Continuous subcutaneous insulin infusion versus multiple daily injections in children and young people at diagnosis of type 1 diabetes: the SCIPI RCT

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Scientific summary

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Background

Type 1 diabetes (T1D) is one of the most common chronic diseases of childhood, affecting > 26,000 children and young people in the UK. The daily treatment burden of T1D is high, requiring the administration of subcutaneous insulin in doses calculated according to carbohydrate intake, energy expenditure and blood glucose readings. In the longer term, complications of T1D may result in blindness, renal failure, premature heart disease, stroke and amputation.

The risk of long-term complications of T1D is related to glycaemic control and is lower in patients treated with intensive insulin treatment regimens: multiple daily injections (MDI) (≥ 4 injections) or continuous subcutaneous insulin infusion (CSII). Despite a lack of evidence that the more expensive treatment with CSII is superior to MDI, both treatments are used widely within the NHS.

The current treatment costs for children and young people with T1D range from £52M to £70M per annum, but this could increase by 50% if all patients used CSII. Previous economic evaluations indicate CSII to be cost-effective in paediatrics, but these were reliant on data from small trials, which were rated as being at risk of bias, and the application of extensive modelling.

Objectives

Internal pilot study

Internal pilot objectives targeted recruitment and generalisability.

Primary objective

- To acquire an understanding of the acceptability of randomisation to MDI or CSII at diagnosis of T1D in children and young people.

Secondary objectives

- To define the characteristics of patients who consent and those who decline to participate.
- To generate data to confirm the standard deviation (SD) used in the sample size calculation of the full study.

Full study

The following objectives were addressed during the first year following the diagnosis of T1D.

Primary objective

- To measure glycaemic control, assessed by glycosylated haemoglobin (HbA1c) concentration 12 months after diagnosis of T1D in participants receiving CSII compared with those receiving MDI.

Secondary objectives

To compare the following outcomes in children and adolescents receiving CSII with those receiving MDI:

- percentage of participants in each group with HbA1c concentrations of < 7.5%
- incidence of severe hypoglycaemia
Methods

Participants
Participants were recruited from 15 children’s diabetes services in England and Wales with experience of treating ≥ 10 patients with CSII. Patients were eligible to participate in the study if they met the following inclusion criteria:

- The patient has newly diagnosed T1D.
- The patient is aged 7 months to 15 years.
- The parent/legal representative of the patient is willing to give consent for the study.
- The parent/legal representative of the patient is able to comply with the treatment regimen and study visits.

Participants with the following characteristics were excluded from the trial:

- previous treatment for T1D
- haemoglobinopathy
- co-existing pathology conditions likely to affect glycaemic control
- psychological or psychiatric disorders
- receipt of medication likely to affect glycaemic control
- allergy to a component of insulin aspart or insulin glargine
- sibling with existing T1D
- known thyroid condition in a non-euthyroid state
- known coeliac disease and inability to maintain a gluten-free diet.

Study procedures
Informed, written consent and, when appropriate, assent was obtained from parents/guardians and patients. Patients were randomised with 1 : 1 web-based block randomisation stratified by centre and age (7 months to < 5 years, 5 years to < 12 years and ≥ 12 years) to treatment with CSII or MDI. Owing to the nature of the interventions, blinding was not possible.

Screening logs were completed at each centre for all newly diagnosed T1D patients. Data were collected on age, sex, ethnicity and deprivation score. The reasons why patients were ineligible, why eligible patients were not approached to participate and why those who were approached declined to participate were recorded along with the dates and times when patients were approached about the SubCutaneous Insulin: Pumps or Injections? (SCIPI) study, when trial information was provided and when consent discussions took place.

The following data, when measured routinely, were collected at baseline:

- biochemical parameters at diagnosis: blood pH, blood glucose, HbA1c, concentration and thyroid function tests
- immunology studies: anti-islet cell and anti-glutamic acid decarboxylase antibodies, tissue transglutaminase or other antibody tests for coeliac disease
- growth: height and weight.
Randomised treatment started within 14 days of diagnosis of T1D. Starting insulin doses were calculated according to weight and age, and titrated against blood glucose readings in accordance with local protocols. To support this process, clinical practice guidelines and written patient information were shared from the lead centre for use by recruiting centres at their discretion.

Study visits coincided with clinic appointments at 3, 6, 9 and 12 months. At each visit, the following data were collected:

- HbA1c concentrations
- adverse events
- height and weight
- insulin usage from general practitioner (GP) prescriptions, glucometer and insulin pump downloads (CSII) and patient-kept records (MDI).

The diabetes module of PedsQL was completed at 6 and 12 months.

The primary outcome was HbA1c concentrations at 12 months. The secondary outcomes were (1) HbA1c concentrations of < 48 mmol/mol, (2) severe hypoglycaemia, (3) DKA, (4) T1D- and treatment-related adverse events (AEs), (5) change in BMI and height SDS, (6) insulin requirements, (7) quality of life (QoL) and (8) partial remission rates. The economic outcome was the incremental cost per QALY gained.

**Sample size**

To achieve 80% power, a sample size of 143 participants in each group was required to detect a difference in means of 0.50, with common SD of 1.50, using a two-group t-test with a 0.05 two-sided significance level. An adjustment was made for 10% loss to follow-up, giving a total of 316 participants (158 per group).

**Statistical analysis**

Primary analysis used the intention-to-treat (ITT) principle. A 0.05 level of statistical significance and 95% confidence intervals (CIs) are used throughout. The statistical analysis plan was developed prior to analysis and is available as a separate document [URL: www.journalslibrary.nihr.ac.uk/programmes/hta/081439/# (accessed 26 July 2018)]. All analyses were conducted using SAS* software (version 9.2; SAS Institute Inc., Cary, NC, USA). SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. * indicates USA registration.

When available, HbA1c measurements from samples analysed centrally were used in preference to samples analysed locally. The primary outcome used least squares regression adjusted for age category and centre as a random effect. Binary outcomes are presented as relative risks. A per-protocol analysis was undertaken for the primary outcome to check the robustness of conclusions to major protocol deviations and a safety analysis was conducted on AE data, which included participants in the group to which they had received their insulin at the time of the event.

**Economic evaluation**

A cost–utility analysis estimated within-trial QALYs based on patients’ or their parents’ responses to the Health Utilities Index questionnaire, which was administered at 3-monthly intervals. Resource use was measured using questionnaires and by accessing prescription records and electronic patient-linked information costing systems. These included the purchase of pumps or MDI injection devices and associated consumables, cost of insulins and contact with health-care services, including with GPs, with school nurses, as a hospital inpatient, as an outpatient and accident and emergency (A&E) department attendances. National tariff and other standard unit costs were applied to calculate the total costs for the ITT population. A lifetime modelled extrapolation was planned if differences were apparent in HbA1c concentrations between the intervention groups at 12 months. The differences between intervention groups in costs and QALYs were compared, with their joint uncertainty represented in cost-effectiveness acceptability curves.
Results

Recruitment data from the internal pilot study showed acceptable consent rates and no evidence of patient bias, and supported the parameters used in the sample size calculation. The Independent Data and Safety Monitoring Committee recommended that the trial progress to the full study. Data from patients recruited to the internal pilot study were included in the full study.

Participants

In total, 976 patients were diagnosed with T1D and assessed for eligibility in the 15 study centres, of whom 689 were eligible and approached for consent. Of these, 294 (42.7%) consented to participate in the trial; however, one participant withdrew consent for their data to be used immediately following randomisation. Of those patients who declined (n = 395), 36 (9%) cited a strong preference for CSII therapy and 259 (66%) cited a strong preference for MDI.

Age, sex and ethnicity did not differ between the group of patients who consented to participate and the group of patients who declined. The median deprivation score for study participants was 17.0 overall (minimum 1.62, maximum 77.23), 27.7 in those who declined owing to a strong preference for CSII (range 3.9–63.9) and 18.0 in those who declined owing to a strong preference for MDI (range 1.2–74.4). A higher score indicates a greater level of deprivation.

In total, 144 patients were randomised to CSII [mean age 9.0 years (SD 4.1 years); 71 (49.3%) female] and 149 patients were randomised to MDI [mean age 9.1 years (SD 4.1 years); 69 (46.3%) female]. Patient characteristics did not differ between treatment arms. All participants received their allocated interventions. One participant who was allocated to CSII and five who were allocated to MDI withdrew from the trial prior to the 12-month follow-up but allowed data collected up to their withdrawal to be used.

Glycosylated haemoglobin levels at 12 months

Intention-to-treat analysis

Data from 97% (CSII, n = 143; MDI, n = 142) of participants were available. The HbA1c concentrations did not differ between treatment arms: CSII, mean 60.9 mmol/mol (95% CI 58.5 to 63.3 mmol/mol); MDI, mean 58.5 mmol/mol (95% CI 56.1 to 60.9 mmol/mol); and least mean squares-adjusted difference (CSII – MDI), 2.4 mmol/mol (95% CI –0.4 to 5.3 mmol/mol; p = 0.09).

Per-protocol analysis

Data from 52.2% (CSII, n = 87; MDI, n = 66) of participants were included. The HbA1c concentrations did not differ between treatment arms and the direction of results were consistent with those obtained under the ITT analysis population: CSII, 60.2 mmol/mol (95% CI 56.4 to 63.9 mmol/mol); MDI, 59.3 mmol/mol (95% CI 55.3 to 63.3 mmol/mol); and the least mean squares-adjusted difference between treatment groups (CSII – MDI) was 0.9 mmol/mol (95% CI –3.2 to 5.0 mmol/mol; p = 0.67).

Percentage of patients with glycosylated haemoglobin levels within the target range 12 months after diagnosis

An ITT analysis was performed on two target values: (1) < 58 mmol/mol, the target set by the National Institute for Health and Care Excellence until August 2015, and (2) < 48 mmol/mol, the new target set in August 2015. Data for 97% (CSII, n = 143; MDI, n = 142) of participants were available for analysis.

There was no difference between treatment arms for either target. For the target HbA1c value of < 58 mmol/mol: CSII, n = 66 (46.2%); MDI, n = 78 (54.9%); relative risk (CSII to MDI ratio), 0.84 (95% CI 0.67 to 1.06); and percentage difference (CSII – MDI), –8.8% (95% CI –2.9% to 20.4%). For < 48 mmol/mol: CSII, n = 22 (15.4%); MDI, n = 29 (20.4%); relative risk (CSII to MDI ratio), 0.75 (95% CI 0.46 to 1.25); and percentage difference (CSII – MDI), –5.0% (95% CI –14.0% to 3.9%).
Related adverse events

Eight episodes of severe hypoglycaemia were reported: six in participants who were treated with CSII and two in participants who were treated with MDI (relative risk 3.1, 95% CI 0.6 to 15.1; \( p = 0.17 \)). Two episodes of DKA occurred in two participants, both of whom were treated with CSII (relative risk 5.2, 95% CI 0.3 to 106.8; \( p = 0.24 \)).

Under the safety analysis population, there were 54 related AEs in 36 participants who were treated with CSII, of which 29 were related to the insulin pump; eight participants had infections at the site of catheter insertion. There were 17 related AEs in 16 participants who were treated with MDI, of which two events were related to injection device; there were no AEs related to injection sites. AEs relating to meter errors, carer errors and incidental illnesses were balanced more evenly across treatment arms.

Change in body mass index and height standard deviation score from diagnosis to 12 months following diagnosis

Data were available for 87% of participants: CSII, \( n = 124 \); MDI, \( n = 132 \). There was no significant difference in change in BMI or height SDS between study arms. The mean change in BMI SDS in the CSII group was 0.6 (SD 0.8) and in the MDI group was 0.5 (SD 0.8); the mean difference was 0.1 (95% CI 0.0 to 0.3; \( p = 0.13 \)). The mean change in height SDS was –0.1 (SD 0.5) in the CSII group and 0.0 (SD 0.4) in the MDI group; the mean difference was –0.1 (95% CI –0.2 to 0.0; \( p = 0.10 \)).

Insulin requirements

Data relating to insulin doses were available for 52% of participants (CSII, \( n = 87 \); MDI, \( n = 64 \)); the least mean squares-adjusted difference for age demonstrated that insulin requirements were higher for participants in the CSII arm than for those in the MDI arm (difference, 0.1 unit/kg/day, 95% CI 0.0 to 0.2 unit/kg/day; \( p = 0.01 \)).

Percentage of participants in each study arm in partial remission

Partial remission was defined as insulin dose-adjusted HbA1c (IDAA1c) level of \( \leq 9 \). Data relating to insulin dose and HbA1c concentration at 12 months were available for 51% of participants (CSII, \( n = 86 \); MDI, \( n = 64 \)). The percentage of participants in partial remission at 12 months was higher in the MDI arm, but the difference was not statistically significant: CSII, 24.4% (21/86 participants); MDI, 32.8% (21/64 participants); and relative risk 0.74 (95% CI 0.45 to 1.24; \( p = 0.28 \)).

Quality of life 12 months after diagnosis of type 1 diabetes

The PedsQL score (diabetes module), as reported by children at 12 months, was available for 71% or participants (CSII, \( n = 104 \); MDI, \( n = 104 \), with 26 children in each treatment group being too young to complete the questionnaire. Least mean squares-adjusted difference at 12 months (3.1, 95% CI –0.6 to 6.8) favoured CSII but the result was not statistically significant. Data were available from 86% of parents (CSII, \( n = 128 \); MDI, \( n = 123 \)). The results for overall QoL favouring CSII, as reported by parents, were statistically significant at 12 months (least mean squares-adjusted difference 4.1, 95% CI 0.6 to 7.6). Parent- and child-reported results are largely consistent and should be considered against a difference of 5 being considered the minimum worthwhile.

Cost-effectiveness of continuous subcutaneous insulin infusion compared with multiple daily injections

Patients randomised to the CSII arm had more than twice as many A&E department visits and inpatient stays relating to the management of T1D than those in the MDI arm. Over the 12-month study period, health-care professionals had a mean of 4.3 (95% CI 0.6 to 8.0) more contacts (texts, e-mails and telephone calls) with patients treated with CSII than with those treated with MDI. The mean total costs were £1863 (95% CI £1620 to £2137) higher for CSII than for MDI, with the majority of this difference being attributable to the additional cost of consumables (£1177) and the device (£520). There were no significant differences in QALYs between the CSII and MDI groups (mean difference –0.006 QALYs, 95% CI –0.031 to 0.018 QALYs). None of the sensitivity analyses affected the base-case result of CSII.
being dominated by MDI. The probability of dominance was 69%, with no likelihood of CSII being cost-effective at a threshold of £30,000 per QALY.

**Conclusions**

**Implications for health care**

Study participants were recruited from diverse clinical settings, the retention rate exceeded 95% and the characteristics of those recruited to the study did not differ from the background population of patients diagnosed during this time. The findings of the study should therefore be applicable to the population of children treated in the NHS. Treatment with CSII has been embraced widely by the NHS, despite the high treatment cost and paucity of evidence of superior clinical outcomes. Our study shows that, during the first year of treatment, CSII is not associated with better clinical outcomes and is not cost-effective.

**Implications for research**

The generalisability of our data beyond the first year of diagnosis is uncertain. The observation period should be extended to determine whether or not treatment outcomes diverge over time and how factors, including child development, influence treatment decisions.

Patient advocates and many health-care professionals have a strong belief in the benefits of CSII treatment. In-depth qualitative research is required to learn more about the drivers influencing these preferences and how they alter as children age.

**Trial registration**

This trial is registered as ISRCTN29255275 and EudraCT 2010-023792-25.

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