SubCutaneous Insulin: Pumps or Injections
Randomised controlled trial of continuous subcutaneous insulin infusion compared to multiple daily injection regimens in children and young people at diagnosis of type I diabetes mellitus.

EudraCT number: 2010-023792-25

ISRCTN: 29255275

Statistical Analysis Plan
Final Analysis

Version 1.0 13/10/2016

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
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Title	Statistician	N/A	Head of Statistics
Date	13/10/2016		
Protocol Version and Date	Version 7.0 (01/08/2016)		

1 Change Control

Protocol version	Updated SAP version no.	Section number changed	Description of change	Date changed

2 Approval and agreement

SAP Version Number being approved: V1.0

Trial Statistician

Name _____

Signed _____ Date _____

Senior Statistician

Name _____

Signed _____ Date _____

Chief Investigator/clinical lead

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

3 Roles and responsibilities

B Arch (Department of Biostatistics, University of Liverpool): Statistician; A McKay (Department of Biostatistics, University of Liverpool): Trial Statistician; C Gamble (Department of Biostatistics, University of Liverpool): Senior Statistician; J Blair (Alder Hey Children's NHS Foundation Trust): Chief Investigator.

Author's contributions

B Arch proposed the statistical analysis plan (SAP) building on the outlined analyses set out in the trial protocol. A McKay is the trial statistician, and helped answer questions relating to trial data and management relevant to the development of the SAP. A McKay, C Gamble and J Blair read, reviewed, and approved the SAP.

4 List of abbreviations and definitions of terms

ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CE	Cost Effectiveness
CSII	Continuous Subcutaneous Insulin Infusion
$HbA1_c$	Glycosylated Haemoglobin
HUI	Health Utilities Index
IDAA1c	Insulin dose-adjusted HbA1c
IQR	Inter-Quartile Range
IR	Insulin Received
ITT	Intention-to-Treat
MDI	Multiple daily injection
NICE	National Institute for Health and Care Excellence
PedsQL™	Measurement tool for paediatric quality of life
QALY	Quality of Adjusted Life Years
SAE	Serious Adverse Event
SD	Standard Deviation
SDS	Standard Deviation Score
TIDM	Type I Diabetes Mellitus
WHO	World Health Organization

Contents

5 Statement of Compliance

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned final analyses for the study “SubCutaneous Insulin: Pumps or Injections” (SCIPI). The planned statistical analyses described within this document are compliant with those specified in brief within the SCIPI protocol 6.0 16/02/16. This SAP comprehensively describes the planned final analyses.

This study is carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

These planned analyses will be performed primarily by statisticians at the CTRC.

This study is a clinical trial of a medicinal product and is registered on the EudraCT database. The statistical analysis plan has been developed to support the posting of results on the EudraCT system. This is a regulatory requirement, which should be fulfilled within 6 months after the end of the study as defined within the clinical trial protocol.

The results of the final analysis described within this statistical analysis plan will be contained within a statistical analysis report. This report will be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (SAS version 9.3 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP TM021 Archiving procedure in CTRC. The testing and validation of the statistical analysis programs will be performed following SOP ST001: Statistical Analysis and Reporting.

6 Background and Rationale

Type I diabetes mellitus (TIDM) is a common disease of childhood. Its management is burdensome for patients. Glycaemic control can be challenging, particularly during adolescence. The NICE guideline recognises that intensive therapy (multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII)) offers greater potential to optimise glycaemic control and minimise long-term complications than conventional insulin regimes of twice daily pre-mixed insulin. However, there are currently no data from which patients, parents or health care professionals can draw to inform their selection of insulin delivery device. See protocol sections 2.1 and 2.2 for further details.

7 SCIPI Study Objectives

The aim of this study is to investigate two methods of insulin delivery during childhood and adolescence, CSII and MDI, and to identify which facilitates superior glycaemic control.
This study also examines the impact of treatment modalities on other predictors of vascular complications of TIDM, adverse events and quality of life.

Primary Objective:
To compare the glycaemic control assessed by HbA1c at 12 months after diagnosis in children and adolescents receiving CSII with those receiving MDI.

Secondary Objectives:
To compare the following:

- Clinical effectiveness of children and adolescents receiving CSII with those receiving MDI.
- The safety of children and adolescents receiving CSII with those receiving MDI.
- Growth of children and adolescents receiving CSII with those receiving MDI
- The quality of life of children and adolescents receiving CSII with those receiving MDI
- Cost effectiveness of providing insulin to children and adolescents by CSII compared to MDI.

8 Investigational Plan and Study Design

8.1 Overall study design and plan- description

SCIPI is an open labelled 2-arm multi-centre randomised controlled trial comparing CSII with MDI in 316 children and young people aged 7 months to 15 years who have been newly diagnosed with type I diabetes mellitus. Patients should be approached and consented as soon after diagnosis as possible. Participants are randomised in a 1:1 ratio to either of the two treatments (MDI or CSII pumps).

An internal-pilot exploring the feasibility of recruitment was also outlined in the protocol. Details of the success criteria of the internal pilot can be found in Section 4.1 of the protocol. The analysis for the internal pilot did not require treatment group knowledge so was presented within the open section of the July 2012 IDSMC report [stored electronically at '\\mwsdept02\d02\ctrcis\Statistical Analysis \SCIPI\Statistical Analysis\IDSMC

reports\IDSMCJul2012\IDSMC Report' and titled 'SCIPI IDSMC open report 09JUL2012.docx']. This was reported to both the IDSMC and TSC and decision made that the trial should continue. This SAP relates to the final analysis of the SCIPI trial only.

8.2 Treatments studied

See Chapter 7 of the protocol.

8.3 Treatment compliance

In order to assess compliance with the trial protocol, insulin usage data will be collected from the participants as described in Section 8.2.2 of the protocol. Instances of treatment non-compliance are:

- Use of a non-protocol specified insulin
- Method used post 14 days diagnosis that is not that randomly allocated
- Permanent change of insulin delivery

A change of insulin delivery is defined as being one that is outside the specification for the treatment arm allocated – see Section 7.3 of protocol for detailed specification for each treatment arm. These can be identified in the CRF: 'Insulin Usage'. Removal of participants from therapy or assessment

8.4 Patient population studied

Children and young people aged 7 months to 15 years who have been newly diagnosed with type I diabetes mellitus.

8.4.1 Inclusion criteria

See Section 5.1 of protocol (version 3.0 for participants screened before 17/08/2012 and version 4.0 onwards for all others.

8.4.2 Exclusion criteria

See Section 5.2 of protocol (version 3.0 for participants screened before 17/08/2012 and version 4.0 onwards for all others.

8.4.3 Removal of participants from therapy or assessment

There are no predetermined reasons for exclusion of a randomised participant from the ITT analysis population as described in Section 17.1.

8.5 Consent process

Consent is sought during the screening period – between 0 and 5 days after diagnosis. See Section 11.3 of the protocol for further details on consent procedures.

8.6 Blinding

No blinding within the SCIPI trial.

8.7 Method of assignment to treatment

Participants are randomised using a secure (24-hour) web based randomisation programme controlled centrally by the MC-CTU. See Sections 6.3 and 9.2 of the protocol for further details. The method of randomisation and strata are contained within the Randomisation

Specification document [stored electronically at '\\mwsdept02\d02\ctrcis\Statistical Analysis\SCIPI\Randomisation\Preliminary output' and titled 'ST002TEM01_Randomisation_specification - SCIPI.docx'].

8.8 Sequence and duration of all study periods

The study duration of each participant (including follow-up period) is one year from the date of randomisation. Following diagnosis, participants will have up to 10 days (up to protocol version 3.0 01/07/2011) or 14 days (from protocol 4.0 17/08/2012 onwards) to commence study treatment. All participants will be reviewed at the diabetes outpatient clinic every three months as per standard clinical practice and will have four follow up visits at 3-, 6-, 9- and 12- months from randomisation. Participants will have a flexible window of ± 15 days to report for each follow up visit.

See Table 1 in Section 8.1 of the protocol for a detailed outline of the assessment schedule.

9 Listing of Outcomes

A full outline of which data are collected at each time-point can be found in Table 1 of Section 8.1 of the protocol, and further details of how they are measured can be found in sections 8.2, 8.3 and 8.4. The main outcomes are:

9.1 Primary outcome

Glycaemic control ($HbA1_c$) 12 months after diagnosis.

9.2 Secondary outcomes

12 months post diagnosis:

a. Percentage of participants in each group with $HbA1_c < 6.5$ [Equivalent to $HbA1_c < 48$ mmol/mol]
b. Incidence of severe hypoglycaemia;
c. Incidence of diabetic ketoacidosis;
d. Change in BMI SDS;
e. Height;
f. Insulin requirements (units / kg /day);
g. PedsQL;
h. Incremental cost-per QALY gained.
i. Partial remission.

10 Determination of Sample Size

The sample size of 143 per treatment group was calculated to provide 80% power to detect a difference in mean $HbA1_c$ at 12-months post diagnosis of 0.5% (equivalently 5.5mmol/mol), assuming a common standard deviation of 1.5% (16.5mmol/mol). Full details of the sample size calculation can be found in Section 9.4 of the protocol.

11 Study Framework

This trial has clear objectives to test for superiority of one treatment over the other with respect to each of the primary and secondary outcomes.

12 Confidence Intervals, p-values and Multiplicity

The protocol outlines that a two-sided p-value of 0.05 or less will be used to declare statistical significance for all analyses. Similarly, all confidence intervals will be calculated at the 95% level.

No adjustment for multiplicity will be made to adjust type 1 error rate for secondary outcomes. Relevant results from other studies already reported in the literature will be taken into account in the interpretation of results.

13 Timing and Objectives of Final Analyses

13.1 Interim monitoring and analyses

No interim analyses of the primary outcome were planned. Descriptive analyses of the accumulating data are performed at regular intervals (at least annually) for review by an IDSMC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all participants or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the TSC (see Section 16 of the protocol) as to the continuation of the trial.

13.2 Final analysis

The trial is due to finish with the last 12-month follow-up appointment (scheduled around the end of March 2016. The final analysis is due to be completed by the end of January 2017.

14 Disposition of Participants

The flow of participants through the study will be displayed in a CONSORT flow diagram (see Figure 1 below for the template that will be used).

14.1 Screening, eligibility and recruitment

Detailed statistics will be compiled overall, split by site, and also by protocol version[1]:

[1] There were changes in eligibility criteria made 14.5 months after the first patient was randomised. Patients screened before 17/8/2012 were assessed for eligibility under the criteria of protocol versions 3; those after this date assessed under the criteria of protocol version 4.

- Number screened
- Of those screened: number and percentage (i) eligible; and (ii) ineligible or consent not sought
- Of those ineligible or consent not sought: number and percentage (i) ineligible; (ii) unsuitable ; and (iii) lack of staff.
- Of those eligible: number and percentage consenting and not consenting
- Of those consenting: number and percentage randomised and not randomised

The demographics (age (as continuous, not as age-group), gender and social deprivation score) of the participants screened will be compared with those of the sample randomised using appropriate descriptive summary statistics e.g. mean (SD), N (%) or median (IQR). See Section 17.2 for further detail of how these variables are categorised and summarised.

The number and percentage of participants that were (a) ineligible (denominator: all screened); (b) declining consent (denominator: all eligible); and (c) not randomised despite being eligible and consenting (denominator: all eligible and consenting) will be tabulated according to the reason categories given below.

Reasons for ineligibility

A: Age not appropriate (less than 7 months, greater than 15 years)
B: Treated previously for diabetes
Cv3: Parent/legal representative of the patient not able to fill out study material (protocol v3)
Cv4: Parent/legal representative of the patient are not able to comply with the treatment regimen and study visits (protocol v4)
Dv3: Patient (aged 8 years and above) is not able to fill out study material (protocol v3)
E: Haemoglobinopathy
F: Co-existing pathology conditions likely to affect glycaemic control
G: Psychological/psychiatric disorders
H: Receipt of medication likely to affect glycaemic control
I: Allergy to component of insulin aspart or insulin glargine
Jv3: First degree family member (sibling or parent) with existing TIDM (protocol v3)
Jv4: Sibling with existing TIDM (protocol v4)
I: Allergy to component of insulin aspart or insulin glargine
Yv4: Has a known thyroid condition and are in a non euthyroid state
Zv4: Has Coeliac disease and are unable to maintain a gluten free diet

Reasons for declining consent:

- Preference for MDI treatment
- Preference for CSII treatment
- Other reason
- Reason not recorded
- *Explanatory notes for consent being declined will be extracted and listed*

Reasons for non-randomisation (where eligible but not approached for consent)

- Lack of trained staff
- Consultant decision

- Other reason
- Reason not recorded

Reasons for non-randomisation (where eligible and consent provided):

- *Reasons to be extracted and listed*

A recruitment graph will be produced showing recruitment growth over time. A recruitment summary table will be presented showing the following for each centre: centre code; centre name; dates site opened and closed to recruitment; dates of first and last randomisations; and the total number randomised and treated.

Post randomisation discontinuations

The number of participants discontinuing treatment and/or followup will be recorded by treatment group at 3,6,9 and 12 months post randomisation. The number and percentage that were (i) not-allocated their randomised treatment (denominator: all randomised); (ii) lost to follow-up (denominator: all randomised and received at least one treatment allocation); or (iii) discontinued treatment allocation (denominator: all randomised and received at least one treatment allocation) will be tabulated according to the reason categories given below.

Non-allocation of randomised treatment:

- *Reasons to be extracted and listed*

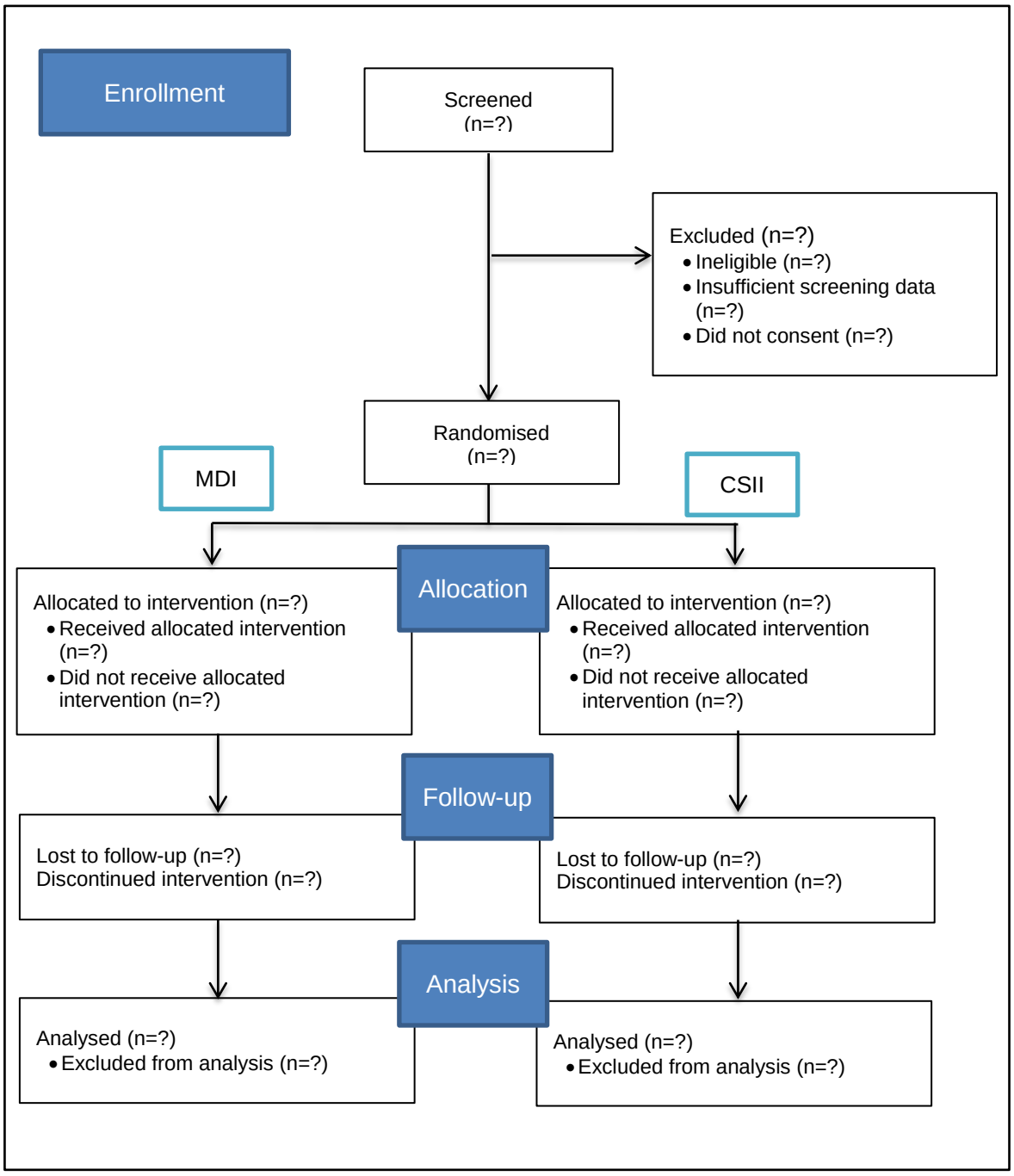
Discontinuation of treatment allocation:

- Decision of parent/legal representative of child
- Decision of participant (withdrawal of assent)
- Decision of clinician
- Death
- Related adverse event
- Unrelated adverse event
- Other

Loss to follow-up:

- Moved home
- Reason unknown

FIGURE 1: CONSORT 2010 DIAGRAM SHOWING FLOW OF PATIENTS THROUGH THE STUDY



15 Protocol Deviations

The overall number of participants experiencing a protocol deviation and the total number of deviations will be reported. Treatment group will be cross-tabulated with type of major and minor deviation. Protocol deviation classifications are taken from the Monitoring Plan V3.0 (date 03/10/2014).

15.1 Deviations relating to inclusion and exclusion criteria

Major:

- Consent not obtained
- Haemoglobinopathy
- Co-existing pathology affecting glycaemic control
- Psychological or psychiatric disorders
- Receipt of medication affecting glycaemic control
- Allergy to a component of insulin aspart or glargine
- Known thyroid condition in a non euthyroid state
- Known Coeliac disease, unable to maintain gluten free diet

Minor:

- Has a previous diagnosis of diabetes
- Outside the age range 7-15 yrs inclusive
- Unable to comply with the treatment regimen and study visits
- Sibling with TIDM

15.2 Deviations relating to treatment and study follow-up visits

Major:

- Start of study treatment from diagnosis being more than 10 days (protocol v3) or more than 14 days (protocol v4)
- Scheduled 12 month FU visit falling outside the +/-15 day window
- Use of non-specified insulin
- Permanent change to insulin delivery

Minor:

- Scheduled 3 month FU visit falling outside the +/-15 day window
- Scheduled 6 month FU visit falling outside the +/-15 day window
- Scheduled 9 month FU visit falling outside the +/-15 day window

Participants to be excluded from analysis populations will be defined in template ST001TEM04: Protocol deviations and data set definitions, which will be agreed and approved prior to any release of randomisation code.

16 Unblinding

Not relevant – this trial is open-label.

17 Efficacy Evaluations

17.1 Data Sets Analysed

The membership of the analysis set for each outcome will be determined and documented and reasons for participant exclusion will be given prior to the randomisation lists being requested. Reasons for exclusions are provided in Section 14.1.2 above

The principle of intention-to-treat, as far as practically possible, will be the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes. These analyses will be conducted on all randomised participants, in the group to which they were allocated, and for whom the outcome(s) of interest have been observed/measured. No imputations will be made.

The primary endpoint will be analysed a second time using the per protocol approach. The per protocol population will mirror the ITT population but exclude any participants defined as having a major protocol deviation (see Section 15). The per protocol analysis will only be considered in the event of major protocol deviations in more than 10% of the ITT analysis population and apply to a secondary analysis of the primary outcome only.
The per protocol analysis set is defined as those participants without a major protocol deviation or less than three minor deviations as specified within the monitoring plan.

Participants to be excluded from analysis populations will be defined in template ST001TEM04: Protocol deviations and data set definitions and the template will be agreed and approved prior to any release of randomisation code.

17.2 Demographic and other baseline characteristics

Baseline characteristics overall and of each treatment group will be summarised using appropriate summary statistics (counts and percentages for categorical variables; mean and SD or median[2] and IQR for numerical variables). Minimum and maximum values will also be presented for numerical variables. See Table 1 for detailed information about the continuous baseline variables to be reported, and Table 2 for the categorical baseline variables. In addition to these, concomitant medications recorded in the CRF: 'Form 8 Concomitant Medication', will be listed and the number of patients taking each drug will be reported both overall and split by treatment group.

Summary statistics for baseline variables will be tabulated split by treatment groups to check that randomisation has worked – i.e. that the treatment groups are balanced.

A table of summary statistics for baseline variables will also be generated for the sample included in the primary analysis, and checked for differences from the sample randomised.

[2] Medians and IQR will be used for data that are sufficiently skewed to incur a clinically relevant difference in the mean and median, and/or if the shape of the distribution is not approximately bell-shaped.

TABLE 1: CONTINUOUS BASELINE VARIABLES TO BE REPORTED

Variable	Unit of measurement	Precision (decimal places)	CRF where data are recorded
Age	Years	1	Form 2: Baseline
Deprivation Score[3]	-	1	Screening Log
BMI SDS	-	1	Derived using the 2006 WHO growth standard[10] (for children <5 years) and 2007 WHO growth reference[11] (for children ≥5 years). *These are calculated using age (years), weight (kg) and height (m) data in* Form 2: Baseline. *See Section 17.4.5.1 below for derivation formula for BMI.*
Height SDS	-	1	Derived using the 2006 WHO growth standard[10] (for children <5 years) and 2007 WHO growth reference[11] (for children ≥5 years). *These are calculated using age (years) and height (m) data in* Form 2: Baseline.
Health Utilities Index	-	1	Questionnaire - Baseline - HUI123 – Children 12-15; or Questionnaire - Baseline - HUI123 – Parent 3-15.
HbA1c	mmol/mol	1	Form 2: Baseline
Blood glucose	mmol/L	1	Form 2: Baseline
Blood pH	-	2	Form 2: Baseline

TABLE 2: CATEGORICAL BASELINE VARIABLES TO BE REPORTED

Variable	Categories	CRF where data are recorded
Age-group[(a)]	7mths – <5 yrs 5 – <12 yrs 12-15 yrs	*Derived from continuous value obtained from* Form 2: Baseline
Age-group[(b)]	In Utero Preterm newborn - gestational age < 37 wk Newborns (0-27days) Infants and toddlers (28days – 23 mths) Children (2-11 yrs) Adolescents (12-17 yrs) Between16-65 yrs From 65 yrs to 84 yrs	*Derived from continuous value obtained from* Form 2: Baseline
Gender	Male Female	Form 2: Baseline
Deprivation	1 (≤ 8.49)	Screening Log

[3] Indice of multiple deprivation 2010 formulated by UK postcode – source Office for National Statistics.

Variable	Categories	CRF where data are recorded
Score Quintile[(c)] (from lowest deprivation to highest)	2 (8.5 – 13.79) 3 (13.8 – 21.35) 4 (21.36 – 34.17) 5 (≥ 34.18)	
Ethnicity	British White Other White Black or British Black Pakistani Asian or Asian British Indian Chinese Mixed Other Not stated	Form 2: Baseline
Thyroid function test	Not done Result Unobtainable Normal Abnormal	Form 15 – Additional tests
Coeliac screening test	Not done Result Unobtainable Normal Abnormal	Form 15 – Additional tests
Islet cell antibodies test	Not done Result Unobtainable Normal Abnormal	Form 15 – Additional tests
GAD 65 Antibodies test	Not done Result Unobtainable Normal Abnormal	Form 15 – Additional tests

[(a)] Stratification variable defined age-groups

[(b)] EudraCT defined age-groups

[(c)] Quintiles defined by NPEU tool (https://tools.npeu.ox.ac.uk/imd), derived from Office for National Statistics indices of multiple deprivation 2010.

17.3 Compliance with treatment

SCIPI is a pragmatic trial and no evaluation of compliance will be performed. Major protocol deviations of relevance to compliance are specified within Section 15.2.

17.4 Analysis of outcomes

17.4.1 Primary Outcome: 12-month HbA1c

The primary outcome is $HbA1_c$ measured 12 months after randomisation. Unit of measurement: mmol/mol[4].

$HbA1_c$ is measured from a blood sample taken at the 12-month follow-up appointment. Two measurements are recorded for each blood sample: a local measurement arising from measurement in situ using a portable machine in clinic; and a measurement made at a central lab at Alder Hey. Both types of measurement are not always recorded – for example, the central lab was not set up till part-way through the trial. For most participants, the central measurement will be used in all analyses. Local measurements will be used when central measurements are not available.

17.4.1.1 Derivation

$HbA1_c$ is measured in mmol/mol. All measurements made centrally are recorded in mmol/mol.

Local measurements are recorded in both mmol/mol (L_M) and the old unit of measurement, % ($L_{\%}$). There is a conversion formula (see Equation [1] below) that enables one to be calculated from the other:

$$L_M = 10.929 \times (L_{\%} - 2.15) \quad [1]$$

HbA1c measurements at 12 months are found in the CRF: 'Form 6: 12-Month Follow-Up Visit' and MACRO database CRF 'Central HbA1c Measurements'. If there is more than one central HbA1c measurement recorded at 12 months then the first result taken on the 12-month visit date or closest post-12-month visit date will be used. This will not be a problem for the local HbA1c measurements because the CRF only has space to collect one result.

17.4.1.2 Analysis

$HbA1_c$ will be compared between the trial groups using mixed-model regression with 12-month $HbA1_c$ as the dependent variable, treatment group as an explanatory factor and the stratification variables: age-group (as defined in the Randomisation Specification document [stored electronically at '\\mwsdept02\d02\ctrcis\Statistical Analysis\SCIPI\Randomisation\Preliminary output' and titled 'ST002TEM01_Randomisation_specification - SCIPI.docx']); and centre as covariates. Centre will be fitted as a random effect. Mean and SD $HbA1_c$ will be reported for each age-group and treatment group. The mean difference in $HbA1_c$ with 95% confidence interval between treatment groups will be the estimated age-group and centre adjusted treatment effect calculated by the fitted mixed model regression.

Model assumptions of the regression analysis will be checked graphically by assessing whether the model residuals appear to be normally distributed.

[4] Note that the standard unit of measurement for HbA1c changed from % to mmol/mol during the course of the trial. Therefore although the protocol assumes that HbA1c is measured in %, this analysis uses mmol/mol, which can be derived if necessary from a measurement in %.

The subgroup of participants with missing primary outcome data will be summarised in terms of demographics using descriptive statistics. These statistics will be compared to the baseline population to check that missingness is at random. If missingness is not at random, subgroups more likely to have missing 12-month $HbA1_c$ will be identified and reported in the results and conclusions drawn.

A Forest plot will be used to display treatment effect by each site with 95% confidence interval and used to consider heterogeneity of treatment effect. In the absence of concerns of heterogeneity (visual and I^2) an unadjusted analysis will also be provided. The subjective judgement of I2 bands as defined in the Cochrane Handbook will be used:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

All statistics involving HbA1c will be reported with a precision of 1 decimal place.

17.4.2 Secondary Outcome 1: Percentage of participants in each group with $HbA1_c$ < 6.5%

HbA1c < 6.5% is equivalent to HbA1c < 48 mmol/mol.

Number of participants in each group with 12-month $HbA1_c$ less than 48 mmol/mol

17.4.2.1 Derivation

Using the values of $HbA1_c$ derived as in 17.4.1.1 above, a binary variable will be derived with values 0: if $HbA1_c \geq 48$ mmol/mol; and 1: if $HbA1_c < 48$ mmol/mol.

17.4.2.2 Analysis

The number and percentage of participants with 12-month $HbA1_c$ less than 48 mmol/mol will be reported overall and for each treatment group. The difference between the two percentages will be presented with a 95% confidence interval and significance tested using the chi-squared test. RR with 95% confidence interval will also be presented. A precision of 1 decimal place will be used for all statistics.

17.4.3 Secondary Outcome 2: Incidence of severe hypoglycaemia

17.4.3.1 Derivation

Severe hypoglycaemia is a type of related adverse event, and when it occurs is recorded in the CRF: 'Related Adverse Events'. Cases of hypoglycaemia mild or moderate in severity will not be counted as events for this analysis. Participants that experience at least one instance of severe hypoglycaemia will be identified.

17.4.3.2 Analysis

The number and percentage of participants in each group that experience at least one instance of severe hypoglycaemia will be calculated. Analysis methods will be as described in 17.4.2.2 above.

In addition, a frequency tabulation for this event will be presented indicating the number of participants experiencing 0, 1, 2, 3, 4, 5 or more events.

17.4.4 Secondary Outcome 3: Incidence of diabetic ketoacidosis

17.4.4.1 Derivation

Diabetic ketoacidosis is a type of related adverse event, and when it occurs is recorded in the CRF: 'Related Adverse Events'. Participants that experience at least one instance of diabetic ketoacidosis (any severity) will be identified.

17.4.4.2 Analysis

See 17.4.3.2 above.

17.4.5 Secondary Outcome 4: Change in BMI SDS

17.4.5.1 Derivation

BMI SDS (BMI_{SDS}) will be derived using the 2006 WHO growth standard[10] (for children <5 years) and 2007 WHO growth reference[11] (for children ≥5 years) from the age (years), weight (kg) and height (m) measurements taken at baseline and at 12 months post diagnosis. BMI is calculated as:

$$BMI = \frac{Weight}{Height^2} \quad [3]$$

Age, weight and height data are found in the CRFs: 'Form 2 Baseline' (calculation of baseline BMI) and 'Form 6 12-Month Follow-Up Visit' (for calculation of 12-month BMI).

For each participant, the change in BMI SDS (ΔBMI_{SDS}) over the first year after diagnosis will be calculated as:

$$\Delta BMI_{SDS} = BMI_{SDS[12]} - BMI_{SDS[0]} \quad [4]$$

where $BMI_{SDS[0]}$ is their BMI_{SDS} at baseline, and $BMI_{SDS[12]}$ is their BMI_{SDS} at the 12-month follow-up appointment.

17.4.5.2 Analysis

Change in BMI SDS (12-month follow-up minus baseline) will be analysed using mixed model ANCOVA.

The outcome in the ANCOVA model will be change in BMI SDS with baseline BMI SDS, age-strata and treatment included as covariates in the model. Centre will be fitted as a random effect. Covariates, in an ANCOVA model, serve to reduce the variability of the outcome measures and, hence, increase the power of the statistical tests.

The ANCOVA model will not adjust for gender as a confounder (age is adjusted for in the calculation of BMI_{SDS}) but age-strata will be because randomisation was stratified by this.

The assumptions that are made when using ANCOVA (i.e. normality of scores at treatment levels, homogeneity of variance, homogeneity of regression slopes, linear regression) will be

assessed. Histogram of scores will be plotted for checking normality and a suitable transformation (e.g. square root, log) will be considered to correct non-normally distributed data. Levene's test will be used to test the assumption of homogeneity of variance.

The ANCOVA model will also be used to derive estimate of the adjusted difference in mean change between the two treatment groups and this will be reported along with the 95% confidence interval and p-value.

This analysis using ANCOVA will not adjust for any missing data. However, reasons for missing outcome data will be reported.

Descriptive statistics of means with standard deviations (or medians with inter-quartile ranges if non-normally distributed) at baseline, 12 months and change from baseline at 12 months will also be presented.

A second analysis will be performed modelling 12-month BMI SDS using mixed model ANCOVA. The outcome in the ANCOVA model will be 12-month BMI SDS with baseline BMI SDS, age-strata and treatment included as covariates in the model. Centre will be fitted as a random effect. This difference in 12-month BMI SDS mean change between the two treatment groups will be reported along with the 95% confidence interval and p-value.

17.4.6 Secondary Outcome 5: Height

17.4.6.1 Derivation

Height SDS ($Height_{SDS}$) will be derived using the 2006 WHO growth standard[10] (for children <5 years) and 2007 WHO growth reference[11] (for children ≥5 years) from the age (years), and height (m) measurements taken at baseline and at 12 months post diagnosis.

Age, and height data are found in the CRFs: 'Form 2 Baseline' and 'Form 6 Follow-up visit [3/6/9/12 month]'.

For each participant, the change in Height SDS ($\Delta Height_{SDS}$) over the first year after diagnosis will be calculated as:

$$\Delta Height_{SDS} = Height_{SDS[12]} - Height_{SDS[0]} \quad [4]$$

where $Height_{SDS[0]}$ is their $Height_{SDS}$ at baseline, and $Height_{SDS[12]}$ is their $Height_{SDS}$ at the 12-month follow-up appointment.

Height is measured in m. For this analysis gender and age-group will also be required. The CRF 'Form 2 Baseline' collects the baseline height, age-group and gender. The CRF 'Form 6 12-Month Follow-Up Visit' collects the 12-month height.

17.4.6.2 Analysis

Change in height SDS will be analysed using the methods given in section 17.4.5.2.

17.4.7 Secondary Outcome 6: Insulin requirements

17.4.7.1 Derivation

Insulin usage is recorded at each follow-up appointment, reflecting the insulin usage for the 4 weeks preceding the appointment. The unit of measurement is units/kg/day. It can be obtained in a number of ways, with data directly available from pump devices for the CSII arm. For the purpose of this analysis, insulin usage will be obtained from a single source type for both arms, i.e. from glucometers; and only data obtained at the 12-month appointment will be analysed.

Insulin requirement (*IR*) is calculated as:

$$IR = \frac{\sum_{jk} I_{jk}}{Weight_{12} \times Days} \quad [5]$$

where I_{jk} is the insulin requirement on day j by device type k. $Weight_{12}$ is the weight of the participant at 12-months post randomisation, and *Days* is the total number of days where total daily insulin received has been recorded in the 28 days preceding the 12-month follow-up appointment.

17.4.7.2 Analysis

IR is a continuous variable and will be analysed using the methods given in 17.4.1.2 above.

17.4.8 Secondary Outcome 7: Paediatric Quality of Life: PedsQL

17.4.8.1 Derivation

PedsQL is a standardised age-targeted questionnaire, generating an overall score between 0 and 100 representing patients' perceived health-related quality of life. Values for each question of each age-specific questionnaire will be uploaded and the overall score calculated as per PedsQL guidelines: "Scaling And Scoring Of The Paediatric Quality of Life Inventory™ PedsQL" found at http://www.pedsql.org /PedsQL-Scoring.pdf. This also provides a strategy for handling missing data: if > 50% of questions are unanswered, then the total score should not be calculated; otherwise, impute the mean score of the questions that have been answered in for the missing ones.

17.4.8.2 Analysis

PedsQL is a pseudo-continuous variable and will be analysed using the methods given in 17.4.1.2 above.

17.4.9 Secondary Outcome 8: Incremental cost per QALY gained

Cost effectiveness based on the incremental cost-per Quality of Adjusted Life Years (QALY) gained. The SCIPI Health Economists at Bangor will be analysing this secondary outcome – see Health Economic Analysis Plan (HEAP) for further details.

17.4.10 Secondary Outcome 9: Partial remission

Number of participants in each group with partial remission (PR) at 12 months.

17.4.10.1 Derivation

Insulin dose-adjusted HbA1c (IDAA1c) is a measure used to define partial remission in children recently diagnosed with Type I diabetes. This is a transient phase in which children partially recover in response to treatment, before they enter the chronic phase of the disease. IDAA1c was proposed by Mortensen et al (2009):

$$IDAA1c = HbA1c + 4 \times \frac{Daily\ Insulin\ Dose\ (units)}{Weight\ (kg)}$$

HbA1c and **Weight** are measured at each follow-up visit. Insulin dose is recorded daily for up to 4 weeks before the follow-up visit. In most cases, two different types of insulin are prescribed – so the total daily dose is the sum of two doses. In this analysis, **Daily Insulin Dose** will be calculated as the average of any daily doses recorded within the two weeks immediately prior to each follow-up visit.

Mortensen et al (2009) define PR in Type I diabetes as 1 if IDAA1c ≤ 9.0. Therefore, partial remission will be derived with values 0: if IDAA1c > 9.0 and 1: if IDAA1c ≤ 9.0.

Weight data are found in the CRFs: 'Form 2 Baseline' (calculation of baseline BMI) and 'Form 6 12-Month Follow-Up Visit'. HbA1c measurements are found in the CRF: 'Form 6 12-Month Follow-Up Visit' and MACRO CRF 'Central HbA1c Measurements'. Dose data will be taken from the glucometer uploads.

17.4.10.2 Analysis

The number and percentage of participants with partial remission at 12 months will be reported overall and for each treatment group. The difference between the two percentages will be presented with a 95% confidence interval and significance tested using the chi-squared test. RR with 95% confidence interval will also be presented. A precision of 1 decimal place will be used for all statistics.

18 Missing data and withdrawals

Randomised participants excluded will be summarised within each treatment arm in terms of baseline characteristics. These summary statistics will be compared with the baseline characteristics of the full sample of randomised participants to explore whether some subgroups were more likely to be excluded from the analysis.

The numbers (with reasons) or losses to follow-up and withdrawals will be summarised within each treatment arm.

18.1 12-month $HbA1_c$

Local measurements will be used in place of central measurements if central measurements are missing.

19 Additional analyses

19.1 Primary outcome

Two secondary analyses will also be carried out to explore whether there is evidence of an association between (i) higher social deprivation quintile and lower outcomes; and (ii) the number of related adverse events and lower outcomes. This will be explored by fitting a linear regression model with 12-month $HbA1_c$ as a dependent variable, and treatment group and the variables in (i) and (ii) as covariates.
Note: Social deprivation quintile is derived from social deprivation score as defined in Table 2 above. Rate of related adverse events will be calculated in person years by total related AEs / time on treatment in years.

19.2 Partial remission

All these analyses will be presented split by age strata.

At each time point (3m, 6m, 9m, 12m) the number and percentage of participants (i) not in partial remission; (ii) entering partial remission; (iii) remaining in partial remission; (iv) leaving partial remission will be reported overall and for each treatment group. No statistical testing will be undertaken.

Mean profile plots by treatment group for the proportions of participants in partial remission will be presented with 1-standard error bars being displayed for each visit.

A table showing the partial remission transitions from 6m to 12m split by treatment group will be presented for (i) In partial remission at 6m then still in partial remission at 12m; and (ii) Not in partial remission at 6m then in partial remission at 12m.

The average length of time participants were in partial remission will analysed as a time to event outcome with leaving the partial remission phase as the outcome. It will be assumed that all participants at baseline have entered the partial remission phase. A sensitivity analysis will be carried out assuming that all participants have entered and left the partial remission phase at baseline. Randomisation date will be used for the baseline date. A Kaplan-Meier plot will be constructed with separate curves for each treatment group and will be presented in the trial report. The units of time for the *x*-axis will be weeks. From inspection of the Kaplan-Meier plot the separation between the curves should remain proportional across analysis time. If the curves cross again this shows that the proportional hazards assumption has been violated. To put this formally, the proportional hazards assumption is that the ratio of hazards is a constant that does not depend on time:

$$\frac{h_A(t)}{h_B(t)} = r$$

When this assumption fails, it is because the hazard ratio changes over time. To test this, we will add predictor for group*time interaction i.e. a time-dependent covariate. Evidence that group*time interaction is not zero is evidence against proportional hazards. In SAS, PROC

PHREG provides the p-value of this test. $p<0.05$ will indicate non-proportional hazards and thus a time-dependent covariate will be included in the Cox model. If $p \geq 0.05$ survival estimates will be calculated using the method of Kaplan-Meier.

In both situations, survival estimates will be calculated using the method of Kaplan and Meier with curves for each treatment group presented graphically with numbers at risk. Survival times (presented in weeks) will be measured from the date of randomisation to the date of treatment failure as identified above. The p-value obtained from the log-rank test, median times with 95% confidence intervals obtained from the Kaplan-Meier plots, and also the hazard ratio with 95% confidence interval will be used to assess differences in failure estimates across treatment groups. The null hypothesis is that there is no difference in outcome between the two treatment groups. The alternative hypothesis is that there is a difference between the two treatment groups. The 2-sided significance level of 0.05 will be used to indicate statistical significance for the comparison between the two treatment groups.

19.3 Permanent changes to insulin delivery

A Forest plot will be used to display the numbers of permanent changes to insulin delivery between MDI and CSII (and vice versa) by each site with 95% confidence interval and used to consider heterogeneity of treatment effect. In the absence of concerns of heterogeneity (visual and I^2) an unadjusted analysis will also be provided. The subjective judgement of I^2 bands as defined in the Cochrane Handbook will be used:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

20 Safety Evaluations

Related adverse events that have occurred will be categorised by type: causing participant harm; or due to a device failure. Instances of severe hypoglycaemia, diabetic ketoacidosis, and site infection will be reported. Other types of event experienced will be listed.

Serious adverse events (SAEs) will be categorised as expected or unexpected and as related or unrelated to insulin drug. Other SAEs (not related to the trial) will be listed.

20.1 Data sets analysed

The safety analysis data set will contain all participants that are randomised and received at least one dose of trial medication. Participants AEs/SAEs will be included in the method of insulin delivery they were actually receiving at the time of AE/SAE onset to take into account any participants that temporarily changed (Form 17: Insulin delivery) or permanently changed (Form 13: Permanent change to insulin delivery) their mode of insulin delivery at any point throughout the trial. If any AE/SAE onset dates or temporary/permanent changes to mode of insulin delivery (to that they were randomised to) are missing, to determine which mode of insulin delivery there were using at the time, these will be looked at on a case-by-

case basis and queried with site if necessary. The insulin type used to assess relationship will also be taken into account.

20.2 Presentation of the data

The number of related adverse events occurring and the number and percentage of participants involved will be reported by treatment arm. The percentage of participants involved will be calculated by dividing the number of related adverse events occurring by the total number of person years for the treatment arm. These will be further split by type: causing participant harm; or due to a device failure. The numbers of instances of Severe Hypoglycaemia, Diabetic Ketoacidosis, and Site Infection will be reported. Other types of event experienced will be listed. The number (and percentage) of participants experiencing each AE will also be presented for each treatment arm categorised by severity “Mild”, “Moderate”, or “Severe”).

Serious adverse events (SAEs) will be summarised and described descriptively and presented as line listings, reporting randomisation number, centre, text description, CI assessment of seriousness, trial intervention, relationship, expectedness, action taken and outcome. No formal statistical tests will be undertaken. A summary table will report frequencies of SAEs that were expected/expected and related/unrelated to insulin drug.

Additionally, the incidence rates of total numbers of AEs/SAEs will be calculated for each treatment group in person-days. This is defined as the total number of AEs/SAEs divided by the total exposure time in days for all participants that received that treatment for a given time regardless of whether it was their randomised treatment or not. Any treatment switches are captured in ‘Form 13 – Permanent change to insulin delivery’.

21 References

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