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| **Project Title:** | Counting the Carbohydrate, Fat and Protein. A novel smartphone insulin dosing app to simplify mealtime insulin dosing in Type 1 Diabetes. |
| **Protocol No:** | 01 |
| **Protocol Version:** | Version 3 |
| **ANZCTR No:** | TBC |
| **Ethics No:** | TBC |
| **Funding Source:** | Australian Diabetes Educators Association (ADEA) |

**Study Personnel: Roles and Responsibilities**

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**1. Study Synopsis**

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| **Full title** | Counting the Carbohydrate, Fat and Protein. A novel smartphone insulin dosing app to simplify mealtime insulin dosing in Type 1 Diabetes. |
| **Short title** | OptimAAPP Efficacy Trial |
| **Lead Investigators** | Dr Carmel Smart (JHCH), Prof Bruce King (JHCH), Prof David O’Neal (Melb) |
| **Study Site** | John Hunter Children’s Hospital, Newcastle, Australia and St. Vincent’s Hospital, Melbourne, Australia |
| **Study Design** | A randomized, cross-over clinical trial |
| **Aim** | To determine if a novel smartphone insulin bolus calculator, “OptimAAPP” that incorporates calculations for carbohydrate, fat and protein improves glycaemia in comparison to usual care using carbohydrate counting. |
| **Sample size** | 48 subjects (n= 24 paediatric, n= 24 adults) |
| **Eligibility criteria** | * Aged between 10- 50 years * HbA1c ≤ 10% (86 mmol/mol) * Type 1 Diabetes > 1 year * Managed with multiple daily injections and insulin: carb ratio > 6 months |
| **Exclusion criteria** | * Complications of diabetes (e.g. gastroparesis) * Any other major medical condition |

**2. Project Background/ Rationale**

Diabetes guidelines acknowledge the need to consider fat and protein when calculating the prandial insulin dose for individuals with Type 1 Diabetes (T1D) using intensive insulin therapy. The American Diabetes Association (ADA) Standards of Medical Care (2018) state "selected individuals who have mastered carbohydrate counting should be educated on fat and protein gram estimation". This project will address this gap and provide a means by which individuals can be educated on fat and protein estimation and dose accordingly. As dosing calculations are complex, clinician researchers at the John Hunter Children’s Hospital in collaboration with System Control Engineers at the University of Newcastle have developed an insulin bolus calculator to calculate the meal-time insulin dose and delivery for meals of mixed macronutrient intake. This is based on over a decade of collaborative dietary intervention studies by our team investigating the separate and combined glycaemic impact of dietary macronutrients (Lopez et al 2018; Lopez et al 2017; Paterson et al 2017; Paterson et al 2016; Smart et al 2013; Smart et al 2013; Smart et al 2010; Ryan et al 2008). In association, an education package has been developed to educate patients on dietary sources of fat and protein.

A smartphone insulin bolus calculator provides a means of directly addressing the primary barrier to guideline adherence, complexity by incorporating decision support systems that can perform complex computations to support optimal insulin dosing. OptimAAPP and the accompanying education package presents a unique opportunity to resolve existing national and international inconsistency in standards of clinical care by providing diabetes clinicians with equitable access to a sustainable, best practice, evidence- based tool and educational resource to improve guideline implementation and promote optimal glycaemic control.

Aim

The proposed trial aims to determine if a novel smartphone insulin bolus calculator, “OptimAAPP” which calculates insulin for carbohydrate, fat and protein improves glycaemia in comparison to usual care (insulin dosing for carbohydrate only).

Hypothesis

OptimAAPP will improve glycaemic control in people with Type 1 Diabetes (T1D) using multiple daily injection therapy, as measured by an increase in time spent in a glycaemic target range of 3.9-10.0mmol/L without an increase in time spent in hypoglycaemia compared to usual care.

**3. Study Design**

3.1 Statement of study design

This is a randomized cross- over clinical trial to be conducted at the John Hunter Children’s Hospital, Newcastle and St Vincent’s Hospital, Melbourne under free- living conditions.

3.2 Study population

Children, adolescents and adults who have Type 1 diabetes mellitus (n= 48)

*3.2.1 Eligibility criteria*

* Aged between 10- 50 years
* HbA1c ≤ 10% (86 mmol/mol)
* Type 1 Diabetes > 1 year
* Managed with multiple daily injections and insulin: carb ratio > 6 months

*3.2.2 Exclusion criteria*

* Complications of diabetes (e.g. gastroparesis)
* Any other major medical condition

**4. Study procedure**

4.1 Study overview



***Visit 1 (1- 3 hours)***

* Baseline data collection
* Refresher on carbohydrate counting
* Insertion of CGMS and education on use

± Education with resources on protein and fat identification

***Run-in period (2 weeks x2)***

Conducted to optimise the participant’s usual insulin: carb ratio, correction factor and basal insulin. Participants will be required to wear CGM to permit adjustments

***Intervention period (24 weeks)***

Participants will be stratified by age group (paediatric or adult) and randomised to usual care or OptimAAPP for 12 weeks using permuted block randomisation. Participants will then cross-over to the alternate study condition. A second run-in period (1 week) will be conducted between the intervention periods to minimise the potential effect of carry-over (see Figure 1).

*Intervention*

The study intervention involves two primary components, the insulin bolus calculator, OptimAAPP and a supporting evidence- based fat and protein curriculum.

OptimAAPP has been developed by expert diabetes clinicians in partnership with control engineers, clinician academics and behavioural scientists and in close consultation with our consumer advisory group. OptimAAPP houses a novel algorithm that calculates prandial insulin based on the meals carbohydrate, fat and protein content, the user’s blood glucose level, insulin on board, individual insulin sensitivity factors and insulin: carbohydrate ratios. Prandial insulin dose calculation is supported by macronutrient reference values derived from an in- built food database, basal insulin and insulin active time settings and records of bolus insulin delivery.

OptimAAPP takes into consideration the following factors;

1. The glycaemic response elicited by carbohydrate, fat and protein differ (time to peak glucose excursion, duration of excursion and magnitude of excursion).
2. The degree of responsiveness (sensitivity) to carbohydrate, fat and protein differs between individuals.
3. Sensitivity to insulin differs between individuals.

OptimAAPP is novel in that it permits the adjustment of insulin to fat and insulin to protein ratios based on individual sensitivities.

To enhance understanding of the insulin dose adjustments required for fat and protein in meals a curriculum with resources will be delivered to educate people with T1D how to identify sources of protein and fat in a meal. This package has been developed locally, at John Hunter Children’s Hospital by accredited practicing dietitians in consultation with credentialed diabetes educators and a consumer advisory group. These resources have been piloted at John Hunter Children’s Hospital and have recently been incorporated into the DAFNE (Dose Adjustment for Normal Eating) Australia (OzDAFNE) curriculum.

4.2 Eligibility Screening and Visit 1

Eligibility will be determined during attendance at quarterly clinic visits. Participants who are deemed to be eligible will be approached by a member of the study team who will give a verbal description of the study procedures and aims as well as an age appropriate written information pack. If the participant consents to being in the study an appointment will be made for Visit 1. Visit 1 will be approximately 2 hours in duration and will involve a review of the participants’ carbohydrate counting ability, education on the use and features of the Dexcom G5 CGMS and if randomised to intervention; delivery of fat and protein and OptimAAPP education.

4.3 Intervention Periods 1 and 2

Intervention periods 1 and 2 will follow the same structure; a 12 week period in a free living environment with the use of CGM at weeks 4, 8 and 12. The difference between the periods will be the method used to calculate the insulin dose for food. Participants will use either their usual method of care or the smartphone insulin bolus calculator OptimAAPP to calculate their insulin dose. The order of these study periods will be randomised for each participant.

4.4 Study measurements

*4.4.1 Baseline measurements*

Baseline investigations to be documented include participant age, gender, ethnicity, height and weight, results of screening pathology (HbA1c), long- acting insulin dose (basal insulin), insulin: carb ratio/s and correction factor/s, the use of any medications and co- existing medical conditions.

*4.4.2 Glucose measurements*

Participant interstitial glucose levels will be measured for 6 non- continuous weeks using the Dexcom G5 mobile® continuous glucose monitoring system.

4.5 Study Outcome Measures

*4.5.1 Primary Outcome*

The primary outcome variable is to compare the proportion of time spent in target glucose range (3.9-10 mmol/L) while using OptimAAPP compared to standard care.

*4.5.2 Secondary Outcomes*

Secondary outcome variables to be measured include;

* Change in HbA1c collected at 3 time points- baseline and 12 weeks post each intervention
* Hypoglycaemic events defined as sensor glucose values < 3.9mmol/L for >15 minutes
* Glycaemic variability defined as Mean Amplitude of Glycaemic Excursions (MAGE) and Co-efficient of Variation (CV).
* Pre and post questionnaires on fat and protein knowledge
* Qualitative assessment of OptimAAPP user experience

4.6 Participant timeline (Figure 1)

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|  | | | **STUDY PERIOD** | | | | |
|  | **Time to complete** | **Location** | **Enrolment** | **Pre-study** | | **Post-randomisation** | **Close-out** |
| **ENROLMENT** | | | | | | | |
| ***Informed consent*** | 20 mins | Clinical setting | X | |  |  |  |
| **INTERVENTION** | | | | | | | |
| ***Visit 1. Collection of baseline data, CGM training and carb counting review*** | 60- 120 mins | Clinical setting |  | |  | X |  |
| ***Run- in 1*** | 2 weeks | Free living environment |  | |  | X |  |
| ***Usual Care*** | 12 weeks | Free living environment |  | |  | X |  |
| ***Visit 2. CGM initiation, carb counting review, dietary education, OptimAAPP education*** | 120- 180 mins | Clinical setting |  | |  | X |  |
| ***Run- in 2*** | 2 weeks | Free living environment |  | |  | X |  |
| ***Use of OptimAAPP*** | 12 weeks | Remote monitoring |  | |  | X |  |
| **ASSESSMENTS** | | | | | | | |
| ***Glucose monitoring*** | 24 hours/day for 6 weeks | Remote monitoring |  | |  | X |  |
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**Figure 1. Participant Timeline.**

4.7 Sample size

Assuming the standard deviation of the percentage time in target is 20 based on our previous studies, and a within-person correlation of 0.3, a sample of 48 subjects will provide the study with 80% power to detect an absolute difference of 10% in the mean percentage time spent with glucose levels within the target range (3.9–10.0 mmol/L) between conditions at the 5% significance level. This is clinically meaningful as per other studies (McCauley et al).

4.8 Statistical analyses

Differences between conditions in the primary outcome variable will be assessed using a linear mixed model. The model will include fixed effects for time, order, and condition, and a random effect for participant. Analyses will follow the intention to treat principle.

**5. Data monitoring, harms and auditing**

5.1 Data Monitoring

The study team will conference fortnightly to review study progress as well as regular email contact. Case files for documentation of data will be in place. An interim analysis of 15 complete data sets will be scheduled post 9 months study start.

5.2 Harms (Reporting adverse circumstances)

The lead investigators will inform the relevant HREC of any adverse events. Adverse events and safety reporting will be completed as per local ethics protocol.  This study will be conducted following guidelines outlined in the note for Guidance in Good Clinical practice (CPMP/ICH/135/95) and the National Statement of Ethical Conduct in Research Involving Humans (2007).

5.3 Auditing

A compliance check for essential document collection and data integrity will be performed periodically (n= 8) by a research team member not involved in primary data collection and cleaning.

**6. Ethics and dissemination**

*6.1 Ethics approval*

Ethics approval will be obtained from Hunter New England Research Ethics Committee and registered with the University of Newcastle Human Research Ethics Committee. Governance approval will be sought from the Research Governance Unit at St Vincent’s Hospital, Melbourne. The study will be registered with the Australia New Zealand Clinical Trials Registry.

*6.2 Approach and recruitment*

Individuals who are eligible to participate in this study and who express interest in participation will have the study protocol explained to them and where applicable, their parent/guardian in full by a member of the research team. Potential participants and where applicable their parent/ guardian will also be provided with written age- appropriate study information packs, these documents will outline the study procedure, the requirements of participants as well as the risks and benefits associated with participation. At this time, potential participants will be encouraged to ask questions. All individuals will be given the contact details of a nominated research team member if further questions were to arise and will be given adequate time to consider this information prior to giving their consent. This will be a minimum of one week but up to 1 month. All participants may withdraw from this study at any time without consequence.

6.3 Informed consent

All individuals who are eligible for this study and who wish to participate will be asked to sign a consent form agreeing to the procedures outlined in the study protocol. Children and adolescents (10 -18 years) will be able to provide informed consent, informed consent will also be obtained from their parent/guardian according to current ICH, Good Clinical Practice (GCP) Guidelines and The National Statement on Ethical Conduct in Human Research 2007 (Updated 2018). All written and signed consent documents will be retained in the study files.

6.4 Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the participant or may affect participant safety, including changes of study objectives, study design, population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the research team and approved by the Ethics Committeeprior to implementation. Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by the research team and will be documented in a memorandum.

7.5 Confidentiality

All study-related information will be stored securely at the study sites. All participant information will be stored in locked file cabinets in dedicated research office space with limited access. All reports, data collection, process, and administrative forms will be identified by a coded ID [*identification*] number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

7.6 Declaration of interests

There are no declarations of interest

7.7 Access to electronic data

All data sets will be stored on a secure server, on a password protected data log which only the research team will have access to.

7.8 Ancillary and Post-trial care

Participants will be encouraged to seek medical care from their usual general practitioner for non- trial related medical conditions throughout the study and post- study.

7.9 Dissemination Policy

*Participants:*

The CGM data collected during the study period will be summarised in a report and sent to participants via a secure pathway at their request. This information may be discussed with the participant during their end- point follow up phone call.

*Health Professionals and wider community:*

De- identified study results will be presented at national and international meetings and conferences as well as published in peer reviewed journals.

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