FIRST1D

A Study of Flat and Circadian Insulin Infusion Rates in Continuous Subcutaneous Insulin Infusion (CSII) in Adults with Type 1 Diabetes

V1.7 – 23.2.18

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Protocol authorised by:

Name & Role	**Date**	**Signature**

Study Management Group

Chief Investigator: Professor Nick Oliver

Co-investigators: Miss Sian Rilstone & Dr Monika Reddy

Statistician: Dr Ian Godsland

Study Management: Miss Sian Rilstone

Clinical Queries

Clinical queries should be directed to Professor Nick Oliver who will direct the query to the appropriate person

Sponsor

Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office 215, Level 2 Medical School
Norfolk Place

London W2 1PG
Tel: 0207 594 1872

Funder

Roche

This protocol describes the FIRST1D study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Contents

GLOSSARY OF ABBREVIATIONS

CGM	Continuous Glucose Monitoring
CSII	Continuous subcutaneous Insulin Infusion (insulin pump)
GI	Glycaemic Index
HbA1c	Haemoglobin A1 C
MDI	Multiple Daily Injections
T1DM	Type 1 Diabetes Mellitus

KEYWORDS

Type 1 Diabetes, Continuous subcutaneous insulin infusion (CSII), flat basal rate, circadian profile, continuous glucose monitoring, glucose, insulin, hypoglycaemia

STUDY SUMMARY

TITLE A Study of Flat and Circadian Insulin infusion Rates in Continuous Subcutaneous Insulin Infusion (CSII) in Adults with Type 1 Diabetes

DESIGN Randomised controlled trial

AIMS To contribute to the evidence base for the optimal initial insulin profile for adults with type 1 diabetes commencing insulin pump therapy.

OUTCOME MEASURES

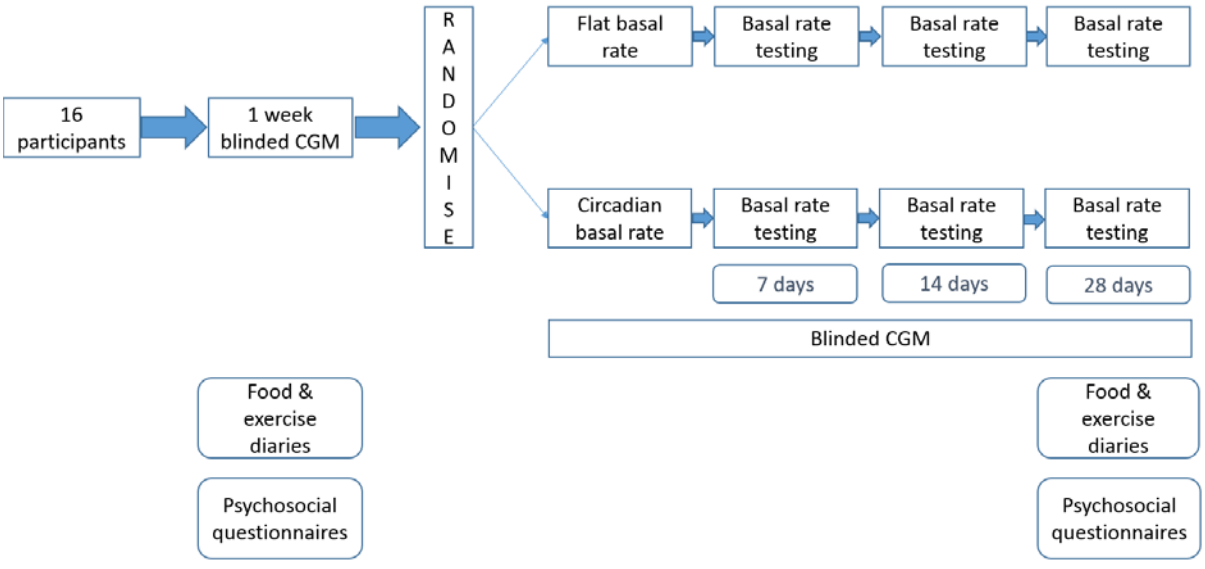
- Absolute change in insulin basal rate over 24 hours after 3 rounds of basal rate testing (calculated by the sum of absolute changes for each 1 hour block compared with baseline)
- Healthcare professional time spent with subject
- Mean sensor glucose from continuous glucose monitoring after 3 rounds of basal rate testing
- Mean sensor glucose from continuous glucose monitoring after 1 round of basal rate testing
- Number of healthcare professional contacts
- CGM outcomes
- Severe hypoglycaemia
- Insulin outcomes
- Healthcare professional qualitative feedback

POPULATION People with Type 1 Diabetes commencing CSII

ELIGIBILITY Participants identified in type 1 diabetes clinics in Imperial College Healthcare NHS Trust

DURATION 4 weeks plus 1 week pre-randomisation assessment

REFERENCE DIAGRAM



1. INTRODUCTION

1.1 BACKGROUND

Initiation of insulin pump therapy in people with type 1 diabetes requires conversion of a basal insulin dose, given as once or twice daily long-acting insulin, to a continuous basal infusion regimen. This conversion may be based on basal insulin dose only, or total daily insulin dose, and may result in a flat basal insulin profile or an initial variable basal rate.

Initial variable basal rates aim to replicate circadian changes in insulin requirements and are derived from total basal insulin in adults over 24 years old, and from weight in adults aged 18 to 24 years. Initial rates were developed from 63 well-controlled people with type 1 diabetes over 14 years of age and have been assessed against a flat basal rate in a small randomised controlled trial with 12 participants. Mean glucose was lower in the circadian basal rate group with particular differences noted in the early morning when glucose rises were more pronounced in the flat basal rate group[1].

In 50 people with type 1 diabetes treated with insulin pump therapy, HbA1c was lower in those with lower basal rates at midnight, and in those with higher basal rates in the afternoon, suggesting a benefit of circadian patterns[2]. In 33 people with type 1 diabetes over 16 years of age basal rate distribution established at commencement of pump therapy did not alter over 6 months[3]. However, a 6 month cross-over study of circadian rates and oligophasic basal rates showed no difference in HbA1c[4].

Following initiation on insulin pump therapy basal rates are personalised to capillary blood and continuous interstitial fluid glucose monitoring.

In adults with type 1 diabetes starting insulin pump therapy there are limited data to guide the optimal insulin profile to rapidly achieve target glucose and minimise healthcare professional input.

1.2 RATIONALE FOR CURRENT STUDY

Hypothesis: Circadian insulin infusion rates in CSII naïve people with type 1 diabetes are closer to optimal basal rates, compared with a flat initial rate

2. STUDY OBJECTIVES

Objective: To contribute to the evidence base for the optimal initial insulin profile for adults with type 1 diabetes commencing insulin pump therapy.

3. STUDY DESIGN

Type of study: Randomised controlled trial

Duration: 4 week trial with 1 week pre-randomisation assessment

Number and type of subjects:
16 participants with type 1 diabetes referred for CSII, randomised 1:1 to circadian insulin infusion rates or flat rates.

Recruitment will be undertaken in the T1DM clinics at Imperial College Healthcare NHS Trust. Participant information sheets will be given to potential subjects who have been assessed and screened for insulin pump therapy, either in person in clinic, or via post with a participant invitation letter. After a minimum of 24 hours and following any questions, informed consent will be taken.

3.1 STUDY OUTCOME MEASURES

Primary outcome:

- Absolute change in insulin basal rate over 24 hours after 3 rounds of basal rate testing (calculated by the sum of absolute changes for each 1 hour block compared with baseline)

Secondary outcomes:

- Healthcare professional time spent with subject
- Mean sensor glucose from continuous glucose monitoring after 3 rounds of basal rate testing
- Mean sensor glucose from continuous glucose monitoring after 1 round of basal rate testing
- Number of healthcare professional contacts
- CGM outcomes
    - %time in hypoglycaemia (<2.8mmol/L)
    - %time in hypoglycaemia (<3.3mmol/L)
    - %time in hypoglycaemia (<3.9mmol/L)
    - %time in target (3.9-10mmol/L)
    - %time spent in hyperglycaemia (>10mmol/L)
    - Measures of glycaemic variability
    - Mean glucose
    - Glucose SD
- Severe hypoglycaemia
- Insulin outcomes
    - Number of insulin time blocks changed
    - Number of insulin basal rate changes
    - Change to total daily insulin dose
- Basal insulin:bolus insulin ratio
- Healthcare professional qualitative feedback

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

- HbA1c
- Serum C-peptide
- Plasma glucose
- Coeliac screen

- Gastroparesis screen

- Thyroid function tests
- GOLD hypoglycaemia score

4.2 INCLUSION CRITERIA

- Adults ≥18 years of age
- Diagnosis of T1DM for > 1 year
- On MDI with decision made to commence CSII
- Structured education in previous 3 years
- HbA1c ≤ 75mmol/mol (9%)
- Stimulated c-peptide <200pmol/L
- No severe hypoglycaemia (defined as needing 3rd party assistance) in previous year

4.3 EXCLUSION CRITERIA

- Previous CSII
- Night or shift worker
- Recurrent severe hypoglycaemia
- Pregnant or planning pregnancy
- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Addison's Disease
- Gastroparesis
- Autonomic neuropathy
- Concomitant use of GLP-1 analogues and gliptins
- Visual impairment
- Reduced manual dexterity

Any participant who is excluded at screening will be replaced by another participant.

4.4 WITHDRAWAL CRITERIA

- Loss of capacity to give informed consent
- Recurrent severe hypoglycaemia
- Terminal illness

Withdrawal will be immediate and subjects will be followed up in the appropriate out-patient diabetes clinic within 4 weeks of withdrawal.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject 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*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.2.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Usual pre-pump assessment and screening
Anyone who is being considered for insulin pump therapy will be assessed by their usual care team to complete documentation for funding and to take some blood samples to measure HbA1c, glucose, kidney function, serum C-peptide, coeliac antibodies and thyroid function test. A urine sample will be taken to do a pregnancy test in woman of child bearing age. A medical and medication history will be taken. Validated questionnaires will be used to screen for gastroparesis and hypo unawareness. An insulin pump will be demonstrated and the pros and cons of insulin pump will be explained to ensure a fully informed decision about commencing insulin pump therapy is made. At this appointment potential participants will be provided with a participant information sheet to read in their own time.

At least 24 hours after this appointment potential participants will be contacted to see whether they want to continue with insulin pump therapy, and if so, whether they would like to do this under their usual care team, or under the research team in this trial. This appointment usually takes between 30 and 60 minutes.

Visit 1 - Informed consent - 30 minutes
Following informed consent, participants will be screened as per inclusion and exclusion criteria. This appointment will take up to 30 minutes. Participants will be provided with a capillary blood glucose monitor to use throughout the study if they do not already have one.

Visit 2 – Pre-pump CGM – 60 minutes
Participants will be taught to insert and replace a Dexcom G4 sensor for use with blinded CGM. They will be asked to wear it for one week prior pump initiation, and continuously after pump initiation until the end of the study. Each sensor lasts for 7 days so participants will learn to replace them themselves. They will be asked to keep a food and exercise diary during the pre-pump CGM week, and during week 4 of insulin pump therapy. Participants will be given copies of the data from the CGM at the end of the study. Diabetes self-management will continue as usual. Participants will be asked to complete questionnaires to measure awareness of hypoglycaemia (Gold), hypoglycaemia fear (HFS), general quality of life (WHOQoLBref), diabetes distress (DDS-2) and diabetes quality of life (DQOL), which will be repeated at the end of the study. Self-help leaflets from Diabetes UK will be available in case participants find these questionnaires distressing, and can approach the researcher for signposting for further help. During this session participants will be randomised to a flat basal rate or circadian rate (defined by Roche Accu-Chek software using a predefined algorithm).

Visit 3 – CSII initiation– 3-4 hours
Participants will initiate CSII in pairs from the same randomisation group, at the metabolic day ward in St Mary's hospital on a Monday. They will be taught how to use their insulin pump by a diabetes specialist dietitian trained in insulin pump therapy. They will be asked to take half their usual background insulin the night before, or to exclude the morning dose if they are on twice daily background insulin. Participants will learn to set up the pump, insert the cannula, and learn how to make adjustments to the settings. Both arms will receive half of 75% of their pre-pump total daily insulin dose via basal rates. These basal rates will be calculated in advance ready for programming at the CSII initiation visit.

Participants will receive the research dietitian's contact details for queries in working hours, and will be given a 24 hour product support number in case of pump failure. They will receive

structured information on what to do manage high and low blood glucose levels. They will be instructed to return to injections in case of pump failure.

Between visits 3 and 4
Participants will be asked to record their blood glucose levels using capillary blood glucose testing a minimum of four times per day – before meals, before bed, and if they feel unwell. These results will be reviewed by the researcher via telephone on day 1, 2 and 4 of pump therapy, and insulin pump settings will be adjusted if needed, based on the criteria below:.

1. Insulin to carbohydrate ratios will be changed by 10% in the event of two values being <4mmol/l within four hours of the meal, or >12mmol/l 4 hours after the meal, in the absence of a precipitating factor2. Insulin basal rates will only be adjusted in the case of:

- Severe hypoglycaemia
- Recurrent hypoglycaemia (<4mmol/L) at the same time on 3 consecutive days
- Recurrent hyperglycaemia (>12mmol/L) at the same time on 3 consecutive days

The use of temporary basal rates during exercise and activity will be standardised. Participants will be asked to refrain from exercising and using temporary basal rates during the fasting basal rate testing.

Fasting basal rate tests

Participants will undertake a series of fasting basal rate testing commencing on day 7, 14 and 28 of insulin pump therapy. The basal rate testing protocol is as follows:

Day 1 Overnight testing with self-monitoring at 22:00, 00:00, 02:00, 04:00 and 06:00
Day 2 Omit breakfast with self-monitoring at 06:00, 08:00, 10:00: 12:00
Day 3 Omit lunch with self-monitoring at 12:00, 14:00, 16:00, 18:00
Day 4 Omit evening meal with self-monitoring at 18:00, 20:00, 22:00, 00:00, 02:00, 04:00, 06:00

Visit 4 and 5 (Day 11 and 18 of pump therapy)
Insulin pumps and CGM will be downloaded, and insulin basal rates will be adjusted based on the fasting basal rate testing as follows:

- Glucose rise more than 1.7mM during sleep or over a 4 hour period when fasting, increase basal rate by 10% for 2 hours at start of rise
- Glucose fall more than 1.7mM during sleep or over a 4 hour period when fasting, reduce basal rate by 10% for 2 hours at start of fall

Visit 6 (Around day 32 of insulin pump therapy)
Insulin pump and CGM will be downloaded. Participants will be asked to repeat the questionnaires to measure awareness of hypoglycaemia (Gold), hypoglycaemia fear (HFS), general quality of life (WHOQoLBref), diabetes distress (DDS-2) and diabetes quality of life (DQOL). Blood samples to repeat HbA1c will be taken. Pump and CGM downloads will be reviewed, and pump settings adjusted to optimise blood glucose control.

At the end of the study, participants will continue using their insulin pumps if they wish, but will return the CGM. They will be followed up in specialist type 1 insulin pump clinics, as per usual care.

Blood samples will be analysed in the Imperial College Healthcare NHS Trust laboratory and discarded after analysis.

7. STATISTICS AND DATA ANALYSIS

This is a single site randomised study with an intervention group and a control group. The primary outcome is absolute change in insulin basal rate over 24 hours after 3 rounds of basal rate testing (calculated by the sum of absolute changes for each 1 hour block compared with baseline). This is a pilot study and will demonstrate the effect size of circadian basal rates. A post hoc power calculation will be performed.

The sample size is comparable to other diabetes technology studies, and is a realistic number for recruitment in the time period. In 2015-2016 47 people with type 1 diabetes commenced insulin pump therapy at Imperial College.

Data will be entered onto a database with restricted fields by the research team and, following data checking and cleaning, analysis will be conducted using Stata statistical software. Analysis will be conducted by Dr Oliver, Dr Ian Godsland (Reader in Human Metabolism) and the Imperial College Statistics Service. The primary and secondary outcomes will be analysed by intention to treat analysis. The difference in basal rate change between the two groups at the endpoint will be assessed by a two-tailed independent t test. Secondary outcomes will be assessed by independent t test or, if data are non-parametric, a Mann-Whitney U test. Missing data will be minimised by reducing manual data entry, using technology to collect glucose data, and by carefully supporting participants. Where present, missing data will be handled by full analysis of the available data only.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period. Anonymised data will be kept on university password-protected computers in a locked room. Access is only available to the clinical research team. The identifier codes will be kept on password-protected NHS computers. The anonymised data includes CGM data, food and exercise diaries and blood test.

The paper copies of the consent forms and questionnaires will be kept in a specifically labelled FIRST1D file in a locked cupboard in the diabetes research office

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the xxx Research Ethics Committee and the HRA. The study must be submitted for confirmation of capacity and capability (CCC) at each participating NHS Trust. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up

and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study

8.5 SPONSOR

Imperial College Londonwill act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

Roche are funding this study. Travel expenses will be provided for participants of the study.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated Sian Rilstone

10. PUBLICATION POLICY

Data from the study will be analysed then published in peer-reviewed scientific journals and presented at Scientific Conferences. A lay summary of the data will be disseminated to all participants and a summary of results will be publically available.

11. REFERENCES

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2. Lüddeke HJ, Renner R, Hepp D. [Analyse von Basalratenprofilen und Bolusabruf bezuglich HbA1c und Hypoglykänierate für IDDM-Patienten unter CSII-Therapie mit multiprogrammierbaren Pumpen. Welches Basalrateprofil ist optimal?] Diabetes Stoffwechsel 1994;178
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12. Appendices

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6. Questionnaire to measure awareness of hypoglycaemia (Gold)
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8. Questionnaire to measure General quality of life (WHOQoLBref)
9. Questionnaire to measure Diabetes distress (DDS)
10. Questionnaire to measure Diabetes QoL (DQOL)

Appendix 1. Summary of investigations, treatment and assessments

				Days post CSII initiation			
	Usual pre pump assessment and screening appointment	Informed consent appointment	Pre-randomisation	0	7	14	28
Informed consent		X					
Blood tests (Thyroid function tests, coeliac serology, plasma glucose, serum c-peptide)	X						X
HbA1c (blood test)	X						X
GOLD score questionnaire	X						X
Blinded CGM			X	X	X	X	X
Psychosocial questionnaires			X				X
Basal rate testing					X	X	X
Pump download					X	X	X

Appendix 2. Participant information sheet

Appendix 3. Consent form

Appendix 4. GP letter

Appendix 5. Participant invite letter

Appendix 6. Questionnaire to measure awareness of hypoglycaemia (Gold)

Appendix 7. Questionnaire to measure Hypoglycaemia fear (HFS-II)

Appendix 8. Questionnaire to measure general quality of life (WHOQoLBref)

Appendix 9. Questionnaire to measure Diabetes distress (DDS)

Appendix 10. Questionnaire to measure Diabetes QoL (DQOL)