Trial Title: Investigation of Appropriate Timing of Additional Insulin Dosing for Fat and Protein in Children with Type 1 Diabetes using Multiple Daily Injections

Internal Reference Number / Short title: Fat and Protein Study

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Funder:	NovoNordisk Research Foundation
Chief Investigator Signature:	

None of the investigators have any conflict of interest with this research proposal

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	Investigation of Appropriate Timing of Additional Insulin Dosing for Fat and Protein in Children with Type 1 Diabetes using Multiple Daily Injections	
Internal ref. no. (or short title)	Fat/Protein Study	
Clinical Phase	Phase 4	
Trial Design	Controlled observational study	
Trial Participants	Children aged 6 to under 18 years of age with type 1 diabetes (T1DM)	
Planned Sample Size	40	
Treatment duration	1 week	
Follow up duration	No follow-up at the end of the trial period	
Planned Trial Period	1 year	
	Objectives	Outcome Measures
Primary	To determine whether additional insulin boluses for the fat and protein content of a meal given before, one or two hours after a meal optimise post-prandial blood glucose levels in children with Type 1 diabetes using multiple daily injections?	Continuous subcutaneous glucose profiles will be examined to determine – • mean post-prandial glucose excursion for 8 hours following the test meal
Secondary	To examine other indices of BG control following additional insulin boluses for the fat and protein content of a meal given before, one or two hours after a meal in children with Type 1 diabetes using multiple daily injections?	Continuous subcutaneous glucose profiles will be examined to determine – • peak BG level • peak BG excursion from baseline (pre-meal BG level) • time of peak BG level from baseline measurement • Rate of BG excursion from baseline to peak • mean post-prandial glucose excursion for 5 and 12 hours following the test meal • area under the curve at time-points 0-3 hours, 3-5 hours, 5-8 hours, 8-12 hours post-meal • Time from baseline BG at which BG returns to baseline level
Investigational Medicinal Product(s)	Insulin	
Formulation, Dose, Route of Administration	Insulin Aspart (NovoRapid) given in a dose according to the protocol, subcutaneously	

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BG	Blood Glucose
CGM	Continuous subcutaneous glucose monitor
CHO	Carbohydrate
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICR	Insulin to carbohydrate ratio
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MDI	Multiple Daily Injections
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions

TMF	Trial Master File
TSG	Oxford University Hospitals Trust / University of Oxford Trials Safety Group

4. BACKGROUND AND RATIONALE

Type 1 Diabetes incidence in children is increasing in the UK and internationally. Blood glucose (BG) control is improved with intensive insulin therapy including multiple daily injections and insulin pump therapy, and long-term complications are known to be related to blood glucose control [1]. Post-prandial BG levels have been linked with the risk of cardiovascular disease, one of the major complications of diabetes [2].

In order to keep BG levels as normal as possible, all children in our clinic on intensive insulin management are taught to match insulin dose to the carbohydrate quantity in food. We and others have previously demonstrated that children and their families can learn to count the quantity of carbohydrate in food [3], and that the link between carbohydrate quantity and insulin dose does affect the post-prandial BG level [4].

There is increasing evidence that the fat and protein content of food affects BG levels in addition to the known effect of the carbohydrate content of the food. Pankowska's group were the first to routinely count fat and protein in food, and to use this value to calculate additional insulin doses given as prolonged boluses in children using insulin pumps to maintain good BG control, demonstrating that those children who used such doses and boluses were more likely to achieve target levels of control [5]. Subsequent studies by the same group and others have refined the technique to demonstrate improved PPBG levels in children using insulin pumps [6,7].

A recent study by Smart et al has shown that the post-prandial BG levels can remain high for several hours after high fat and high protein meals when insulin is given purely for the carbohydrate content [8]. Furthermore, the effect is additive, with high protein and high fat meals causing high post-prandial BG levels which had not returned to pre-prandial levels up to 6 hours after a meal [8].

A recent systemic review of ten studies examining insulin bolus dose and delivery patterns required for high fat and/or high protein meals has generated recommendations for clinical practice [9]. Although all the studies included have been conducted in patients using insulin pumps (adults and children) the authors have extrapolated their conclusions to make recommendations for changes to insulin dose calculations and delivery options in both CSII and MDI therapy.

It is suggested that for high fat meals containing over 40g fat that insulin doses should initially be increased by 30-35% on the usual dose calculated using their ICR with the extra insulin given as a separate injection 1 hr after the meal. This dose should be monitored and increased according to individual response [9].

They also recommend that for meals containing 30g fat and 40g protein that the insulin dose calculated with usual insulin:carbohydrate ratios should be increased by 15-20% but do not suggest a delivery method for this extra insulin [9]. It should be noted that all these recommendations are intended for an adult population.

The review recognises gaps in knowledge and evidence base to support specific recommendations and algorithms to calculate insulin doses and delivery patterns according to the fat and protein content of meals. Furthermore, they identified significant inter-individual variability in post-prandial glycaemic response to high fat and protein meals which may be a confounding factor to research and meaningful conclusions in this area [9].

We therefore plan to investigate how to appropriately administer additional insulin for the fat and protein content of high protein and high fat meals to children on multiple daily injections (MDI) to improve BG levels up to 12 hours after a meal.

In line with our previous studies (3,4) and as indicated from a power calculation, we will recruit forty patients from the Oxfordshire Children's Diabetes Service aged from 6 to under 18 years and obtain full informed consent. There will be a run-in period of 7 days during which time the children's insulin to carbohydrate ratios will be optimised.

The children will then be asked to wear continuous subcutaneous glucose monitors (CGM) which are a well-recognised and validated method of monitoring BG levels over several days. The particular version we will use for this study lasts for 7 days.

During the 7 day study period, the children will be asked to consume a standard high-fat, high-protein test meal on 3 separate evenings. They will asked to give insulin for the carbohydrate (CHO) content of the meal before the meal on all 3 days. Additional insulin will be calculated for the fat and protein content on the basis of the Pankowska equation [6] and recommendations from the most recent systemic review of current research [9] and will be given in a random order, either before, 1 hour after, or 2 hours after the first insulin dose before meal. The child and family will be able to choose which days during the study period on which they complete the study meals but will be advised to avoid the day that the CGM sensor was inserted, days when the participant has undertaken lots of exercise, is hypoglycaemic immediately before the meal, or has had frequent hypoglycaemic episodes earlier in the day or has been unwell.

BG levels will be monitored using the CGM for the evening and overnight until the next morning.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To determine whether additional insulin boluses for the fat and protein content of a meal given before, one or two hours after a meal optimise post-prandial blood glucose levels in children with Type 1 diabetes using multiple daily	Continuous subcutaneous glucose profiles will be examined to determine – • mean post-prandial glucose excursion for 8 hours following the test meal	Continuous Glucose Monitoring profiles during the 12 hours following the test meals

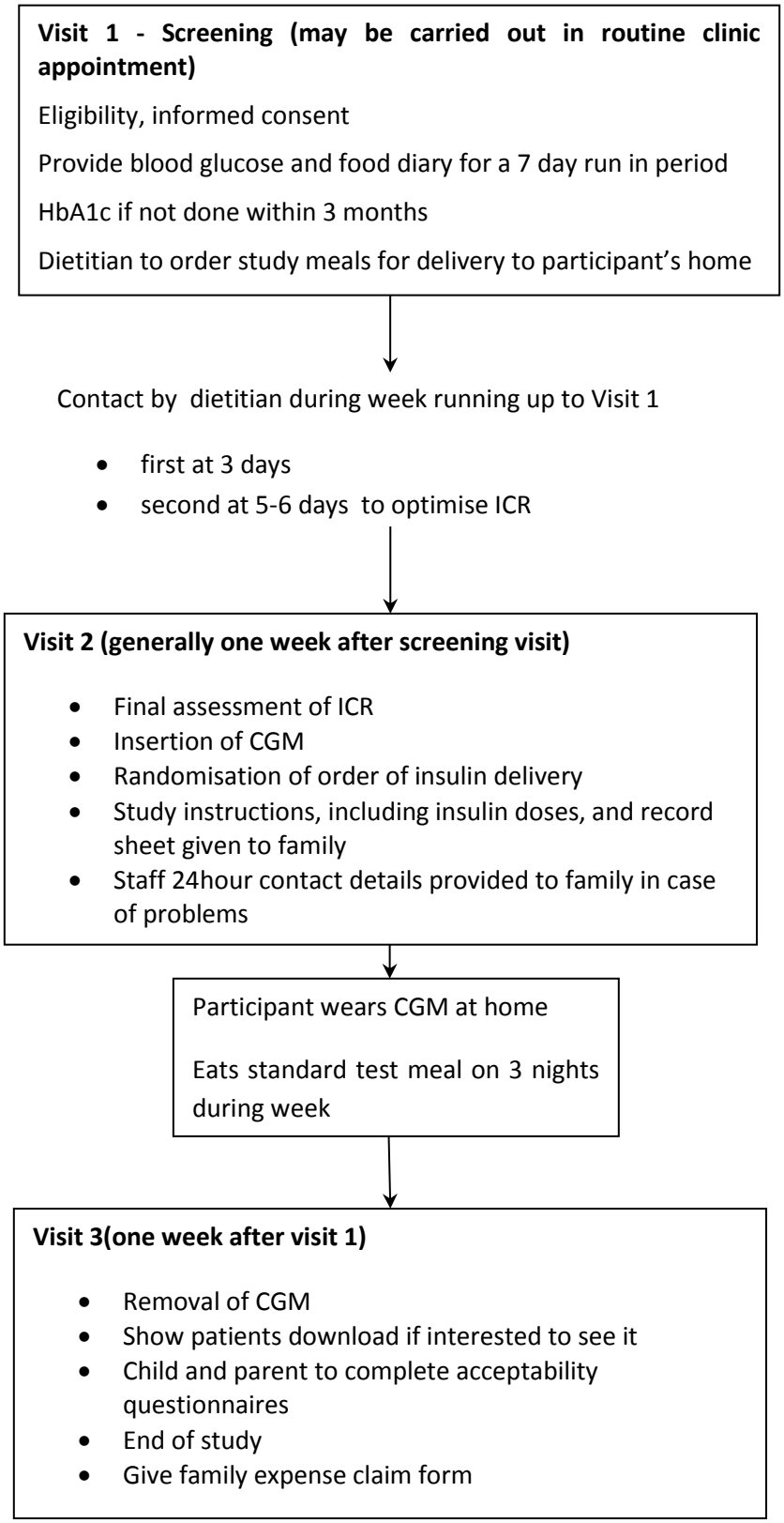
injections?		
Secondary Objectives To examine other indices of BG control following additional insulin boluses for the fat and protein content of a meal given before, one or two hours after a meal in children with Type 1 diabetes using multiple daily injections?	Continuous subcutaneous glucose profiles will be examined to determine – • peak BG level • peak BG excursion from baseline (pre-meal BG level) • time of peak BG level • timing of peak BG excursion area under the curve at time-points 0-3 hours, 3-5 hours, 5-8 hours, 8-12 hours post-meal	Continuous Glucose Monitoring profiles during the 12 hours following the test meals
Tertiary Objectives 1. To assess the acceptability of giving additional insulin doses for fat and protein to children using MDI 2. To assess the safety of giving additional insulin doses for fat and protein to children using MDI	1. Questionnaires to parents and children during and at the end of the study 2. All episodes of hypoglycaemia (BG less than 4 mmol/l) or hyperglycaemia (BG >12 mmol/l) either on CGM or self-monitoring of BG	Collection of data during and at the end of the study

6. TRIAL DESIGN

6.1. Summary –

The study design is a repeated measures study involving the provision of a standard high protein/high fat evening test meal on 3 different evenings within a 7-day period in the same study subject. The children/adolescents will be instructed to give an insulin dose for the carbohydrate before the meal (calculated using their optimal insulin to carbohydrate ratio (ICR)). In addition they will have an extra dose for the fat and protein content either before (together with the dose for the carbohydrate in the meal [control meal]), 1 hour after, or 2 hours after the first insulin dose given before the meal. These will be carried out in a random order in each subject. Glucose monitoring will be carried out using CGM for the whole 7 day period.

6.2. Study Flow Chart -



6.3. Detail –

The clinical diabetes team in each participating hospital will identify children in the service who are using multiple daily injections to manage their diabetes and who would be eligible for the study. In addition, in Oxford, an e-mail will be sent to all patients signed up to the e-mail service to alert them that the study is open to recruitment. The study will also be advertised in the Oxford 3 monthly newsletter and families could volunteer if they are interested in their children taking part. There will also be a poster made for both the Oxford and Reading clinics to advertise the study. Once the family has expressed an interest in hearing more about the study, the relevant information sheets will be handed to the patients in clinic or sent by post.

After the initial contact, the research nurse or dietitian will telephone the patient and family after a week to answer any questions they may have about the study. If they are keen to participate, an appointment will be arranged for consent and to commence the study (Visit 1). If the patient or family do not wish to take part at this point this would be documented on the approach log.

At Visit 1 we will obtain informed consent (see section 7.2) and commence a week-long run-in period for participants to optimise insulin to carbohydrate ratio at the evening meal. During this week subjects will be requested to test BG levels at 7 points throughout the day (pre-meals, 2 hrs after meals and bed). They will be asked to eat a fat and protein free meal on one of these days. If necessary, adjustments to the insulin to carbohydrate ratio (ICR) or long-acting insulin doses will be made over the telephone or via email by an experienced member of their clinical team. This is to decrease the likelihood of a high or low BG level at the evening meal during the study week which would require the meal to be abandoned.

At the end of the run-in week, participants will then attend the outpatient clinic or day care ward research facility at the Oxford Children's Hospital or the Horton Hospital outpatient clinic in Banbury or the Royal Berkshire Hospital in Reading (Visit 2). At this visit, the subcutaneous glucose sensor will be inserted by the research nurse and children and young people and their families will be trained on its use prior to the study commencing. CGM records BG levels every 5 minutes over 7 days and thus provides much more information than routine BG testing. These systems are regularly used by the Paediatric Diabetes team in clinical care and are well accepted by patients. The CGM records will enable researchers to calculate the area under the curve for post-prandial BG response to determine if there are significant differences between the test insulin dosing schedules. Children and young people will also record their BG levels from routine finger pricks, pre-prandially and before bed and on waking in the morning.

We considered using a blinded CGM system which does not reveal current blood glucose levels in order to reduce participant and parental anxiety, however the only system like this on the market does not alarm on hypoglycaemia which is an essential safety measure for this study and this option was therefore rejected.

Also at Visit 2, the study dietitian will review BG readings and food diary from the previous week and optimise ICR doses of rapid acting insulin. This ratio will then be used to calculate insulin doses for the study meals according to the following algorithm based on the Pankowska (Warsaw) equation [6] and recommendations from the latest systemic review of current research [9]

Insulin dose for carbohydrate = g CHO x ICR
Insulin dose for fat and protein = FPU x (0.3 x ICR)
TOTAL Insulin dose = (g carbs x ICR) + (FPU x (0.3 x ICR))

Where FPU = fat-protein unit and 1 FPU = 100kcal from fat and protein

On three evenings over the next 7 days, the children will eat a standard high protein/high fat meal. The evenings will not be set, but will depend on the child and family schedule. The study meal will not be eaten on the evening that the CGM is inserted as sensor accuracy takes 24 hours to maximise accuracy. The child and family will be able to choose which days during the study period on which they complete the study meals but will be advised to avoid days when the participant has undertaken lots of exercise, is hypoglycaemic immediately before the meal or has had frequent hypoglycaemic episodes, or has been unwell.

The standard meal will be a portion controlled gluten-free meal provided and delivered by Wiltshire Farm Foods consisting of a meat-based main course and dessert. These will be kept frozen until used by participants and prepared according to manufacturer instructions. These meals come in two sizes which allow portion sizes to be adjusted for different ages of child, but the proportions of fat, protein and carbohydrate will be kept constant for each child, and by definition the meals will be high in protein and high in fat.

Insulin doses with the standard meal will be given according to calculations carried out by the dietitian and administered in one of three ways.

The three evenings in random order will be as follows -

1. Insulin units based on ICR and fat/protein dose given together immediately before the meal [control meal].

2. Insulin units based on ICR given immediately before the meal plus extra insulin for fat/protein units given 1 hour after the first meal dose.

3. Insulin units based on ICR given immediately before the meal plus extra insulin for fat/protein units given 2 hours after the first meal dose.

Participants will be asked not to give a correction dose before the meal if the BG level is between 7-12mmol/l as this would interfere with the analysis. They will be asked, if possible, not to carry out the test meals if their pre-meal BG is greater than 12 mmol/l But If they have to do the test meal with a high pre-meal BG (above 12 mmol/l) they will be instructed to give their usual correction bolus in addition to the prescribed insulin dose for the test meal. This data will be analysed separately. If BG is below 4mmol/l (hypoglycaemic) or above 16mmol/l participants will be asked to abandon the study evening and repeat on another evening. Full written instructions will be provided to the family for all aspects of the insulin dosing for the study meals.

During the study on the standardised meal days children will be instructed not to eat any food after the meal during the evening, and not to correct any later BG levels unless they are dangerously high (BG over 16 mmol/l with ketones over 0.5 mmol/l). If BG levels go low at any time (BG less than 4 mmol/l) children will be instructed to treat the hypoglycaemia according to their usual management, and omit

any further study doses of insulin if the hypoglycaemia occurs after a first study dose and a second is due. This data will be analysed separately. Children and families will be asked to complete diaries during the trial week.

At the end of the study period (the day after the third meal), children will come back to the research facility or clinic for the end of study visit (visit 3). A research nurse or dietitian will remove the CGM sensor and download the data onto a secure laptop. Children and their families will then be asked to complete a short questionnaire about the acceptability of using the extra insulin doses, and their perceptions as to whether there were any beneficial or adverse effects.

The study dietitian will calculate standard outcomes from each patient's sensor download and pass on anonymously to the study statistician to analyse the data.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

Children and young people aged between 6 and under 18 years with Type 1 diabetes on multiple insulin injection regimes who are under regular out-patient review by the Oxfordshire Children's Diabetes Service or the Royal Berkshire Children's Diabetes Service.

7.2. Inclusion Criteria

- Diagnosis of Type 1 diabetes (for at least a year)
- Aged 6 to under 18 years.
- On multiple daily insulin injections, including basal long-acting insulin and rapid-acting insulin before each meal.
- HbA1c < 75 mmol/mol (9.0%)
- Participant and/or parent/legal guardian willing and able to give informed consent for participation in the study.
- Family have a freezer in which to safely store the test meals.
- In the Investigator's opinion, is able and willing to comply with all trial requirements.

7.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- HbA1c greater than 75 mmol/mol (9.0%)
- Child unwilling to agree to second insulin injection at a meal-time
- Untreated coeliac disease or other concomitant condition likely to affect BG control
- Food allergies (other than controlled Coeliac Disease)

- Vegetarians, vegans or patients with religious dietary restrictions (as the standard meal contains meat)
- Participant taking any glucose-containing medication concurrently

8. TRIAL PROCEDURES

8.1. Recruitment

The clinical diabetes team in each participating hospital will identify children in the service who are using multiple daily injections to manage their diabetes and who would be eligible for the study. In addition, in Oxford, an e-mail will be sent to all eligible patients' families signed up to the e-mail service to alert them that the study is open to recruitment. In Oxford, the study will be advertised generally in the routine 3 monthly newsletter which is available in the clinic, with details of who to contact for more information about the study. Once the family has expressed an interest in hearing more about the study, the participant and parent information sheet will be given to eligible children and young people and their parents at their routine diabetes clinic visit or sent in the post if interest has been expressed.

The information sheets will provide contact details of the researchers if the potential participants want more information before making a decision. After allowing a week for the child and parent to read the information sheets, the research nurse or dietitian will telephone the family asking if they have any further questions about the study, to provide further information, and enquire if the child and family are willing to consent. If they are willing to participate, an appointment will then be made to obtain informed consent.

8.1. Screening and Eligibility Assessment

The HbA1c level taken at the preceding clinic (maximum of 3 months before approach) will be used to assess eligibility. If the clinic visit was more than 3 months before the start of the study, a further HbA1c level will be measured by rapid analysis at the time of the first visit. All other screening and eligibility assessments can be carried out on the telephone by the research nurse or research dietitian.

8.2. Informed Consent

Informed consent will be undertaken by a nurse or doctor on the research or clinical team who has had GCP training with specific training in informed consent and has been authorised to do so by the Chief Investigator. Verbal and written information will be given to potential participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Information will be presented to children and young people both verbally and in written form in an age- appropriate manner. Written assent will be sought from children 8-16 years of age.

The participant will be allowed as much time as wished to consider the information and will be given the opportunity to question the doctor or nurse, their consultant, their GP or other independent parties to decide whether they will participate in the study.

Written Informed Consent will then be obtained by means of parent/legal guardian dated signature and dated signature of the person who presented and obtained the Informed Consent. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site. For children >8 years of age a dated signature will be sought on an assent form. Young people over the age of 16 will be able to sign their own consent form.

The parent/legal guardian or young person over the age of 16 must personally sign and date the latest approved version of the informed consent form before any trial specific procedures are performed.

8.3. Randomisation, blinding and code-breaking

Randomisation is required only for the order of the insulin dosing. The study statistician will provide the randomisation codes and the study dietitian will make up sealed envelopes with all the instructions inside for the schedule for the participant according to the randomised order of treatment. This schedule will form part of the study diary for each participant. The envelopes will be kept in the research office in Oxford until they are needed, when the next one will be taken for the next participant entering the study at any of the participating sites. The envelope will be opened by the research nurse or dietitian at the first study visit when the CGM is being inserted. As the same research team will be working at all sites there is no requirement for separate codes for each site.

Unblinding will not be required as this is not a blinded study. Participants and researchers will know the order of the insulin doses for the test meal from the start of the study.

8.4. Baseline Assessments

At visit 1, after the informed consent and assent forms have been signed, the dietitian will collect details of the insulin to carbohydrate ratios currently being used at the evening meal-time. A record book will be provided to the child and family to record their blood glucose levels, carbohydrate quantities and insulin doses for the run-in week. During the run in week the participant will be requested to record blood glucose levels before and 2 hours after meals, snacks and before bed. They will also be asked to record CHO intake and insulin doses given.

After 3 days the dietitian will telephone to obtain BG levels and work out whether any adjustments need to be made to the ratios. A further telephone call will be made on day 5-6, with further adjustment if necessary. After this first visit, the study meals will be ordered by the dietitian or nurse to be delivered to the participant's home.

8.5. Subsequent Visits

Visit 2 – Study visit

- A review of the BG levels in the preceding week will be carried out by the study dietitian, in order to determine whether any further adjustments in insulin dose need to be made.
- The CGM will be inserted.
- Randomisation of the insulin dose order will be carried out and final dose calculations will be done by the dietitian according to the equations in section 5.3.
- Full written instructions will be provided to the participants, including insulin doses and timings for the three study meals, contact details and what to do if BG levels should be high (greater than 16mmol/L) or low (less than 4mmol/L).
- There will also be instructions about what they should do in the event of a sensor malfunction.
- The child and family will be informed that they can call the research team during office hours at any stage to discuss events during the week of the study, and they will be provided with contact details. If any advice is required outside office hours, they will be advised to contact their clinical diabetes team in the usual way.

Visit 3: End of study visit - The participant will return to their original outpatient or day-care setting and the CGM sensor will be removed by the study nurse and data downloaded onto the web-based system Diasend which is regularly used in clinics. Participants and their family will have the opportunity of viewing the download from the sensor. The participant and parent will be asked to complete the short questionnaires about the acceptability of the additional insulin doses.

8.6. Sample Handling

No samples will be taken during the trial. The only sample for eligibility is the HbA1c finger-prick sample which will be taken and managed routinely according to protocols in the relevant clinical service.

8.7. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- Severe hypoglycaemia occurring during the trial week, whether or not this is as a result of the evening meal dose of insulin
- Withdrawal of Consent
- Loss to follow up

Any CGM data available up to the time of patient withdrawal or exclusion will be included in the data analysis.

The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

8.8. Definition of End of Trial

The end of trial is the date of the last visit of the last participant.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. IMP Description

The trial IMP is Insulin Aspart (NovoRapid). This is provided to the participant as part of normal standard care. The trial medication will be dispensed according the standard procedures at each site and is being used in its normal indication and standard therapeutic dose. The only change in this study is the insulin dosage around the evening meal.

9.2. Storage of IMP

No specific storage requirement above those stated for standard care are required for the IMP in this trial. There will be no temperature monitoring for the IMP.

9.3. Compliance with Trial Treatment

Participants and their families will be asked to complete a diary including the actual insulin doses given. This will be viewed at the end of the study and data may be removed from analysis if significant non-compliance has occurred, for example the advised dose was not given, or the timing was not accurate to within 15 minutes.

9.4. Accountability of the Trial Treatment

IMP is supplied as part of normal standard care and therefore no accountability records will be maintained for the trial.

9.5. Concomitant Medication

Any glucose-containing medication is contraindicated.

9.6. Post-trial Treatment

Not relevant for this trial

10. SAFETY REPORTING

10.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not

	necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific

event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”.

10.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

10.3. Procedures for Recording Adverse Events

As insulin is a well-known IMP, not all non-serious AEs will be recorded. Mild hypoglycaemia responding to treatment does not need to be reported as an AE, but will be recorded on the daily diary as well as on the CGM records.

Children with Type 1 diabetes are always at risk of hypoglycaemia which may result in hospitalisation. It is not anticipated that the project would increase the risk of severe hypoglycaemia (a low blood glucose level that is associated with unconsciousness or convulsion) but a child/young person may have one of these episodes during the study. The participants will all be wearing a continuous glucose monitor with an alarm if the BG becomes low or high. The alarm will therefore warn the participant and family if the BG level falls below a certain level, reducing the risk of severe hypoglycaemia. However severe hypoglycaemia resulting in unconsciousness or convulsions would be reported immediately as a SAE (see below).

The child and family will be informed that they can call the research team during office hours at any stage to discuss events during the week of the study, and they will be provided with contact details. If any advice is required outside office hours, they will be advised to contact their clinical diabetes team in the usual way.

It is not anticipated that the CGM will cause any adverse effects. However infection or inflammation at the insertion site would be reported at the end of the trial as an AE. If the sensor stops working or needs to be replaced for any reason during the trial week, this does not need to be reported as an AE, but the participant or family will contact the research team to have it re-sited.

The following information will be recorded for all reportable AEs: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

10.4. Reporting Procedures for Serious Adverse Events

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported on the Oxford University Hospitals NHS Trust SAE reporting form to OUH study team within 24 hours of the Site Study Team becoming aware of the event by email or fax.

Once the SAE has been received the OUH study team will forward the report to the R&D office immediately. **SAE reports should be faxed or emailed to: (01865) 572242 or ouhsae.reports@nhs.net**

R&D will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. It will also be reviewed at the next Trial Safety Group meeting. All SAE information must be recorded on an SAE form and faxed, or scanned and emailed, to R&D. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed/emailed to R&D.

10.5. Expectedness

Expectedness will be determined according to the Summary of Product Characteristics.

10.6. SUSAR Reporting

All SUSARs will be reported by the CI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

10.7. Safety Monitoring Committee

The Oxford University Hospitals Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

10.8. Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.

11. STATISTICS

This section has been written by our statistician.

11.1. Description of Statistical Methods

Descriptive statistics will be used to describe the group demographics and outcomes.

The continuous glucose records will be analysed methodically by the CI, research dietitian and statistician. Data to be obtained include –

- pre-meal BG level
- peak BG level
- peak BG excursion from baseline at 3, 5, 8 and 12 hours following the meal
- time of peak BG level
- time of peak BG excursion
- area under the curve at time-points 0-4 hours, 4-6 hours, 6-8 hours, 8-12 hours post-meal

The relationship between the insulin timing and the mean change in postprandial blood glucose levels will be analysed and described.

Comparisons using paired t tests for normally distributed data, and Mann-Whitney U tests for non-parametric data will be used to examine the differences in areas under the postprandial BG curves and the postprandial BG levels by insulin timing.

11.2. The Number of Participants

We estimate that using a three-treatment, three period cross-over design, 36 people will achieve 80% power to detect a 2 mmol/L difference in mean 5 hour postprandial glucose excursion at the 5% significance level. Although we do not anticipate any losses to follow-up or withdrawals due to side-effects from the study we will aim to recruit 40 to ensure power is maintained if this does arise. This power calculation has been carried out by our study statistician.

In order to allow for drop-outs, we have made the decision to recruit 40 patients.

Previous intervention studies of fat/protein interventions in children using insulin pumps have used 24-42 patients with significant differences in BG levels at the 0.04 and 0.03 levels of significance (5-8).

11.3. The Level of Statistical Significance

$P<0.05$ will be used to demonstrate statistical significance.

11.4. Criteria for the Termination of the Trial

We would only anticipate 10 episodes of severe hypoglycaemia in 340 patients per year. Therefore the likelihood of a severe hypo occurring during this study under normal circumstances would be very small. So if we assume there is no increase in risk then we would only expect to see 2 severe hypos in one of the two arms in 3 out of every 10,000 trials, for a single hypo in either arm this increases to about 1 in every 100 trials. Therefore we would terminate the trial if we had 2 severe hypos occurring on any arm of the trial.

11.5. Procedure for Accounting for Missing, Unused, and Spurious Data.

We will use boxplots to identify outlying, unusual or spurious data using pre-defined decision rules (e.g. upper or lower quartiles +- 1.5*IQR). In the case of implausible or unlikely outcome data we will look back at CRF's to rule out data handling errors. If outliers cannot be resolved then we will exclude this particular result from the main analysis. We intend to use a complete case analysis but we will conduct to a sensitivity analysis to assess the impact of any missing data using appropriate multiple imputation methods.

11.6. Inclusion in Analysis

All data available from all participants will be used for the analyses. If a child has become hypoglycaemic (BG <4.0mmol/l) during the profile period then subsequent data will be analysed separately. If any child has had to treat a high BG level with additional insulin (except for a correction dose at the evening meal), then subsequent profile data will be analysed separately. However in either instance, the data up to the event will be included in all analyses. The two other meals would still be eligible for the study analyses if there were no similar events.

If there have been any protocol breaches, such as further food during the evening after the main meal, then all the subsequent data will not be used in the analysis for that meal. Education of the participants and parents will be vital to ensure that such eventualities are rare.

11.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

The trial protocol will be made available to reviewers of any publication arising from this study. Any amendments to the original protocol or additional analysis not previously specified in the protocol will also be made available to reviewers.

12. DATA MANAGEMENT

12.1. Source Data

Source documents will be the hospital records for the basic demographics and HbA1c level. During the trial they will be the patient diaries, both during the run-in week and for the trial week. This is where data is first recorded, and from which participants' CRF data are obtained.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.3. Data Recording and Record Keeping

All trial data will be entered on to paper CRFs and/or a to an Excel spreadsheet (Microsoft Office).

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

All study data will be held until the last participant has reached the age of 21 or up to 5 years from the end of the trial, whichever is the later date.

13. QUALITY ASSURANCE PROCEDURES

Regular monitoring will be performed by authorised individuals from the sponsor according to GCP.

14. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

15.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

15.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

15.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

15.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

The test meals will be provided by the service, and a funding application has been made for these. In addition, if funding is granted, each child will be offered a £10 high street voucher in return for their help with the study.

15.7. Other Ethical Considerations

The use of Children

The participation of children and young people is indispensable for this study because there is a lack of research on the appropriate dietary management of children and adolescents with Type 1 diabetes using MDI. Adult data cannot be extrapolated to children because of their very different life-styles, body size, insulin requirements and dietary differences. Evidence based dietary interventions for children need to be examined in the paediatric population. In particular, the acceptability for giving additional insulin injections at meal-times may be very different in children compared to adults.

Consent

It is important that both the child and parent/legal guardian has an adequate opportunity to ask questions, and to fully understand the implications of the study before agreeing to take part. Children's wishes will not be over-ridden. The leaflets and discussion will make it clear that withdrawal from the study can occur at any time with no disadvantage in terms of normal medical care.

16. FINANCE AND INSURANCE

16.1. Funding

Part-funding for the study has been received from the NovoNordisk Research Foundation. Additional funding has been provided by the OUH Research Capability Funding to employ a Dietitian for one day per week for a year. A research nurse is employed within the department.

16.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the trial team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

17. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the body which provided the funding. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Study results will be disseminated to research participants by the usual clinic newsletter and by presenting the results to the Parents' support group (Oxfordshire Young Diabetics) open meeting, and to similar groups in other participating hospitals.

18. REFERENCES

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9. Impact of Fat, Protein and Glycaemic Index on Postprandial Glucose Control in Type 1 Diabetes: Implications for Intensive Diabetes Management in the CGM Era. Bell KJ, Smart CE, Steil GM, Brand-Miller JC, King B, Wolpart HA. Diabetes Care. 2015;38:1008-1015

19. APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	Visit 1 Day 0	Telephone call day 3-4	Telephone call Day 5-6	Visit 2 Day 7-10	Visit 3 Day 14-16
	Screening			Baseline	
Informed consent/assent	X				
Demographics	X				
Medical history	X				
HbA1c measurement if not done in last 3 months	X				
Eligibility assessment	X				
Provide diaries for run-in week	X				
Dietitian to order standard meals	X				
Assessment ICR		X		X	
Optimise ICR			x		
Randomisation				X	
Insert CGM				X	
Explain trial insulin doses				X	
Provide diaries and all instructions for trial week				X	
Provide contact details for trial week				X	
Remove CGM and show download to family					X
Questionnaires to participant and					X

parent/carer					
Adverse event assessments					X

20. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2	20/11/15	AM Frohock	Minor typographical errors Additional Research Nurses added Confirmed protocol met REC recommendations to remove patient initials from all data collection
2	3	21/6/16	AM Frohock	Adjusted the original calculation used in the protocol. This reduces the amount of additional insulin administered for fat and protein and therefore reduces the risk of hypoglycaemia in future participants. *(Page 8 and Page 11)* We also changed guidance for completing the study evenings following hypoglycaemic episodes immediately before the study meal – stating that in this incidence the meal should be abandoned. This also reduces the risk of hypoglycaemia afterwards. *(Page 12)* Minor changes were made to the flowchart to remove giving the voucher at visit 3 – this will now happen once all participants have completed the study at the end *(Page 10)*
3	4	1/4/17	AM Frohock	Change of Chief Investigator
3	4	1/4/17	AM Frohock	Clarification that the second insulin dose should be given at a time interval after the first insulin dose as there had been ambiguity from participants about the meaning of 'after the meal' Change in management of correction doses pre-evening meal. It has

				become clear that it will be very difficult to analyse change in BG level from pre-meal levels once a correction dose of insulin is given. So we have asked participants only to correct if BG above 12mmol/l and if possible to avoid doing the study on evenings when BG is above 12 mmol/l before the meal if possible. They should definitely not complete the meal if BG is above 16mmol/l

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.