Clinical trial results:
The Relative Effectiveness of Pumps Over MDI and Structured Education.

Summary

EudraCT number	2010-023198-21
Trial protocol	GB
Global end of trial date	25 June 2015

Results information

Result version number	v1 (current)
This version publication date	10 May 2017
First version publication date	10 May 2017

Trial information

Trial identification

Sponsor protocol code	STH15295

Additional study identifiers

ISRCTN number	ISRCTN61215213
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sheffield Teaching Hospitals NHS Foundation Trust
Sponsor organisation address	Clinical Research Office Sheffield, Royal Hallamshire Hospital, D Floor, Glossop Road, Sheffield, United Kingdom, S10 2JF
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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	29 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2015
Global end of trial reached?	Yes
Global end of trial date	25 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical and cost effectiveness of insulin pump therapy compared to multiple daily injections for adults with type 1 diabetes, with both groups receiving equivalent structured training in flexible insulin therapy.

Protection of trial subjects:

Participants were provided with a contact card and encouraged to get in touch with their diabetes team if they had experienced any adverse health events. Any that were not picked up through general contact were identified at follow up visits through educators enquiring about problems that the patients have had. SAEs were reported in accordance with the study SOPs. SAEs were assessed by the local principal investigator and reported to Sheffield CTRU within 24 hours, with the exception of events that had been stated as exempt from immediate reporting, where 28 days were allowed. These exemptions were: episodes of severe hypoglycaemia requiring hospitalisation; episodes of DKA; and, pregnancy. SAEs were assessed for; seriousness, frequency, intensity, relationship to study product and, where applicable, relationship to pump. SAEs were monitored throughout the trial by the Trial Steering Committee and Data Monitoring Committee.

Background therapy:

The DAFNE course is a one-week structured education course teaching adults with T1DM skills in insulin self-adjustment and carbohydrate counting. The DAFNE course is designed to teach individuals with diabetes how to live a less restricted life, whilst effectively keeping blood sugar levels under control, therefore minimizing long-term health complications associated with diabetes. The key modules are: what is diabetes?; food and diabetes; insulin management; management of hypoglycaemia; sick day rules. Courses are conducted over five consecutive days, providing an average of 38 hours of structured education, delivered to groups of 5-8 adults aged 18 years or above, in an outpatient setting. Courses are delivered by diabetes specialist nurses and dietitians.

Evidence for comparator:

We aimed to assess the effectiveness and cost-effectiveness of insulin pump therapy compared to multiple daily injections (MDI) for people with type 1 diabetes (T1DM), when both have received high quality structured education. The purchase and use of pumps is more expensive than MDI. Pumps may be used by around 40% of people with Type 1 diabetes in the USA and over 15% in Europe. In contrast, the proportion in the UK was around 6% in adults in 2012.
Proponents of pump treatment have proposed that far more patients should be offered treatment in the UK and that current policies are depriving many of the opportunity to improve glycaemic control, reduce hypoglycaemia and improve quality of life. The UK's National Institute for Health and Care Excellence (NICE) have recently extended recommendations for the use of pumps in adults with T1DM. The guidance suggests that pump treatment be considered for individuals experiencing problems with hypoglycaemia particularly when this limits the ability to improve glycaemic control. NICE have noted the paucity of evidence for efficacy from RCTs. We hypothesised that much of the benefit of pumps may come from the re-training and education in intensive insulin management that allows patients to use pumps safely.

Actual start date of recruitment	23 November 2012
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: 267
Worldwide total number of subjects	267
EEA total number of subjects	267

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	257
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place from November 2011 till April 2013 in eight secondary care diabetes centres in Sheffield, Cambridge, Dumfries & Galloway, Edinburgh, Glasgow, Harrogate, London and Nottingham

Pre-assignment

Screening details:

Invited to take part n=1278
Responders n=885 (69%)
Interested to take part n=362 (41%)
Eligible n=334 (92%)
Eligible & consented to take part n= 321 (96%)
Dropped out prior to randomisation n=4
Randomised n=317
Allocated to CSII n=156, MDI n=161
Dropped out prior to intervention n=50

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Continuous subcutaneous insulin infusion (CSII)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Insulin aspart (NovoRapid®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received insulin aspart (NovoRapid®) via the Medtronic MiniMed Paradigm Veo Insulin pump (model 754)

Arm title	Multiple daily injections (MDI)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Insulin detemir (Levemir®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin detemir (Levemir®) is to be administered subcutaneously, once or twice daily. The dose is adjusted individually depending on the subjects' needs.

Number of subjects in period 1	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)
Started	132	135
Completed	132	135

Period 2	
Period 2 title	Follow up 24m
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Continuous subcutaneous insulin infusion (CSII)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Insulin aspart (NovoRapid®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received insulin aspart (NovoRapid®) via the Medtronic MiniMed Paradigm Veo Insulin pump (model 754)

Arm title	Multiple daily injections (MDI)

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Insulin detemir (Levemir®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin detemir (Levemir®) is to be administered subcutaneously, once or twice daily. The dose is adjusted individually depending on the subjects' needs.

Number of subjects in period 2	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)
Started	132	135
Completed	128	120
Not completed	4	15
Consent withdrawn by subject	1	1
Lost to follow-up	3	14

Baseline characteristics

Reporting groups	
Reporting group title	Continuous subcutaneous insulin infusion (CSII)
Reporting group description: -	
Reporting group title	Multiple daily injections (MDI)
Reporting group description: -	

Reporting group values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)	Total
Number of subjects	132	135	267
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	41.5	39.9	
standard deviation	± 14.2	± 12.5	-
Gender categorical Units: Subjects			
Female	54	53	107
Male	78	82	160
Previous severe hypoglycaemia in past 12 months Units: Subjects			
At least 1 severe hypo	16	15	31
No severe hypo	116	120	236
Ethnicity Units: Subjects			
White British	125	119	244
Other	7	16	23
Body Mass Index Units: Kg/M2			
arithmetic mean	27.4	27	
standard deviation	± 5	± 5	-

End points

End points reporting groups

Reporting group title	Continuous subcutaneous insulin infusion (CSII)
Reporting group description: -	
Reporting group title	Multiple daily injections (MDI)
Reporting group description: -	
Reporting group title	Continuous subcutaneous insulin infusion (CSII)
Reporting group description: -	
Reporting group title	Multiple daily injections (MDI)
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
a) all participants randomised to either MDI or CSII b) at least one HbA1c measurement after baseline c) treatment assignment as randomised	
Subject analysis set title	Per protocol (baseline HbA1c>=7.5%)
Subject analysis set type	Per protocol
Subject analysis set description:	
a) subset of ITT set meeting compliance criteria defined by - Adherence to DAFNE course: in general, a participant was adherent to the course if they attended at least 4 of the 5 days, including the first 2 days (as adjudicated by the course leader). - Adherence to the pump or MDI: a participant was classed as adherent to treatment if they adhered to the pump/MDI for the full two years (excluding any reasonable temporary interruptions of around 2 weeks).	
Subject analysis set title	Primary ITT (baseline HbA1c>=7.5%)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Change in HbA1c among participants with baseline >=7.5% / 58mmol/mol (Primary analysis population)	
Subject analysis set title	Complete case, baseline HbA1c>=7.5%
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subset of participants with baseline HbA1c>=7.5%/58mmol/mol and who were followed up to 24 months	

Primary: Change in HbA1c in participants whose baseline HbA1c was ≥ 7.5%

End point title	Change in HbA1c in participants whose baseline HbA1c was ≥ 7.5%
End point description:	
End point type	Primary
End point timeframe:	
24 months	

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)	Per protocol (baseline HbA1c>=7.5%)	Primary ITT (baseline HbA1c>=7.5%)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	119	116	217	235
Units: mmol/mol				
arithmetic mean (standard deviation)	-9.3 (± 13.66)	-4.5 (± 13.19)	6.34 (± 10.14)	6.93 (± 10.18)

Attachments (see zip file)	Forest plot/Forest plot.jpg

Statistical analyses

Statistical analysis title	Primary

Statistical analysis description:

The mean change in HbA1c at 24 months post DAFNE course was compared between those allocated to CSII and MDI using a mixed effects model. The model was adjusted for clustering by DAFNE course (random effect), centre, and baseline HbA1c (fixed effects). The mean (SD) HbA1c change from baseline for the CSII and MDI groups and the number in each group are displayed. The efficacy of the intervention is reported as mean difference (MD) in HbA1c change at 2 years, with associated 95% CI and p-value.

Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	Mixed models analysis
Parameter estimate	Mean difference in change
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	0.5

Statistical analysis title	Per protocol
Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	-0.8

Secondary: Proportion of participants with HbA1c≤7.5% at 24 months

End point title	Proportion of participants with HbA1c≤7.5% at 24 months
End point description:	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	120		
Units: Participants				
≤7.5%	32	28		

Statistical analyses

Statistical analysis title	Proportion of participants with HbA1c≤7.5% at 24 m
Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.566
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	2.39

Secondary: Severe hypoglycaemia events over 2 years

End point title	Severe hypoglycaemia events over 2 years
End point description: Severe hypoglycaemic episodes were collected on an ongoing basis over the 2 year study duration.	
End point type	Secondary
End point timeframe: 24 months	

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	135		
Units: Events				
Events	25	24		

Statistical analyses

Statistical analysis title	Incidence of severe hypoglycaemia over two years
Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.766
Method	Mixed models analysis
Parameter estimate	Incident rate ratio
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	2.51

Secondary: Change in body weight

End point title	Change in body weight
End point description:	
End point type	Secondary
End point timeframe: 24 months	

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	117		
Units: Kg				
arithmetic mean (standard deviation)	0.71 (± 5.45)	0.2 (± 6.37)		

Statistical analyses

Statistical analysis title	Mean change in body weight

Statistical analysis description:

The mean change from baseline in weight was compared between treatment groups using a mixed effects linear regression model with independent correlation adjusted for clustering by DAFNE course (random effect), centre, and baseline HbA1c (fixed effects).

Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.607
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	2.01

Secondary: Change in total insulin dose

End point title	Change in total insulin dose

End point description:

End point type	Secondary

End point timeframe:

24 months

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: i.u/weight				

arithmetic mean (standard deviation)	-0.06 (± 0.27)	-0.01 (± 0.23)		

Statistical analyses

Statistical analysis title	Mean difference in change in insulin dose

Statistical analysis description:

The mean change from baseline in insulin dose was compared between treatment groups using a mixed effects linear regression model with independent correlation adjusted for clustering by DAFNE course (random effect), centre, and baseline HbA1c (fixed effects).

Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.152
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.02

Secondary: Mean change in SF12 Physical Component Summary

End point title	Mean change in SF12 Physical Component Summary

End point description:

Physical health is scored according to US normative data (Ware et al, 2007) in which the population mean is 50 and standard deviation is 10. Higher values indicate better health.

End point type	Secondary

End point timeframe:

24 months

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	112		
Units: SF-12 scale				
arithmetic mean (standard deviation)	0.3 (± 7.9)	1 (± 8.3)		

Statistical analyses

Statistical analysis title	Mean difference in change in SF12 PCS
Statistical analysis description:	
Calculated using mixed effects regression adjusted for baseline QoL score, centre, course, baseline HBA1c.	
Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.657
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.3

Secondary: Mean change in SF-12 Mental Component Summary

End point title	Mean change in SF-12 Mental Component Summary
End point description:	
Mental health is scored according to US normative data (Ware et al, 2007) in which the population mean is 50 and standard deviation is 10. Higher values indicate better health.	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	114		
Units: SF-12 score				
arithmetic mean (standard deviation)	2.1 (± 11.2)	0.5 (± 10.3)		

Statistical analyses

Statistical analysis title	Mean difference in change in SF12 MCS

Statistical analysis description:

Calculated using mixed effects regression adjusted for baseline QoL score, centre, course, baseline HBA1c.

Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	4

Secondary: Mean change in EQ-5D

End point title	Mean change in EQ-5D

End point description:

The EQ-5D score is a health utility in which 1 relates to perfect health and 0 relates to a state equivalent to death. Negative states are possible.

End point type	Secondary

End point timeframe:

24 months

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	113		
Units: EQ-5D scale				
arithmetic mean (standard deviation)	0 (± 0.18)	-0.02 (± 0.18)		

Statistical analyses

Statistical analysis title	Mean difference in change in EQ-5D

Statistical analysis description:

Calculated using mixed effects regression adjusted for baseline QoL score, centre, course, baseline HBA1c.

Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)

Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.464
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.06

Secondary: Change in HDL cholesterol

End point title	Change in HDL cholesterol
End point description: Mean change in HDL cholesterol	
End point type	Secondary
End point timeframe: 24 months	

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	112		
Units: mmol/L				
arithmetic mean (standard deviation)	0.03 (± 0.3)	0.06 (± 0.39)		

Statistical analyses

Statistical analysis title	Mean difference in change in HDL cholesterol

Statistical analysis description:

The mean change from baseline in HDL cholesterol was compared between treatment groups using a mixed effects linear regression model with independent correlation adjusted for clustering by DAFNE course (random effect), centre, and baseline HbA1c (fixed effects).

Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.428
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.05

Secondary: Change in total cholesterol

End point title	Change in total cholesterol
End point description:	
Mean change in total cholesterol	
End point type	Secondary
End point timeframe:	
24 months	

End point values	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	116		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.21 (± 0.95)	-0.19 (± 1.03)		

Statistical analyses

Statistical analysis title	Mean difference in change in total cholesterol
Statistical analysis description:	
The mean change from baseline in total cholesterol was compared between treatment groups using a mixed effects linear regression model with independent correlation adjusted for clustering by DAFNE course (random effect), centre, and baseline HbA1c (fixed effects).	
Comparison groups	Continuous subcutaneous insulin infusion (CSII) v Multiple daily injections (MDI)
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.848
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 months

Adverse event reporting additional description:

SAEs reported on an ongoing basis from baseline to 24 months
AEs were reported at 6, 12 and 24 months

Assessment type	Systematic

Dictionary used

Dictionary name	CI review EMA IME
Dictionary version	19.0

Reporting groups

Reporting group title	Continuous subcutaneous insulin infusion (CSII)

Reporting group description: -

Reporting group title	Multiple daily injections (MDI)

Reporting group description: -

Serious adverse events	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 132 (25.00%)	26 / 135 (19.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Chest pain			
subjects affected / exposed	2 / 132 (1.52%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	6 / 132 (4.55%)	4 / 135 (2.96%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 132 (0.76%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Blood glucose increased			
subjects affected / exposed	13 / 132 (9.85%)	6 / 135 (4.44%)	
occurrences causally related to treatment / all	9 / 16	2 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	7 / 132 (5.30%)	3 / 135 (2.22%)	
occurrences causally related to treatment / all	1 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Continuous subcutaneous insulin infusion (CSII)	Multiple daily injections (MDI)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 132 (56.82%)	35 / 135 (25.93%)	
Injury, poisoning and procedural complications			
Suture insertion			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences (all)	0	2	
Eye disorders			
Vitreous haemorrhage			
subjects affected / exposed	2 / 132 (1.52%)	1 / 135 (0.74%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	2 / 132 (1.52%)	0 / 135 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			

Blood glucose increased			
subjects affected / exposed	55 / 132 (41.67%)	16 / 135 (11.85%)	
occurrences (all)	215	29	
Hyperinsulinaemic hypoglycaemia			
subjects affected / exposed	10 / 132 (7.58%)	8 / 135 (5.93%)	
occurrences (all)	10	8	
Infections and infestations			
Soft tissue infection			
subjects affected / exposed	2 / 132 (1.52%)	0 / 135 (0.00%)	
occurrences (all)	2	0	
Tonsillitis bacterial			
subjects affected / exposed	2 / 132 (1.52%)	0 / 135 (0.00%)	
occurrences (all)	2	0	
Product issues			
Device malfunction			
subjects affected / exposed	25 / 132 (18.94%)	0 / 135 (0.00%)	
occurrences (all)	27	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2011	Updates to the protocol including: 1) General Information: PI and site details 2) Urine samples and albumin-creatinine ratio: clarified that this test will be taken during the trial 3) Inclusion and exclusion criteria: one inclusion and one exclusion criteria added: • Extra inclusion criteria: Has a need for structured education to optimise diabetes control in the opinion of the investigator. • Extra exclusion criteria: Has a need for pump therapy in the opinion of the investigator. 4) DAFNE pre-course pump session: clarified when pump use on saline would be taking place. Updates to the participant information sheet including: 1) Geographical areas for the trial have been amended according to site removal and additions. 2) Sentence amended to clarify process of continuation of pump therapy in England and Scotland. 3) Northwest 3 Research Ethics Committee-Liverpool East listed as ethics committee for whom approval has been granted. Updates to REPOSE leaflet including: 1) Addition to clarify that urine samples will be taken in addition to blood samples at baseline, 6-, 12- and 24-months Updates to the CTA including: 1) Sites amended 2) Inclusion/exclusion critiera added 3) Contact details, typographical errors and updated details (ethics approval details, ISRCTN number) added
04 October 2011	Protocol (NRES & MHRA- substantial amendment) 1) General information - p.4: Change to details of PIs and sponsor contact 2) Protocol amendment details - p.6: Text inserted to detail protocol amendments from version 3 to 4. 3) Trial summary - p.7: List of sites amended to correspond with removal/addition of sites. 4) Demographic measures - p.14: Removal of religion as part of the demographic analyses. 5) Randomisation - p.23: Time at which REPOSE educator finds out which treatment arm participants has been allocated to altered from one month to six weeks. 6) Table 1: Documents for Data collection - p.26-30: Details of severe and moderate hypos recording process amended in table 7) Typographical errors and formatting - References to appendices removed from protocol. Formatting of figures undertaken.

23 February 2012	1) Blinded review of HbA1c (measure of the level of blood glucose control) To allow the trial statistician to conduct a blinded review after Course 2, 4 and 5 to examine the proportions of recruited participants who are in each HbA1c category (i.e. ≥7.5% or <7.5%). The trial statistician will look at the proportions in each HbA1c category, and numbers of participants with an HbA1c ≥ 7.5% threatens the ability of the trial to detect a difference in primary outcome (i.e. there are substantially more subjects recruited with an HbA1c <7.5% than anticipated), then an additional inclusion criteria will be added to limit recruitment only to participants with an HbA1c of ≥7.5% in order to ensure the trial can detect a difference in the primary outcome. 2) Withdrawal from the pump criteria Removal of 'Participant becomes pregnant' as a reason for withdrawal from the pump. Amended so that the decision as to whether a participant who becomes pregnant during the trial stays on the pump is purely a clinical decision based on the participant's blood glucose control on the pump i.e. if the participant was managing their diabetes well on the pump, they remain on the pump. 3) To add and remove sites • Addition of Royal Infirmary of Edinburgh (PI: Dr Alan Jaap) • Removal of University of Edinburgh (Dr Julia Lawton) and Monklands Hospital (Dr Thekkepat Sandeep) 4) Notification that Harrogate and District NHS Foundation Trust (PI: Dr Peter Hammond) are delivering part of the trial intervention using a venue that is not owned by Harrogate and District NHS Foundation Trust: Henshaws Society for Blind People, Bogs Lane, Harrogate, North Yorkshire, HG1 4ED.
01 October 2012	To increase the number recruited to the study. Drop-outs are occurring prior to DAFNE course attendance and thus these participants do not count towards the ITT. This change does not increase the number of participants who will receive the intervention or comparator treatment.
04 April 2014	Updates to the REPOSE Protocol v11: - clarified withdrawal from treatment criteria for participants who develop the need for renal replacement therapy or who are found to be abusing alcohol or drugs - clarified that pregnancies will be recorded as SAEs & that they are exempt from immediate reporting Participant Retention and Return of Data - Where participant do not live locally, appropriate research staff may arrange to visit the participant in their home or at an alternative NHS location to carry out data collection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported