is a delay between blood glucose reading (blood glucose check on your finger using a glucose meter) and interstitial (reading on the skin tissue) glucose (flash glucose meter Libre). During rapidly changing glucose measures there may be differences between the sensor reading and blood glucose reading via finger glucose meter check. It is important to monitor your symptoms, treat your symptoms first and perform a blood glucose reading via finger glucose meter check if symptoms are not consistent with sensor reading. The Libre sensor cannot be worn during medical imaging procedures such as MRI.

It is important that women participating in this study are not pregnant and do not become pregnant during the course of the study. If you are a woman of child-bearing potential and there is any possibility that you are pregnant, the researchers will perform a pregnancy (urine) test before you start in the study. There is no risk for participants who are pregnant, it is just that pregnancy can affect blood sugar levels, so the results of the study may be altered. If at any time you think you may have become pregnant, it is important to let the researchers know immediately.

Incidental Findings:

Unexpected findings of low or high blood glucose readings can occur during the study periods. Participants will be asked to confirm these findings with a finger prick glucose check using a glucose monitor. We define low blood glucose readings as below 3.9 mmol/L, and low blood glucose needs to be treated to avoid significant consequences. Symptoms can be shaking, sweating, hunger, heart racing, irritability, dizziness, headache, nausea, confusion or odd behaviour. If this occurs, the treatment is to eat sugar containing food items such as jelly beans, honey or juice followed by a meal containing carbohydrates such as a sandwich.

We define high blood sugar as above 10 mmol/L. Symptoms can be thirst, blurry vision, urinating more than usual and weight loss. We strongly encourage you to notify the investigator team or a health practitioner if you discover any of the above findings, as we do not routinely monitor your data.

6.2. PARTICIPANT RECRUITMENT AND SCREENING

Will participants be screened?	**YES**

If yes, what data will be collected? (NB, if participant is not eligible, will data collected be destroyed or kept?) This should be mentioned in PIS/CF)	Only background information will be collected during the screening process (data collection sheet No 1-6). If ineligible, this data will be destroyed after completion of the trial.
Who will make initial contact with participants?	CF research team members.
Who will perform the consent process? How will this be carried out?	CF physician research team members
Will participants be consented verbally/explicitly/using eConsent? SLHD Research Forms Link	Verbally (consent form)
Will participants be given a specific time period to consider participating?	YES – at least 24 hours to review patient information sheet and consent prior to clinic visit or a mutually convenient time to discuss this study with the study team members. Patients can make a final decision on whether to participate in the study at their own time.
Review of existing databases or databanks (please identify the database/databank and the custodian)	CF mutation database held by RPA CF unit.
Review of clinic files (please include who will be reviewing these files, for example a research coordinator).	Review of clinic files will be done during the screening process by the CF physicians.
Advertisements (please include where the advertisement will be placed for example, in a newspaper, poster in a clinic or hospital foyer, radio announcements, website etc.)	Healthy Volunteers will be recruited via advertisement placed in the clinic waiting room
Information Letter to Medical practitioners	**NO**
Explain how potential participants will be screened for the study	Please see section 4.5 study procedures.
Any other potential recruitment methods.	Personal approach of RPAH respiratory staff. Please see section 4.5

6.3. PARTICIPANT ENROLMENT

Please see section 4.5

6.4. INFORMATION AND CONSENT

Please see section 4.5

6.5 END OF STUDY TREATMENT/WITHDRAWAL PROCEDURE

Participants can withdraw at any time during the study for any reason.

7. OUTCOMES

Please see section 4.4

8. DATA COLLECTION

Please refer to section 4.4 of this protocol for more detail on the data collected.

- PRIMARY ENDPOINT: Frequency of hypoglycaemia in the 48 hours after supervised exercise session (% time below 3.9 mM).
- SECONDARY ENDPOINTS:
- CGM data: Frequency of hypoglycaemia during the 4-10 day trial period (% time below 3.9 mM); Frequency of any severe hypoglycaemia events; CGM time in range, glucose variability, time above range, mean glucose (Chan, Vigers et al. 2018); Percent of time in normal glucose range time in range BGL 4-10 mmol/L; Frequency of hyperglycaemia during the 10 day trial period (time above range BGL>7.2 mmol fasting or >10 mmol/L 2-3 hours postprandially)
- Timing of meals prior to exercise
- Physical activity data (measured from activPAL): Time spent in moderate-vigorous physical activity; Time spent sedentary (sitting or lying down when awake); Daily step count
- Hypoglycaemia questionnaires: Edinburgh hypoglycaemia symptoms scale within 48 hours after observed exercise, if hypoglycaemia is observed (Deary, Hepburn et al. 1993); Clarkes hypoglycaemia awareness questionnaire; Cystic Fibrosis hypoglycaemia questionnaire
- Clinical data: Body mass index, presence of liver disease, pancreatic insufficiency and lung function (FEV1) and association with glucose levels during exercise

For those who are ineligible for the study, their background information (Data collection items 1-6 only) will be destroyed in a confidential manner (shredder) at the end of the study.

9. STATISTICAL METHODS

This is a pilot observational study evaluating the impact of physical activity and exercise on glycaemic control in patients with CF. Descriptive data will be expressed as mean ± SD, unless otherwise stated. Pair-wise comparisons will be tested by paired t-test or Wilcoxon signed-rank test depending on the normality of data distribution. Unpaired t-tests and Mann-Whitney U tests will be used for between group comparisons where appropriate. Associations will be tested by either Pearson or Spearman tests also based on normality of distribution.

The ActivPal data will be used to identify “exercise days” and “sedentary days”. For exercise days, we will divide time into 4hr blocks for the 24hr post exercise and assess the association with the standard CGM output as previously outlined (both supervised and unsupervised exercise). Secondarily, we will compare CGM data averaged over the whole 24 hours comparing exercise to sedentary days (00:00-24:00).

10. QUALITY CONTROL AND ASSURANCE

All testing procedures included in this study are part of routine care. Quality control is done as per hospital policy (eg CGM use and exercise testing).

11. SAFETY

Please see section 6.1.

12. CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY

Data collection will be on SLHD installation of REDCap. Paper food diaries will be stored in lockable filing cabinets located in a locked office on Level 11, Building 75 and access will be restricted to the investigators only. Access to designated representatives of Regulatory bodies for the purpose of study audits will be provided (if required), however strict confidentiality will be maintained.

Investigators will have access to this database and be responsible for managing user rights to this database. De-identified data collected in this survey may be presented at a cystic fibrosis conference or published in a peer reviewed journal.

13. TRIAL FINANCING

University of Sydney research account, held by Dr. Tiffany Dwyer, funded by a philanthropic donation from PS Davis Holdings. This account will pay for the CGM devices, consumables for the activPAL monitor, postage and hypoglycaemia kits. All other equipment is on loan from the University of Sydney and there are no staff costs, as this study is part of their routine duties. The donor has no involvement in the research study.

14. COMPENSATION

If a participant suffers any injuries or complications as a result of the research project, they will be advised to contact the study team and will be assisted with arranging appropriate medical treatment. If participants are eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

15. REFERENCES

Armaghanian, N., J. C. Brand-Miller, T. P. Markovic and K. S. Steinbeck (2016). "Hypoglycaemia in cystic fibrosis in the absence of diabetes: A systematic review." J Cyst Fibros **15**(3): 274-284.

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16. APPENDICES

1. Participant Information Statement
2. CF glucose monitoring study ActivPAL information sheet

3. CF glucose monitoring study participant consent form
4. CF glucose monitoring study participant info sheet (CF)
5. CF hypoglycaemia questionnaire
6. Data Collection Sheet
7. Advertisement for healthy volunteers
8. RPAH Food diary
9. Master Code Sheet
10. RDMP
11. CF glucose monitoring study participant info sheet (healthy volunteers)