Clinical trial results:
A randomised controlled trial of continuous subcutaneous insulin infusion(CSII) compared to multiple daily injection(MDI) regimens on insulin in children and young people at diagnosis of type I diabetes mellitus (TIDM).

Summary

EudraCT number	2010-023792-25
Trial protocol	GB
Global end of trial date	30 January 2017

Results information

Result version number	v2 (current)
This version publication date	08 February 2019
First version publication date	17 August 2017
Version creation reason	• Correction of full data set • Changes to summary attachments An error spotted during copy-editing stage of HTA final report submission needs to be corrected within EudraCT database. The value that needs to be corrected is the difference in percentages in 'Table 6.6-13: Percentage of participants in each group with 12-month HbA1c < 58.5 mmol/mol – Results (ITT)'. This is presented as a secondary analysis within the attachment for the 'Percentage of participants in each group with 12-month HbA1c < 48 mmol/mol' secondary outcome.
Summary attachment (see zip file)	SCIPI Final analysis report v3.0 (SCIPI Final analysis report v3.0.pdf)

Trial information

Trial identification

Sponsor protocol code	HTA08/14/39

Additional study identifiers

ISRCTN number	ISRCTN29255275
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CTA no: 21362/0002/001-0001, REC no: 10/H1002/80, Funder Reference No: HTA 08/14/39

Notes:

Sponsors

Sponsor organisation name	Alder Hey Children's NHS Foundation Trust
Sponsor organisation address	Eaton Road, Liverpool, United Kingdom, L12 2AP
Public contact	Carrol Gamble, Clinical Trials Research Centre, University of Liverpool, +44 151 795 8751, ctrcqa@liverpool.ac.uk
Scientific contact	Carrol Gamble, Clinical Trials Research Centre, University of Liverpool, +44 151 795 8751, ctrcqa@liverpool.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2016
Global end of trial reached?	Yes
Global end of trial date	30 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Inbuilt pilot: The primary objective for the inbuilt pilot is to acquire an understanding of the acceptability of randomisation to multiple daily injections or infusion pumps at diagnosis of type 1 diabetes mellitus in children and young people.

Full study: The primary objective for the full study is to compare the control of the blood glucose levels, measured by glycosylated haemoglobin (HbA1c), at 12 months after diagnosis of type 1 diabetes mellitus in children and adolescents receiving infusion pumps with those receiving multiple daily injections.

Protection of trial subjects:

SCIPI was a pragmatic trial set in routine clinical practice. All interventions were in common use in the age range of the trial. No additional measures were required.

Background therapy:

No additional interventions were provided.

Evidence for comparator:

This study is designed to provide an evidence base to inform future NHS investment in health care services for children and young people with TIDM. The role of intensive insulin therapy in optimizing glycaemic control and thereby reducing the risk of vascular complications of TIDM is unquestioned however the optimal way in which to achieve this and the cost effectiveness of the tools currently available is unknown. This study will compare two methods of insulin delivery during childhood and adolescence to identify which facilitates superior glycaemic control, and examine the impact of treatment modalities on other predictors of vascular complications of TIDM, adverse events and QoL. Both methods are currently available and used within the SCIPI target population.

Actual start date of recruitment	16 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 293
Worldwide total number of subjects	293
EEA total number of subjects	293

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	14
Children (2-11 years)	198
Adolescents (12-17 years)	81
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 15 children's diabetes services in England and Wales with experience of treating ten of more patients with CSII. The study opened to recruitment on 16/05/2011, and was closed on 30/01/2017.

Pre-assignment

Screening details:

976 patients were screened. 98 (10%) were not eligibile. 189 (22%) were not approached about participation due to time or clinical reason. 689 approached, 294 consented (1 withdrew). 395 eligible who declined consent 36 (9%) cited a preference for CSII therapy and 259 (66%) a preference for MDI.

Pre-assignment period milestones

Number of subjects started	976[1]
Number of subjects completed	293

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not eligible: 98
Reason: Number of subjects	Eligible Consent not sought: Lack of trained staff: 52
Reason: Number of subjects	Eligible Consent not sought: Reason not recorded: 22
Reason: Number of subjects	Eligible Consent not sought: Consultant decision: 115
Reason: Number of subjects	Eligible Consent sought: MDI preference: 259
Reason: Number of subjects	Eligible Consent sought: Pump preference: 36
Reason: Number of subjects	Eligible Consent sought: Other: 100
Reason: Number of subjects	Consent withdrawn by subject: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 976 patients screened with 293 randomised. Please override warning.

Period 1

Period 1 title	Main trial (visits at: 0m/3m/6m/9m/12m) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Trial was open-label. Blood samples sent to the laboratory did not indicate allocated intervention.

Arms

Are arms mutually exclusive?	Yes
Arm title	CSII group

Arm description:

Roche CSII Insulin pump. Medtronic and Omnipod could also be used as per clinical judgement.

Arm type	Experimental

Investigational medicinal product name	Novorapid 100 U/ml solution for injection (Insulin Aspart)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart will be administered using CSII insulin pumps (Refer to Insulin Pump Manual Guide). Participants will be given insulin aspart using basal insulin infusion with bolus doses of insulin aspart when 5g or more carbohydrate is consumed.
Starting Dose Calculations:
Total daily starting dose of insulin will be calculated from body weight. In pre pubertal subjects 0.5units/kg body weight/day with 50% of calculated dose given as a continuous 24hour infusion (0.5x kg body weight, ÷ 2 ÷ 24 = hourly rate) (CSII). The remaining 50% will be given as 3 divided pre-prandial doses at meal times. If the doses are not equal more insulin will be given before breakfast and the evening meal than at lunch time to account for diurnal variation in insulin sensitivity. In pubertal participants the initial dose calculation will be based on 0.7units/kg body weight /day.

Arm title	MDI group

Arm description:

Insulin delivered subcutaneously using an insulin pen injection device in accordance with manufacturer instructions for use.

Arm type	Experimental
Investigational medicinal product name	Insulin Glargine (Lantus 100 units/ml solution for injection)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine was delivered subcutaneously using an insulin pen injection device in accordance with manufacturer instructions for use. Participants were given insulin glargine (long acting analog) once or twice daily according to their needs.
Starting Dose Calculations: Total daily starting dose of insulin will be calculated from body weight. In pre pubertal subjects 0.5units/kg body weight/day with 50% of calculated dose given as insulin glargine injection into the anterior-lateral aspect of the thigh, arm, abdomen or the upper outer quadrant of the buttocks (MDI). The remaining 50% will be given as 3 divided pre-prandial doses at meal times. If the doses are not equal more insulin will be given before breakfast and the evening meal than at lunch time to account for diurnal variation in insulin sensitivity. In pubertal participants the initial dose calculation will be based on 0.7units/kg body weight /day.

Investigational medicinal product name	Insulin Aspart (Novorapid 100 U/ml solution for injection)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart was delivered subcutaneously using an insulin pen injection device in accordance with manufacturer instructions for use. Participants were given boluses of insulin aspart (short acting analog) when 10g or more of carbohydrate were consumed.

Starting Dose Calculations:
Total daily starting dose of insulin was calculated from body weight. In pre pubertal subjects 0.5units/kg body weight/day with 50% of calculated dose given either as insulin injection into the anterior-lateral aspect of the thigh, arm, abdomen or the upper outer quadrant of the buttocks (MDI). The remaining 50% will be given as 3 divided pre-prandial doses at meal times. If the doses are not equal more insulin will be given before breakfast and the evening meal than at lunch time to account for diurnal variation in insulin sensitivity. In pubertal participants the initial dose calculation will be based on 0.7units/kg body weight /day.

Investigational medicinal product name	Insulin Detimir. Levemir Cartridge 100 units/ml - Penfill, Levemir Pre-filled Pen 100 units/ml - FlexPen and InnoLet
Investigational medicinal product code	

Pharmaceutical forms	Solution for injection in pre-filled injector
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin detimir was delivered subcutaneously using an insulin pen injection device in accordance with manufacturer instructions for use.

Starting Dose Calculations: Total daily starting dose of insulin will be calculated from body weight. In pre pubertal subjects 0.5units/kg body weight/day with 50% of calculated dose given as insulin glargine injection into the anterior-lateral aspect of the thigh, arm, abdomen or the upper outer quadrant of the buttocks (MDI). The remaining 50% will be given as 3 divided pre-prandial doses at meal times. If the doses are not equal more insulin will be given before breakfast and the evening meal than at lunch time to account for diurnal variation in insulin sensitivity. In pubertal participants the initial dose calculation will be based on 0.7units/kg body weight /day.

Number of subjects in period 1	CSII group	MDI group
Started	144	149
Completed	143	144
Not completed	1	5
Personal circumstances	-	1
No longer wished to participate	1	-
Coeliac disease Can't comply with gluten free diet	-	1
Lost to follow-up	-	1
Relocated	-	2

Baseline characteristics

Reporting groups	
Reporting group title	CSII group
Reporting group description:	
Roche CSII Insulin pump. Medtronic and Omnipod could also be used as per clinical judgement.	
Reporting group title	MDI group
Reporting group description:	
Insulin delivered subcutaneously using an insulin pen injection device in accordance with manufacturer instructions for use.	

Reporting group values	CSII group	MDI group	Total
Number of subjects	144	149	293
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	8	6	14
Children (2-11 years)	96	102	198
Adolescents (12-17 years)	40	41	81
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	9	9.1	
standard deviation	± 4.1	± 4.1	-
Gender categorical Units: Subjects			
Female	71	69	140
Male	73	80	153
Age (strata categories) Units: Subjects			
7mths – <5 yrs	33	32	65
5 – <12 yrs	71	76	147
12-15 yrs	40	41	81
Ethnicity Units: Subjects			
Missing	1	3	4
Asian or Asian British	3	3	6
Black or British Black	0	3	3
British White	124	118	242
Indian	2	2	4
Mixed	4	6	10
Other White	6	8	14
Other	3	2	5
Pakistani	1	4	5

Deprivation score (quintile categories) Units: Subjects			
Missing	7	6	13
1 (<=8.49)	32	40	72
2 (8.5 – 13.79)	23	30	53
3 (13.8 – 21.35)	18	22	40
4 (21.36 – 34.17)	25	18	43
5 (>=34.18)	39	33	72
Thyroid test result			
* Test not a requirement of the study protocol.			
Units: Subjects			
Not done	25	19	44
Missing	7	6	13
Abnormal	6	3	9
Normal	105	118	223
Results unobtainable	1	3	4
Coeliac screen test result			
* Test not a requirement of the study protocol.			
Units: Subjects			
Not done	28	30	58
Missing	14	10	24
Abnormal	3	9	12
Normal	97	97	194
Results unobtainable	2	3	5
Islet Cell Antibodies test result			
* Test not a requirement of the study protocol.			
Units: Subjects			
Not done	39	34	73
Missing	17	17	34
Negative	35	31	66
Positive	39	53	92
Weak positive	13	10	23
Results unobtainable	1	4	5
GAD 65 Antibodies test result			
* Test not a requirement of the study protocol.			
Units: Subjects			
Note done	65	65	130
Missing	13	14	27
Equivocal	4	4	8
Negative	11	16	27
Positive	50	50	100
Results unobtainable	1	0	1
Conmeds prescribed up to baseline Units: Subjects			
Missing	2	0	2
No	102	114	216
Yes	40	35	75
Deprivation score (continuous)			
CSII missing = 7 MDI missing = 6 Total missing = 13			
Units: IMD			

median	19.4	14.7	
inter-quartile range (Q1-Q3)	8.9 to 37.9	7.8 to 31.8	-
BMI SDS			
CSII missing = 20 MDI missing = 17 Total missing = 37			
Units: SDS			
arithmetic mean	0.2	0.1	
standard deviation	± 1.3	± 1.4	-
Height SDS			
CSII missing = 20 MDI missing = 17 Total missing = 37			
Units: SDS			
arithmetic mean	0.3	0.3	
standard deviation	± 1.1	± 1.1	-
Local HbA1c			
CSII missing = 22 MDI missing = 27 Total missing = 49			
Units: mmol/mol			
arithmetic mean	105.9	103.6	
standard deviation	± 24.2	± 26.3	-
Central HbA1c			
CSII missing = 80 MDI missing = 78 Total missing = 158 * High levels of missing data for 'Central HbA1c' because the central laboratory for sending all blood samples to for measuring HbA1c was only set up part-way through the trial.			
Units: mmol/mol			
arithmetic mean	101.2	96.4	
standard deviation	± 24.9	± 24	-
HbA1c#			
# When available central lab HbA1c measurement taken in preference of local lab HbA1c measurement. CSII missing = 12 MDI missing = 18 Total missing = 30			
Units: mmol/mol			
arithmetic mean	104.6	102.6	
standard deviation	± 24.4	± 26.7	-
Blood glucose			
CSII missing = 3 MDI missing = 3 Total missing = 6			
Units: mmol/L			
arithmetic mean	26.8	26.9	
standard deviation	± 9.2	± 10	-
Blood pH			
CSII missing = 17 MDI missing = 16 Total missing = 33			
Units: pH			
arithmetic mean	7.3	7.3	
standard deviation	± 0.2	± 0.1	-
Health Utilities Index			

CSII Not done (HUI not completed properly) = 7 CSII Not done (HUI not completed at all) = 22 MDI Not done (HUI not completed properly) = 3 MDINot done (HUI not completed at all) = 19 Total Not done (HUI not completed properly) = 10 Total Not done (HUI not completed at all) = 41			
Units: HUI			
arithmetic mean	0.9	0.9	
standard deviation	± 0.19	± 0.1	-

End points

End points reporting groups

Reporting group title	CSII group
Reporting group description:	
Roche CSII Insulin pump. Medtronic and Omnipod could also be used as per clinical judgement.	
Reporting group title	MDI group
Reporting group description:	
Insulin delivered subcutaneously using an insulin pen injection device in accordance with manufacturer instructions for use.	
Subject analysis set title	Per protocol - CSII
Subject analysis set type	Per protocol
Subject analysis set description:	
The primary endpoint will be analysed a second time using the per protocol approach. 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.	
Subject analysis set title	Per protocol - MDI
Subject analysis set type	Per protocol
Subject analysis set description:	
The primary endpoint will be analysed a second time using the per protocol approach. 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.	

Primary: Primary outcome: HbA1c measured 12 months after randomisation

End point title	Primary outcome: HbA1c measured 12 months after randomisation
End point description:	
HbA1c is measured from a blood sample taken at the 12-month follow-up appointment . Unit of measurement: mmol/mol. 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. Local measurements will be used when central measurements are not available. HbA1c will be compared between the trial groups using mixed-model regression with 12-month HbA1c as the dependent variable, treatment group as an explanatory factor and the stratification variables: age-group and centre as covariates. Centre will be fitted as a random effect.	
End point type	Primary
End point timeframe:	
Measured 12 months after randomisation.	

End point values	CSII group	MDI group	Per protocol - CSII	Per protocol - MDI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	143	142	87	66
Units: mmol/mol				
arithmetic mean (standard deviation)				
7mths - < 5yrs	63.9 (± 12.1)	58.4 (± 9.9)	62.6 (± 13.1)	56.2 (± 11)

5yrs - <12yrs	58 (± 11.4)	59.3 (± 11.4)	57.9 (± 11.8)	59.7 (± 10.8)
12yrs - <16yrs	61.3 (± 13.3)	54.7 (± 14.7)	57.6 (± 14.2)	57.8 (± 16.8)
Overall	60.3 (± 12.3)	57.9 (± 12.2)	59 (± 12.8)	58.4 (± 13.1)

Attachments (see zip file)	All tables and figures for outcome/Primary outcome results.pdf

Statistical analyses

Statistical analysis title	HbA1c at 12 months - Mixed model analysis (ITT)

Statistical analysis description:

HbA1c will be compared between the trial groups using mixed-model regression with 12-month HbA1c as the dependent variable, treatment group as an explanatory factor and the stratification variables: age-group and centre as covariates. Centre will be fitted as a random effect.

Comparison groups	CSII group v MDI group
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	5.3

Notes:

[1] - Not significant.

Statistical analysis title	HbA1c at 12 months - Mixed model analysis (PP)

Statistical analysis description:

HbA1c will be compared between the trial groups using mixed-model regression with 12-month HbA1c as the dependent variable, treatment group as an explanatory factor and the stratification variables: age-group and centre as covariates. Centre will be fitted as a random effect.

Comparison groups	Per protocol - CSII v Per protocol - MDI
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	5

Notes:

[2] - Not significant. Confirms the robustness of the ITT analysis result.

Secondary: Secondary outcome 1: Percentage of participants in each group with 12-month HbA1c < 6.5%

End point title	Secondary outcome 1: Percentage of participants in each group with 12-month HbA1c < 6.5%

End point description:

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

Number of participants in each group with 12-month HbA1c less than 48 mmol/mol.

End point type	Secondary

End point timeframe:

Measured 12 months after randomisation.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	142		
Units: mmol/mol	22	29		

Attachments (see zip file)	Secondary outcome 1/Secondary outcome 1.pdf

Statistical analyses

Statistical analysis title	12-month HbA1c < 48 mmol/mol

Statistical analysis description:

The number and percentage of participants with 12-month HbA1c less than 48 mmol/mol (equivalent to 6.5%) 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.

Comparison groups	CSII group v MDI group
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28 [3]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.25

Notes:

[3] - Not significant.

Statistical analysis title	12-month HbA1c < 58.5 mmol/mol

Statistical analysis description:

The number and percentage of participants with 12-month HbA1c less than 48 mmol/mol (equivalent to 7.5%) 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.

Comparison groups	CSII group v MDI group
Number of subjects included in analysis	285
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	= 0.16 [5]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.06

Notes:

[4] - Analysis not post-hoc as such as was detailed in earlier version of SCIPI trial protocol. See substantial amendment (01/08/2016): "Updated the HbA1c recommendations in line with the recent NICE guidance: Change to the Secondary Objective. HbA1c reduced from 7.5% to 6.5% and HbA1c also provided in mmol. Change to secondary endpoint - Percentage of participants in each group with HbA1c reduced from <7.5% to <6.5%. Added partial remission and height as endpoints."
[5] - Not significant which matches conclusion from the < 48 mmol/mol analysis.

Secondary: Secondary outcome 2: Incidence of severe hypoglycaemia

End point title	Secondary outcome 2: Incidence of severe hypoglycaemia

End point description:

Severe hypoglycaemia is a type of related adverse event. Participants that experience at least one instance of severe hypoglycaemia will be identified.

End point type	Secondary

End point timeframe:

Measured 12 months after randomisation.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	149		
Units: N/A	6	2		

Attachments (see zip file)	All tables and figures for outcome/Secondary outcome 2.pdf

Statistical analyses

Statistical analysis title	Incidence of severe hypoglycaemia

Statistical analysis description:

The number and percentage of participants in each group that experience at least one instance of severe hypoglycaemia 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.

Comparison groups	MDI group v CSII group
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17 [6]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	15.1

Notes:

[6] - Not significant.

Secondary: Secondary outcome 3: Incidence of diabetic ketoacidosis

End point title	Secondary outcome 3: Incidence of diabetic ketoacidosis

End point description:

Diabetic ketoacidosis is a type of related adverse event. Participants that experience at least one instance of severe hypoglycaemia will be identified.

End point type	Secondary

End point timeframe:

Measured 12 months after randomisation.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	149		
Units: N/A	2	0		

Attachments (see zip file)	All tables and figures for outcome/Secondary outcome 3.pdf

Statistical analyses

Statistical analysis title	Incidence of diabetic ketoacidosis

Statistical analysis description:

The number and percentage of participants in each group that experience at least one instance of diabetic ketoacidosis 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.

Comparison groups	CSII group v MDI group

Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 [7]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	106.8

Notes:

[7] - Not significant.

Secondary: Secondary outcome 4: Change in BMI SDS

End point title	Secondary outcome 4: Change in BMI SDS

End point description:

BMI SDS will be derived using the 2006 WHO growth standard (for children <5 years) and 2007 WHO growth reference (for children ≥5 years) from the age (years), weight (kg) and height (m) measurements taken at baseline and at 12 months post diagnosis.

End point type	Secondary

End point timeframe:

Baseline and at 12 months post diagnosis.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	122		
Units: SDS				
arithmetic mean (standard deviation)	0.6 (± 0.8)	0.5 (± 0.8)		

Attachments (see zip file)	All tables and figures for outcome/Secondary outcome 4.pdf

Statistical analyses

Statistical analysis title	Change in BMI SDS mixed model ANCOVA

Statistical analysis description:

Change in BMI SDS (12-month followup 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.

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.

Comparison groups	CSII group v MDI group

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [8]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.3

Notes:

[8] - Not significant.

Secondary: Secondary outcome 5: Height

End point title	Secondary outcome 5: Height

End point description:

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

End point type	Secondary

End point timeframe:

Baseline and at 12 months post diagnosis.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	122		
Units: SDS				
arithmetic mean (standard deviation)	-0.1 (± 0.5)	0 (± 0.4)		

Attachments (see zip file)	All tables and figures for outcome/Secondary outcome 5.pdf

Statistical analyses

Statistical analysis title	Change in height SDS mixed model ANCOVA

Statistical analysis description:

Change in height SDS (12-month followup minus baseline) will be analysed using mixed model ANCOVA.

The outcome in the ANCOVA model will be change in height SDS with baseline height SDS, age-strata and treatment included as covariates in the model. Centre will be fitted as a random effect.

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

Comparison groups	CSII group v MDI group

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1 [9]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0

Notes:

[9] - Not significant

Secondary: Secondary outcome 6: Insulin requirements

End point title	Secondary outcome 6: Insulin requirements

End point description:

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 per SAP.

End point type	Secondary

End point timeframe:

Measured 12 months after randomisation.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	64		
Units: Units/kg/day				
arithmetic mean (standard deviation)				
7mths - < 5yrs	0.7 (± 0.2)	0.7 (± 0.1)		
5yrs - <12yrs	0.6 (± 0.2)	0.6 (± 0.3)		
12yrs - <16yrs	0.8 (± 0.2)	0.5 (± 0.4)		
Overall	0.7 (± 0.2)	0.6 (± 0.3)		

Attachments (see zip file)	All tables and figures for outcome/Secondary outcome 6.pdf

Statistical analyses

Statistical analysis title	Insulin requirements mixed model analysis

Statistical analysis description:

Insulin requirement will be compared between the trial groups using mixed-model regression with 12-month HbA1c as the dependent variable, treatment group as an explanatory factor and the stratification

variables: age-group and centre as covariates. Centre will be fitted as a random effect.

Comparison groups	CSII group v MDI group
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.2

Notes:

[10] - Significant.

Secondary: Secondary outcome 7: Paediatric Quality of Life (PedsQL)

End point title	Secondary outcome 7: Paediatric Quality of Life (PedsQL)

End point description:

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.

End point type	Secondary

End point timeframe:

Measured 12 months after randomisation.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	149		
Units: 0-100				
arithmetic mean (standard deviation)				
Children 5-7 years old (12 month follow-up)	72.6 (± 15.5)	70 (± 15.2)		
Children 8-12 years old (12 month follow-up)	79 (± 12)	74.4 (± 14.3)		
Children 13-16 years old (12 month follow-up)	73.7 (± 13.8)	72.4 (± 14.4)		
Parents / carers 2-4 years old (12 month follo	73 (± 12.7)	67 (± 15.7)		
Parents / carers 5-7 years old (12 month follo	73.1 (± 15.8)	71 (± 9.3)		
Parents / carers 8-12 years old (12 month foll	73.9 (± 11.9)	68.2 (± 14.9)		
Parents / carers 13-16 years old (12 month fol	69 (± 14.5)	67.5 (± 15.7)		

Attachments (see zip file)	All tables and figures for outcome/Secondary outcome 7.pdf

Statistical analyses

Statistical analysis title	Children - Overall QoL at 12m - Mixed model

Statistical analysis description:

Overall QoL score will be compared between the trial groups using mixed-model regression with 12-month Overall QoL score as the dependent variable, treatment group as an explanatory factor and the stratification variables: questionnaire age-group and centre as covariates. Centre will be fitted as a random effect.

Comparison groups	CSII group v MDI group
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1 [11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	6.8

Notes:

[11] - Not significant.

Statistical analysis title	Parent - Overall QoL at 12m - Mixed model

Statistical analysis description:

Overall QoL score will be compared between the trial groups using mixed-model regression with 12-month Overall QoL score as the dependent variable, treatment group as an explanatory factor and the stratification variables: questionnaire age-group and centre as covariates. Centre will be fitted as a random effect.

Comparison groups	CSII group v MDI group
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	7.6

Notes:

[12] - Not significant. The Estimated G matrix was not positive definite which indicates that the variance component in the RANDOM statement (site) are estimated to be zero so were removed from the model.

Secondary: Secondary outcome 8: Cost effectiveness

End point title	Secondary outcome 8: Cost effectiveness

End point description:

This analysis is reported separately by Health Economists at Bangor. See HTA report for full detail once published.

End point type	Secondary

End point timeframe:

This analysis is reported separately by Health Economists at Bangor. See HTA report for full detail once published.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	149		
Units: N/A	144	149		

Attachments (see zip file)	All tables and figures for outcome/Secondary outcome 8.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary efficacy outcome 9: Partial Remission

End point title	Secondary efficacy outcome 9: Partial Remission

End point description:

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). The variables included in the calculation are HbA1c, daily insulin dose (units) up to 4 weeks before the follow-up visit and weight (kg). See SAP for details.

End point type	Secondary

End point timeframe:

Measured at 12 months after randomisation.

End point values	CSII group	MDI group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	64		
Units: N/A	21	21		

Attachments (see zip file)	All tables and figures for outcome/Secondary outcome 9.pdf

Statistical analyses

Statistical analysis title	Partial remission at 12m

Statistical analysis description:

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.

Comparison groups	MDI group v CSII group
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28 [13]
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.24

Notes:

[13] - Not significant.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious ARs/AEs: Reported to the CTU within 24 hours.

Non serious ARs/AEs: Reported to the CTU as per routine schedule.

Adverse event reporting additional description:

Participants AEs/SAEs are 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/permanently changed their mode of insulin delivery at any point throughout the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	CSII group

Reporting group description:

Total person years (total patients) = 144.1 (144)

Reporting group title	MDI group

Reporting group description:

Total person years (total patients) = 151.9 (149)

Serious adverse events	CSII group	MDI group	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 144 (6.25%)	7 / 149 (4.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 144 (0.69%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood ketone body			
subjects affected / exposed	1 / 144 (0.69%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Drug administration error			

subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Social problem			
subjects affected / exposed	0 / 144 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Treatment noncompliance			
subjects affected / exposed	0 / 144 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 144 (0.00%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Administration site infection			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			

subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 144 (1.39%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 144 (1.39%)	2 / 149 (1.34%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 144 (1.39%)	1 / 149 (0.67%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	CSII group	MDI group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 144 (19.44%)	8 / 149 (5.37%)	
Investigations			
Blood glucose increased			
subjects affected / exposed	3 / 144 (2.08%)	0 / 149 (0.00%)	
occurrences (all)	7	0	
Injury, poisoning and procedural complications			
Drug administration error			
subjects affected / exposed	1 / 144 (0.69%)	2 / 149 (1.34%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences (all)	2	0	
Device failure			
subjects affected / exposed	5 / 144 (3.47%)	1 / 149 (0.67%)	
occurrences (all)	8	1	
Device issue			
subjects affected / exposed	2 / 144 (1.39%)	0 / 149 (0.00%)	
occurrences (all)	2	0	
Implant site bruising			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	0 / 144 (0.00%)	2 / 149 (1.34%)	
occurrences (all)	0	2	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Skin reaction			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Administration site infection			
subjects affected / exposed	7 / 144 (4.86%)	0 / 149 (0.00%)	
occurrences (all)	7	0	
Penile infection			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences (all)	1	0	
Scrotal infection			
subjects affected / exposed	1 / 144 (0.69%)	0 / 149 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 144 (0.00%)	1 / 149 (0.67%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	7 / 144 (4.86%)	1 / 149 (0.67%)	
occurrences (all)	7	1	
Hypoglycaemia			
subjects affected / exposed	7 / 144 (4.86%)	3 / 149 (2.01%)	
occurrences (all)	7	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2011	Inclusion criteria amendment to include patients and parents able to complete study material. HbA1c samples will be collected, analysed and destroyed according to local clinical practice rather than analysis at a central laboratory Pharmacovigilence: Only related SAEs and related AEs will be reported for this trial. RUSAEs related to medical devices will be reported as per user vigilance reporting
01 July 2011	The time period to start the randomised treatment was changed from within 3-5 days to within 10 days. The study information will be provided and the consent should occur as close to the time of diagnosis as possible, ideally between the time of diagnosis (Day 0) and Day 5. Timelines for providing information and approaching the patient for consent will be recorded on the screening log. Web randomisation system to be used instead of telephone, with randomisation envelopes as a back-up. Up to this point all randomisations completed using backup envelopes. PedsQL (Quality of life) questionnaire booklets were removed from baseline and will only be administered at 6 and 12 month study visit.
17 August 2012	Revision to the inclusion criteria, change to patients and parents able to comply with the treatment regimen and study visits. Addition to exclusion criteria list: g. Known thyroid condition in a non Euthyroid state and; h. Known coeliac disease unable to maintain a gluten free diet. Exclusions previously specified within the protocol but not numbered within the exclusion criteria. Revision to the exclusion criteria change to: a. have a sibling with existing TIDM rather than first degree relative Additional guidance and change to recruitment window period to 14 days and further guidance on patients being approached and consented as soon after diagnosis as possible. HbA1c samples to be collected, analysed and destroyed at a central laboratory.
21 January 2015	Removal of the following from the eligibility criteria: Patient aged 8 years and over are able to comply with the treatment regimen and study visits. Addition of Omnipod as a pump that can be supplied in line with normal clinical practice Addition of text permitting use of the insulin Detemir

01 August 2016	Updated the HbA1c recommendations in line with the recent NICE guidance: Change to the Secondary Objective. HbA1c reduced from 7.5% to 6.5% and HbA1c also provided in mmol. Change to secondary endpoint - Percentage of participants in each group with HbA1c reduced from <7.5% to <6.5%. Added partial remission and height as endpoints Outcomes may be presented as mmol/mol or equivalent %

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes: