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A cluster randomised trial, cost-effectiveness analysis and psychosocial evaluation of insulin pump therapy compared with multiple injections during flexible intensive insulin therapy for type 1 diabetes: the REPOSE Trial

Simon Heller, David White, Ellen Lee, Julia Lawton, Daniel Pollard, Norman Waugh, Stephanie Amiel, Katharine Barnard, Anita Beckwith, Alan Brennan, Michael Campbell, Cindy Cooper, Munyaradzi Dimairo, Simon Dixon, Jackie Elliott, Mark Evans, Fiona Green, Gemma Hackney, Peter Hammond, Nina Hallowell, Alan Jaap, Brian Kennon, Jackie Kirkham, Robert Lindsay, Peter Mansell, Diana Papaioannou, David Rankin, Pamela Royle, W Henry Smithson and Carolin Taylor on behalf of the REPOSE Study Group



**National Institute for
Health Research**

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Abstract

A cluster randomised trial, cost-effectiveness analysis and psychosocial evaluation of insulin pump therapy compared with multiple injections during flexible intensive insulin therapy for type 1 diabetes: the REPOSE Trial

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Background: Insulin is generally administered to people with type 1 diabetes mellitus (T1DM) using multiple daily injections (MDIs), but can also be delivered using infusion pumps. In the UK, pumps are recommended for patients with the greatest need and adult use is less than in comparable countries. Previous trials have been small, of short duration and have failed to control for training in insulin adjustment.

Objective: To assess the clinical effectiveness and cost-effectiveness of pump therapy compared with MDI for adults with T1DM, with both groups receiving equivalent structured training in flexible insulin therapy.

Design: Pragmatic, multicentre, open-label, parallel-group cluster randomised controlled trial, including economic and psychosocial evaluations. After participants were assigned a group training course, courses were randomly allocated in pairs to either pump or MDI.

Setting: Eight secondary care diabetes centres in the UK.

Participants: Adults with T1DM for > 12 months, willing to undertake intensive insulin therapy, with no preference for pump or MDI, or a clinical indication for pumps.

Interventions: Pump or MDI structured training in flexible insulin therapy, followed up for 2 years. MDI participants used insulin analogues. Pump participants used a Medtronic Paradigm® Veo™ (Medtronic, Watford, UK) with insulin aspart (NovoRapid, Novo Nordisk, Gatwick, UK).

Main outcome measures: Primary outcome – change in glycated haemoglobin (HbA_{1c}) at 2 years in participants whose baseline HbA_{1c} was $\geq 7.5\%$ (58 mmol/mol). Key secondary outcome – proportion of participants with HbA_{1c} $\leq 7.5\%$ at 2 years. Other outcomes at 6, 12 and 24 months – moderate and severe hypoglycaemia; insulin dose; body weight; proteinuria; diabetic ketoacidosis; quality of life (QoL); fear of hypoglycaemia; treatment satisfaction; emotional well-being; qualitative interviews with participants and staff (2 weeks), and participants (6 months); and ICERs in trial and modelled estimates of cost-effectiveness.

Results: We randomised 46 courses comprising 317 participants: 267 attended a Dose Adjustment For Normal Eating course (132 pump; 135 MDI); 260 were included in the intention-to-treat analysis, of which 235 (119 pump; 116 MDI) had baseline HbA_{1c} of $\geq 7.5\%$. HbA_{1c} and severe hypoglycaemia improved in both groups. The drop in HbA_{1c}% at 2 years was 0.85 on pump and 0.42 on MDI. The mean difference (MD) in HbA_{1c} change at 2 years, at which the baseline HbA_{1c} was $\geq 7.5\%$, was -0.24% [95% confidence interval (CI) -0.53% to 0.05%] in favour of the pump ($p = 0.098$). The per-protocol analysis showed a MD in change of -0.36% (95% CI -0.64% to -0.07%) favouring pumps ($p = 0.015$). Pumps were not cost-effective in the base case and all of the sensitivity analyses. The pump group had greater improvement in diabetes-specific QoL diet restrictions, daily hassle plus treatment satisfaction, statistically significant at 12 and 24 months and supported by qualitative interviews.

Limitation: Blinding of pump therapy was not possible, although an objective primary outcome was used.

Conclusion: Adding pump therapy to structured training in flexible insulin therapy did not significantly enhance glycaemic control or psychosocial outcomes in adults with T1DM.

Research priority: To understand why few patients achieve a HbA_{1c} of $< 7.5\%$, particularly as glycaemic control is worse in the UK than in other European countries.

Trial registration: Current Controlled Trials ISRCTN61215213.

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BOX 1 National Institute for Health and Care Excellence guidance on the MiniMed Veo insulin pump

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List of abbreviations

ACR	albumin-to-creatinine ratio	EQ-5D-3L	EuroQol-5 Dimensions, 3-level version
AE	adverse event		
AIC	Akaike information criterion	ESRD	end-stage renal disease
A-level	Advanced level	FA	fidelity assessor
BIC	Bayesian information criterion	FT	fidelity testing
BMI	body mass index	GCP	Good Clinical Practice
CGM	continuous glucose monitoring	GP	general practitioner
CI	confidence interval	HADS	Hospital Anxiety and Depression Scale
CONSORT	Consolidated Standards Of Reporting Trials	HbA _{1c}	glycated haemoglobin
CP	carbohydrate portion	HDL	high-density lipoprotein
CSII	continuous subcutaneous insulin infusion	HF	heart failure
CTRU	Clinical Trials Research Unit	HFS	Hypoglycaemia Fear Survey
DAFNE	Dose Adjustment For Normal Eating	HTA	Health Technology Assessment
DCCT	Diabetes Control and Complications Trial	ICC	intraclass correlation coefficient
DCF	data collection form	ICER	incremental cost-effectiveness ratio
DEP	DAFNE Educator Programme	IMP	investigational medicinal product
DH	Department of Health	IQR	interquartile range
DKA	diabetic ketoacidosis	IRR	incidence rate ratio
DMEC	Data Monitoring and Ethics Committee	ITT	intention to treat
DQOL	Diabetes Quality of Life (questionnaire)	LDL	low-density lipoprotein
DRC	diabetes-related contact	LGS	low glucose suspend
DSQOL	diabetes-specific quality of life (scale)	MD	mean difference
DTSQ	Diabetes Treatment Satisfaction Questionnaire	MDI	multiple daily injection
DTSQc	Diabetes Treatment Satisfaction Questionnaire (change)	MDT	multidisciplinary team
EEACT	Economic Evaluation alongside Clinical Trials	MHRA	Medicines and Healthcare products Regulatory Agency
EQ-5D	EuroQol-5 Dimensions	MI	myocardial infarction
		NICE	National Institute for Health and Care Excellence
		NIHR	National Institute for Health Research
		NPH	neutral protamine Hagedorn
		OR	odds ratio

LIST OF ABBREVIATIONS

PAD	peripheral arterial disease	SF-12	Short Form questionnaire-12 items
PGfAR	Programme Grants for Applied Research	SF-6D	Short Form questionnaire-6 Dimensions
PI	principal investigator	SF-36	Short Form questionnaire-36 items
PSA	probabilistic sensitivity analysis	SIGN	Scottish Intercollegiate Guidelines Network
QALY	quality-adjusted life-year	SMBG	self-monitoring of blood glucose
QoL	quality of life	SOP	standard operating procedure
R&D	research and development	T1DM	type 1 diabetes mellitus
RCT	randomised controlled trial	TC	total cholesterol
REC	Research Ethics Committee	TMG	Trial Management Group
SAE	serious adverse event	TSC	Trial Steering Committee
SD	standard deviation		
SE	standard error		

Plain English summary

People with type 1 diabetes (T1DM) need insulin therapy to sustain life. The most common treatment is injecting insulin several times a day. Another approach uses insulin pumps, the size of mobile phones, which are attached under the skin through fine tubing and which provide small amounts of insulin. In the UK, pumps are recommended for people struggling to control their diabetes with injections, and are used far less often than in other countries. The research conducted so far on pumps has weaknesses. We wanted to conduct a fair test to see if pumps would benefit adults with T1DM.

We conducted a large study (a randomised controlled trial) in which 267 people attended a structured education course: half were assigned to a pump for 2 years, whereas the other half used injections. We compared average blood sugar levels [by a test measuring glycated haemoglobin (HbA_{1c})] to compare diabetes control after 2 years.

Our results showed that both groups improved diabetes control after training. Participants using pumps had slightly better control, but differences were small (HbA_{1c} was 0.24% lower than in the injections group). We found that pumps were not cost-effective, although people using pumps reported better satisfaction with their treatment and in some aspects of their quality of life.

Our study suggests that making insulin pumps more widely available before structured training is unlikely to improve diabetes control or be cost-effective. Providing structured education to more people could be highly beneficial, with pumps made available to those needing better ways of delivering insulin to reach glucose targets.

Scientific summary

Background

People with type 1 diabetes mellitus (T1DM) require insulin therapy to sustain life. Insulin is generally administered using multiple daily injections (MDIs), but can also be delivered using an infusion pump (continuous subcutaneous insulin infusion). Pump therapy is a more costly option, but has potential benefits. The UK National Institute for Health and Care Excellence (NICE) has approved the use of pumps only for patients with the greatest need (such as inability to achieve reasonable control without hypoglycaemia). Far fewer UK adults use pumps than in comparable countries. Previous trials of pump therapy have been small and of short duration, and have failed to control for training in flexible insulin therapy.

Objectives

We aimed to assess the clinical effectiveness and cost-effectiveness of insulin pump therapy compared with MDIs for people with T1DM, when both have received high-quality structured education.

The specific objectives were to:

1. measure, over 2 years, (1) biomedical, (2) psychosocial (quantitative and qualitative) and (3) adverse event (AE) outcomes
2. undertake a cost-effectiveness analysis to determine whether or not the marginal benefits of pump therapy over optimised MDI (if demonstrated) are commensurate with the marginal costs, as reflected in a cost per quality-adjusted life-year (QALY) acceptable to NICE
3. conduct a mixed-methods psychosocial evaluation of pump therapy in order to identify factors that predict and/or help explain outcomes on pump therapy.

Methods

Design

We undertook a pragmatic, multicentre, open-label, parallel-group cluster randomised controlled trial, with embedded cost-effectiveness analysis and mixed-methods psychosocial evaluation. Participants were allocated a place on a 1 week-long DAFNE (Dose Adjustment For Normal Eating) course in flexible insulin therapy. The course groups were then randomly allocated in pairs to either pump or MDI treatment, with allocation concealed. Following the course, participants received the trial treatment for 2 years.

Setting and participants

Eight secondary care diabetes centres in the UK took part (five in England and three in Scotland). DAFNE courses (clusters) comprised between five and eight participants. Participants were adults with T1DM for at least 12 months, willing to undertake intensive insulin therapy, with self-monitoring of blood glucose levels, carbohydrate counting and insulin self-adjustment, who had no preference for either pump or MDI and had a need for structured education to optimise diabetes control. People were excluded if they had already completed a diabetes education course or used a pump within the past 3 years, or had strong clinical indications or a strong desire for pump therapy.

Interventions

Participants in the MDI arm attended a standard DAFNE structured education course. Courses were conducted over five consecutive days and were delivered to groups of five to eight adults in an outpatient

setting. Participants in the pump arm attended a modified DAFNE course, which had been tested in a pilot study. The 5-day structure of the course was maintained, while incorporating the additional skills and learning outcomes that were considered necessary to use pumps successfully. The need to introduce 'pump skills' required an additional pre-course group session, delivered 1–3 weeks before the 'proper' DAFNE course. All of the participants were invited to an additional DAFNE follow-up group session at 6 weeks post course. MDI participants used insulin analogues. Pump participants used a Medtronic Paradigm® Veo™ (Medtronic, Watford, UK) insulin pump, loaded with insulin aspart (NovoRapid, Novo Nordisk, Gatwick, UK). All of the participants had access to a bolus calculator to aid calculation of insulin doses.

Outcome measures

Clinical outcomes

The primary outcome was the change in glycated haemoglobin (HbA_{1c}) at 2 years in those participants whose baseline HbA_{1c} was $\geq 7.5\%$ (58 mmol/mol). The key secondary outcome was the proportion of all participants meeting the NICE target of HbA_{1c} of $\leq 7.5\%$ at 2 years. Other outcomes measured at 6, 12 and 24 months included moderate and severe hypoglycaemia, insulin dose, body weight, proteinuria and diabetic ketoacidosis.

All analyses were intention to treat (ITT) unless stated otherwise. A per-protocol analysis was also performed, excluding participants who had switched treatment.

Health economic outcomes

Two economic analyses were undertaken: the Economic Evaluation alongside the Clinical Trials (EEACT) and a model-based evaluation of lifetime outcomes. Both analyses took a UK NHS and Personal Social Services perspective. All costs and health benefits were discounted at a rate of 3.5%. The yearly cost of insulin pump therapy, including the cost of insulin pumps and consumables, was estimated using a survey of REPOSE Trial centres. The economic analysis alongside the trial took a 2-year time horizon, and the model-based evaluation took a lifetime time horizon. Both economic analyses measured outcomes in terms of an incremental cost-effectiveness ratio (ICER).

The EEACT used EuroQol-5 Dimensions (EQ-5D) data collected in REPOSE to construct a QALY for each trial participant and estimate their use of NHS resources. In the base case, differences in cost and QALYs between the two trial arms were estimated in the ITT population. Uncertainty in the economic analysis alongside the trial was explored using deterministic sensitivity analyses. In the deterministic sensitivity analyses, the effects of the cost of insulin pumps and consumables, imputing missing data and estimating the effects in the per-protocol population were explored.

The Sheffield Type 1 Diabetes Policy Model version 1.3, henceforth 'the model', was used to estimate the lifetime costs and QALYs associated with both trial arms. The model is an individual-level simulation that includes tracking of risk factors over time, including HbA_{1c}, and the subsequent occurrence of clinical events, including all microvascular, macrovascular and AEs associated with T1DM. Uncertainty in the long-term modelling was explored using probabilistic and deterministic sensitivity analyses. In the deterministic sensitivity analyses, the effects of the cost of insulin pumps and consumables, the use of different estimates of clinical effectiveness and the effects in different participant subgroups were explored.

Psychosocial outcomes

We used both quantitative (questionnaires) and qualitative (interviews) methods. Quantitative psychosocial outcomes were collected using participant self-report questionnaires at 6, 12 and 24 months. We measured diabetes-specific quality of life (QoL) [Diabetes Quality of Life (DSQOL) scale], generic QoL [World Health Organization Quality of Life Abbreviated Questionnaire (WHOQOL-BREF), Short Form questionnaire-12 items (SF-12) and EQ-5D], fear of hypoglycaemia (Hypoglycaemia Fear Survey), diabetes treatment satisfaction [Diabetes Treatment Satisfaction Questionnaire (DTSQ)], and anxiety and depression (Hospital Anxiety and Depression Scale). We undertook in-depth qualitative interviews with participants and staff at 2 weeks post course and again with participants at 6 months post course.

Results

Between November 2011 and April 2013, we randomised 46 courses comprising 317 participants, aged 18–77 years, of whom 267 attended a DAFNE course (132 pump and 135 MDI). A total of 260 participants was included in the ITT analysis set, of which 235 (119 pump and 116 MDI) had baseline HbA_{1c} of $\geq 7.5\%$. Among these, the mean HbA_{1c} change at 2 years in the pump group was a decrease of 0.85% (9.3 mmol/mol), whereas the mean decrease in the MDI group was 0.42% (4.5 mmol/mol). After adjusting for centre, DAFNE course and baseline HbA_{1c}, and accounting for missing data, the mean difference (MD) in HbA_{1c} change at 2 years in favour of the pump group was -0.24% [95% confidence interval (CI) -0.53% to 0.05%] or -2.7 mmol/mol (95% CI -5.8 to 0.5 mmol/mol; $p = 0.098$). The treatment difference was larger for the per-protocol analysis; MD in change of -0.36% (95% CI -0.64% to -0.07%) or -3.9 mmol/mol (95% CI -7.0 to -0.8 mmol/mol) in favour of the pump ($p = 0.015$). The proportion of participants with HbA_{1c} of $\leq 7.5\%$ (58 mmol/mol) at 2 years was similar across the groups: 29 (22.7%) in pump and 25 (20.8%) in MDI, translating to an odds ratio of 1.26 (95% CI 0.62 to 2.58; $p = 0.523$). The number of severe hypoglycaemia episodes/participant episodes per year was 25/0.10 in the pump group and 24/0.10 in the MDI group. After adjusting for centre, DAFNE course, baseline HbA_{1c} and presence of at least one severe hypoglycaemic episode in the 12 months before baseline, there were no statistically significant differences between the treatment groups [incidence rate ratio (IRR) 1.13, 95% CI 0.51 to 2.51; $p = 0.766$]. Across both treatment groups, the IRR for the number of severe hypoglycaemic episodes in the 24-month follow-up, compared with the year before baseline, was 0.46 (95% CI 0.24 to 0.89; $p = 0.021$).

The annual cost of an insulin pump and insulin pump consumables was estimated to be £2060. In the EEACT base case, insulin pump therapy generated fewer QALYs (-0.004) at a higher cost (£2959) than MDI. This meant that in the base case the insulin pump therapy was dominated by MDI. In the long-term modelling base case, insulin pump therapy, compared with MDI, generated more discounted lifetime QALYs (0.1447) at a higher discounted lifetime cost (£20,448). The ICER was £141,312 per QALY gained. The most favourable ICER was in the sensitivity analysis, for which the cost of insulin pumps and insulin pump consumables was reduced by 50% in the long-term model. In this sensitivity analysis, the ICER was £46,578 per QALY gained. This ICER is above the usual cost-effectiveness threshold range of £20,000–30,000 per QALY gained used by NICE.

The quantitative psychosocial questionnaires had high completion rates at 2 years (90%). In total, 45 participants (25 pump and 20 MDI) and 18 educators took part in qualitative interviews post course. Three participants could not be contacted for the follow-up interview. The quantitative measures showed improvement across most outcomes and time points for both treatment groups. The generic quality-of-life and health status instruments (SF-12, WHOQOL-BREF and EQ-5D) and the HADS score for depression and anxiety showed no between-group differences. The overall DSQOL score (on a 100-point scale) was improved by mean (standard deviation) of 8.2 (13.1) points in the pump group and 4.2 (13.2) points in the MDI group, translating to a MD in improvement of 3.8 points (95% CI 1.1 to 6.5 points; $p = 0.006$). The improvement in DSQOL diet restrictions was larger for the pump group than the MDI group at both 12 and 24 months (12-month adjusted MD in change from baseline -4.1 , 95% CI -7.2 to -1.0 ; $p = 0.010$; 24-month adjusted MD in change from baseline -5.1 , 95% CI -8.6 to -1.6 ; $p = 0.004$; lower scores represent better outcomes). A slightly smaller difference was observed at 6 months, which was just outside the 5% significance threshold (MD -3.3 , 95% CI -6.9 to 0.2 ; $p = 0.061$). The pump group also had a better improvement in DSQOL daily hassle or functions at both 12 and 24 months; at 24 months the score had decreased by 10 points in the pump group compared with 4 points in the MDI group (adjusted MD -6.3 , 95% CI -10.9 to -1.8 ; $p = 0.006$). Participants in the pump group had better improvement in treatment satisfaction at all time points. The difference was statistically significant at 12 and 24 months only ($p = 0.067$ at 6 months; $p < 0.001$ at both 12 and 24 months). These observations were supported by findings from the qualitative interviews. A recurrent theme was that after doing the DAFNE course, patients in both arms felt more in control and more confident in self-management. However, those on

pump therapy reported some additional benefits from the pump, including increased flexibility of lifestyles, avoidance of the frequent injections with MDI, more effective self-management around sporting activities and dietary variations, and the ability to administer very small doses of insulin, with different basal rates, at different times of day and night.

Conclusions

Insulin pump therapy did not provide additional significant improvement in glycaemic control compared with MDI, when both groups had received structured education in flexible insulin therapy. Our study suggests that extending the availability of pumps to adults with T1DM in suboptimal glycaemic control, and no firm desire to use this form of insulin delivery, is unlikely to result either in lower levels of glycaemia, as measured by HbA_{1c}, or lower rates of hypoglycaemia, and is unlikely to be cost-effective.

Implications for health care

1. Extending the availability of pumps to adults with T1DM with suboptimal glycaemic control, and no firm desire to use them, is unlikely to result either in lower levels of glycaemia, as measured by HbA_{1c}, or lower rates of hypoglycaemia or be cost-effective.
2. It is important that REPOSE is not considered to be a 'negative trial' of pumps. The failure to show a significant benefit of pump over MDI was because both groups improved following DAFNE training.
3. The current clinical pathway, as proposed by NICE, seems appropriate, in which people desiring improved diabetes control should initially undertake structured training in flexible insulin therapy with MDI alone.
4. The NICE guideline on the importance of providing structured training programmes is reinforced. Most individuals with T1DM are still not being offered evidence-based structured education despite considerable evidence for its effectiveness.
5. The evidence from REPOSE suggests that far more people with T1DM should participate in high-quality, structured self-management training. They may recognise the limitations of insulin delivery by MDI only once they are attempting to maintain flexible intensive insulin therapy following training. Those individuals could then be offered pump therapy to help them reach the stringent glucose target, as recommended by NICE, which is necessary to achieve an optimal HbA_{1c} or overcome problematic hypoglycaemia.

Recommendations for future research

1. It is important to understand why so few patients achieve the target for glycaemic control of HbA_{1c} of < 7.5%, particularly as there is evidence that levels of glycaemic control are worse in the UK than in other European countries.
2. There is an urgent need to explore the barriers to successful self-management in adults with TD1M in the UK and understand why accessing appropriate training is left so long and rates of participation are so low.
3. Further research is needed to explain why some people do so well after training, whereas others do not.

Trial registration

This trial is registered as ISRCTN61215213.

Funding

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Chapter 1 Introduction

Background

Type 1 diabetes mellitus and its treatment

People with type 1 diabetes mellitus (T1DM), around 250,000 individuals in the UK, have lost the ability to make insulin because of autoimmune destruction of the insulin-secreting β cells within the islets of the pancreas. Insulin is essential in the short term to prevent the onset of ketoacidosis, a potentially fatal condition. In the long term, the aim of insulin therapy is to keep blood glucose close to normal and so prevent the development of microvascular complications, such as retinopathy, neuropathy and diabetic kidney disease. Insulin is generally administered by intermittent subcutaneous injection, with the dose adjusted according to eating and other activities, such as exercise. Traditionally, insulin was given twice a day, often as premixed insulin, but such an approach imposes a rigid lifestyle and makes it difficult to maintain a glucose level close to normal. The need for intensification of therapy and its integration into flexible lifestyles is promoted in DAFNE (Dose Adjustment for Normal Eating) and other structured education courses. It involves giving quick-acting insulin just before eating and administering longer-acting background insulin, preferably twice daily, to maintain blood glucose levels in between meals.^{1,2} This multiple daily injection (MDI) regimen involves a total of five or six injections a day. Blood glucose levels are monitored from finger-prick samples using a portable meter, and insulin dose calculations are based on self-assessed carbohydrate estimations on a meal-by-meal basis.

Insulin given subcutaneously cannot reproduce the physiological insulin profiles of non-diabetic individuals because of the limitations of insulin formulations and the site of delivery. The relatively slow rate of insulin absorption leads initially to postprandial hyperglycaemia, followed, 1 or 2 hours later, by an increased risk of postabsorptive hypoglycaemia, particularly during the night. Thus, keeping blood glucose close to normal can delay or prevent complications, but brings with it frequent periods of hypoglycaemia. These are categorised as mild, moderate or severe episodes, ranging from mild symptoms, self-managed by ingesting rapid-acting carbohydrate, through to greater disruption in daily routine due to cerebral dysfunction, through to major episodes of coma and seizure requiring third-party assistance. The inability of intermittent injection therapy to control blood glucose tightly without an attendant risk of hypoglycaemia results in many individuals keeping their blood glucose at higher than desirable levels. This leads to an increased risk of serious diabetic complications, which can affect the eyes, feet and kidneys. These complications, plus the associated high risk of cardiovascular disease, reduce both the length and quality of the individuals' lives.

Insulin analogues

Short- and long-acting insulin analogues have slightly more physiological profiles than insulins of human or animal structure, but cannot reproduce those observed in people without diabetes.² Systematic reviews of clinical trials of insulin analogues involving people with T1DM have reported only minor advantages compared with human insulin, with a reduced risk of symptomatic hypoglycaemia, particularly at night.^{3,4} This may be, in part, because those people who are at the greatest risk of hypoglycaemia are frequently excluded from clinical trials. Interestingly, in a recent crossover trial comparing MDI of human insulin with analogue insulin, the investigators specifically recruited individuals who had experienced problems with hypoglycaemia, and found that those using analogue insulin had significantly lower risks of severe hypoglycaemia, particularly at night.⁵

Insulin pumps

There is clearly an urgent need for better methods of insulin delivery. Insulin pumps were first used clinically in the early 1980s, but randomised controlled trials (RCTs) conducted in the UK failed to show any clinical benefit. At the time, the technology was poorly developed, but has advanced considerably, particularly in the last few years. Insulin pumps are now the size of a small mobile phone and deliver

insulin continuously under the skin via a small plastic tube and cannula [continuous subcutaneous insulin infusion (CSII)].^{6,7} These devices are filled with reservoirs of quick-acting insulin only (usually an insulin analogue), which provides insulin replacement by delivering both the mealtime and background insulin. When infused continuously at low rates they 'mimic' basal insulin secretion, and this is generally delivered more consistently and accurately than is achievable by the longer-acting insulins, particularly at night. The insulin boluses used to cover meals and correct high blood glucose levels are delivered much more rapidly. All of the insulin doses can be controlled by the patient, based on calculations similar to those required for insulin dosing with a MDI regimen.

The purchase and use of pumps is more expensive than MDI, with pumps at current prices costing around £2500 each, plus £1500 per year extra for running costs.⁸ The marginal cost per annum over MDI is about £1800.⁹ The potential advantages are more stable blood glucose levels, a reduced risk of hypoglycaemia and a more flexible lifestyle. Pump treatment may deliver insulin more effectively than MDI but does not provide a technological 'cure'. The same competencies needed for successful insulin self-management, previously described for MDI, are required for pumps, but with additional skills required to operate the pump device itself. Thus, pumps are probably more useful to those individuals who are actively and effectively self-managing their diabetes rather than those who expect the pump to 'manage' their diabetes for them.

Pumps are currently used by around 40% of people with T1DM in the USA and > 15% in Europe.¹⁰ In contrast, the proportion in the UK was around 6% in adults in 2012.^{11,12} 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 (QoL).¹² The UK's National Institute for Health and Care Excellence (NICE) has recently extended recommendations for the use of pumps for adults with T1DM. The guidance suggests that pump treatment be considered for individuals who are experiencing problems with hypoglycaemia, particularly when this limits the ability to improve glycaemic control. NICE has noted the paucity of evidence for efficacy from RCTs.¹³

Problems with evidence in National Institute for Health and Care Excellence appraisals

There have been two appraisals^{9,14} of pumps by NICE, both supported by technology assessment reports undertaken by some of the present authors, which reviewed the evidence on clinical effectiveness and cost-effectiveness. The first report¹⁴ noted that there were no trials of pumps against 'best MDI' with long- and short-acting analogue insulins; some trials had unequal amounts of education in the arms (with more in the pump arms); and the trials had focused on easily measurable outcomes such as glycated haemoglobin (HbA_{1c}), rather than on benefits in terms of flexibility of lifestyle and QoL. The report recommended trials of pumps against analogue-based MDI.

The second report⁹ found that few such trials had been done: one in children, not relevant to this work, and three in adults. Furthermore, the three adult studies¹⁵⁻¹⁷ presented data for a small number of participants who were followed over a short period only. The first of these studies was a 24-week pilot study¹⁵ in adults with altered hypoglycaemia awareness and debilitating hypoglycaemia. The three study arms consisted of seven patients each and compared (1) analogue MDI, (2) pump and (3) education and relaxation of glycaemic targets. All of the subjects were naive to analogue insulin use and some had never tried MDI, and so were not representative of the type of patients for whom NICE recommends pumps.

The second trial¹⁶ recruited 39 adults with T1DM, who had already been on pump therapy for at least 6 months, and who were randomised to stay on pump or switch to glargine (Lantus, Sanofi-Aventis, Guildford, UK)-based MDI for 4 months. The primary end point was glucose variability, which was 5–12% less with the pump. Despite this, there was no significant difference in the frequency of hypoglycaemic episodes or HbA_{1c}.

The third study¹⁷ studied 50 patients with T1DM from Italy, UK (Newcastle, Bournemouth) and France, who were naive to pumps and glargine, to which they were switched for the trial, having been previously managed on neutral protamine Hagedorn (NPH)-based regimens. Follow-up was for 24 weeks. Patients were randomised to pump or analogue MDI in an equivalence study. The difference in HbA_{1c} at the study end was only 0.1% (approximately 1 mmol/mol) and the costs with the pump were three times higher.

Thus, the evidence base from trials for comparing pumps and 'best MDI' remains weak in terms of numbers, with a total of only 103 patients and short-term follow-up. Furthermore, the patients in the trials were dissimilar to those considered suitable for a pump by NICE, which expects patients to have tried analogue-based MDI before using the pump.

Given the paucity of RCTs, the assessment group also looked at observational studies of adults in which a pump was clinically indicated, mostly because of the limitations of intermittent injections. This comparison has the advantage of measuring change in glycaemic control and hypoglycaemia in those who have most to gain, and these studies showed improved HbA_{1c} of the order of around 0.5% (5.5 mmol/mol). Interpretation of data from observational studies face limitations from bias, and, furthermore, of the 48 observational studies, only nine reported QoL. Study numbers were small and duration was usually short. The longest study noted that initial benefits from pumps might not be sustained.

Therefore, again, NICE was faced with an evidence base with considerable shortcomings, too few trials, durations too short, numbers too small and a need to use observational studies. A recent meta-analysis by Monami *et al.*¹⁸ concluded that 'available data justify the use of CSII for basal-bolus insulin therapy in type 1 diabetic patients unsatisfactorily controlled with MDI'. However, most of the RCTs in their analysis were NPH-based and the Bolli *et al.*¹⁷ trial, with its negative result, was missed.

A systematic review of the cost-effectiveness of insulin pump therapy in adults with T1DM was conducted by Roze *et al.*¹⁹ They identified four cost-effectiveness studies in the UK setting, three of which presented an incremental cost-effectiveness ratio (ICER).^{9,14,20,21} The ICERs in these studies were £11,461 per quality-adjusted life-year (QALY) gained, £25,648 per QALY gained and £37,712 per QALY gained. Two out of the three studies had ICERs that lie within, or below, the £20,000 to £30,000-per-QALY-gained range that NICE usually uses to determine if a health technology is cost-effective.²² These two studies did receive commercial sponsorship, whereas the study with an ICER of £37,712 was commissioned on behalf of NICE.

Rationale for the trial

We hypothesised that much of the benefit of pumps may come from the retraining and education in intensive insulin management, which allows patients to use pumps safely.²³ In many DAFNE centres, reimbursement for pump use is conditional on patients having attended a DAFNE education course and so some patients undertake DAFNE training with the intention of moving to pump treatment thereafter. It has been our clinical experience that many individuals decide not to switch to the pump after attending a DAFNE course, as they then realise that what they required was training in insulin self-adjustment rather than a different technical way of delivering insulin. Ray *et al.*²⁴ found that 69% of those being considered for insulin pump therapy stay on MDI after completing DAFNE. Importantly, trials and observational studies of high-quality training alone (with standard insulin injections) show benefits in blood glucose control, hypoglycaemia and QoL, which are as good, if not better, than those reported after pump therapy.^{2,25,26}

To our knowledge, no trials in adults, comparing pump treatment with modern MDI, used the same structured training in insulin adjustment, resulting in the added benefit of the pump technology remaining unclear.²³ There was an urgent need to establish this, and identify patients who benefit the most. A RCT was needed to establish these outcomes without bias.

The DAFNE course is a 1-week structured education course, teaching adults with T1DM the skills in insulin self-adjustment and carbohydrate counting.² DAFNE courses are currently delivered in more than 70 centres

across the UK, with over 37,000 individuals (DAFNE graduates) now trained. We therefore set out to conduct a novel study in which adults waiting for a DAFNE course were randomly allocated to undertake either the standard MDI course or DAFNE incorporating use of pump therapy.

The investigators involved in this work have been undertaking research into other aspects of DAFNE for many years. During recent work funded by a National Institute for Health Research (NIHR) programme grant [Programme Grants for Applied Research (PGfAR)] we measured cost-effectiveness and identified which components of the course are crucial, as well as identifying the factors determining which DAFNE patients managed their diabetes more effectively.²⁷ This work included funding to pilot a combined DAFNE and pump course, which enabled us to develop a pump curriculum and associated pump-specific resources, ensure that the outcome measures that we wanted to use were feasible and estimate the likely recruitment and retention rates.

We then assembled a study group with expertise in structured T1DM education, pump therapy (having trained in total over 700 pump patients) and health economic assessment of diabetes interventions.

Decision problem: aim of the REPOSE Trial

The aim of our trial was to establish for patients, professionals and those funding the service, the added benefit of using a pump during intensive insulin therapy. We conducted a RCT comparing optimised MDI therapy (using rapid and twice-daily, long-acting insulin analogues) with pump therapy in adults with T1DM, for which both were provided with high-quality structured education (DAFNE).

Research objectives

The project had the following specific objectives:

1. To measure, over 2 years, (1) biomedical, (2) psychosocial (quantitative and qualitative) and (3) adverse event (AE) outcomes. The primary outcome was HbA_{1c} at 2 years, with a minimum clinically significant difference defined as 0.5% (5.5 mmol/mol).
2. To undertake a cost-effectiveness analysis to determine whether or not the marginal benefits of pump therapy over optimised MDI (if demonstrated) are commensurate with the marginal costs, as reflected in an ICER, expressed in terms of a cost per QALY gained that is acceptable to NICE.
3. To conduct a mixed-methods psychosocial evaluation of pump therapy in order to identify factors that predict and/or help explain outcomes on the pump.

Members of the research team have been involved in the NICE appraisal of insulin pumps, have been members of NICE appraisal committees and have a good understanding of what evidence NICE needs. Thus, a further objective was to inform the next NICE reviews of insulin pumps and structured education.

Chapter 2 Overview of evidence base for pump therapy

As noted in *Chapter 1*, the evidence on the clinical effectiveness and cost-effectiveness up to June 2007 was reviewed in the two assessment reports for NICE,^{9,14} both published in this monograph series. This chapter is concerned mainly with studies that have emerged since 2007, but we also provide a complete overview of all of the trials.

Methods

Searches were performed for RCTs that compared the clinical effectiveness of pump and MDI in adults, from June 2007 to the present in MEDLINE and EMBASE (see *Appendix 1* for search methods). We checked inclusion lists of seven past systematic reviews.^{9,14,18,28–31}

Reasons for exclusion included:

- control group not on MDI
- pump therapy from diagnosis of diabetes
- studies in pregnancy
- paediatric age group
- studies in type 2 diabetes mellitus
- pump plus continuous glucose monitoring (CGM) versus MDI plus self-monitoring of blood glucose (SMBG) levels
- closed-loop trials
- low-glucose suspend (LGS) pumps
- all on pump therapy, with different pumps
- trials of catheter duration in pump therapy
- not a trial
- peritoneal infusion
- protocols
- pumps infusing substances other than insulin
- reviews
- trials of exercise on pump therapy.

During the course of the REPOSE Trial, weekly auto-alerts were run in MEDLINE and EMBASE to identify any emerging research that might affect the trial. The search strategy used was:

1. (insulin and pump*).tw.
2. (CSII or continuous subcutaneous insulin infusion).tw.
3. (continuous adj3 insulin adj3 infusion).tw.
4. (subcutaneous adj3 insulin adj3 infusion).tw.
5. 1 or 2 or 3 or 4.
6. DAFNE.tw.
7. (dose adjust* adj2 normal eating).tw.
8. 6 or 7.
9. 5 or 8.

In addition, final searches were performed for RCTs that compared the clinical effectiveness of pump and MDI in adults, from 2007 to 7 January 2016 in MEDLINE, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials.

Trials may be done in selected groups of patients and, as noted in *Chapter 1*, they are often of short duration. We therefore carried out a search for longer-term observational studies in large groups of patients as a guide to the results of pump therapy in routine care. We selected studies with at least 3 years of follow-up, and ≥ 100 patients, published since January 2008. Older observational studies were reviewed in a previous monograph,⁹ and the findings summarised as follows:

- There were much greater improvements in HbA_{1c} in observational studies than reported in the RCTs.
- There were considerable reductions in severe hypoglycaemia. This may reflect selection for pump therapy of people having particular problems with hypoglycaemia, but that would make the results more applicable to the patients who would get a pump in routine care.
- The majority of studies showed no increase in diabetic ketoacidosis (DKA).
- Weight gain was reported but usually minor.
- There was a reduction in daily insulin dose, which will provide some savings to offset the cost of pump therapy.
- There were gains in QoL, with comments on items such as flexibility of meal choices and timings and other aspects of lifestyle, and diabetes being easier to manage.

During the course of the REPOSE Trial, we looked for any important developments in:

- pump therapy
- structured education
- new insulins used in MDI or pump
- the evidence base on QoL on pump and MDI.

Findings

Pump therapy

Table 1 shows the trials of pump therapy against MDI in adults with T1DM, excluding those in pregnancy. There have been only four trials of pump versus MDI with analogue insulin use in both arms, and the longest follow-up period was 24 weeks, which, as we will show in *Chapter 3*, is insufficient to achieve the full potential of pump therapy.

Table 1 shows that only five trials (assuming that Lepore *et al.*⁴⁴ is a trial – the paper does not mention randomisation but Misso *et al.*³¹ in the Cochrane review say it was a RCT and that it had access to unpublished data) had a duration of ≥ 12 months, and none used analogue MDI. Lepore *et al.*⁴⁴ report HbA_{1c} only at baseline and 12 months.⁴⁴ Dahl-Jørgensen *et al.*⁵⁴ reported a steep drop in HbA_{1c} with a plateau after 3 months, but this reduction started in the 2-month run-in period before pump therapy was started.

Four trials^{15–17,40} used analogue insulin in both arms. The Hirsch *et al.*⁴⁰ trial had patients on pump and MDI for only 4 weeks. The Thomas *et al.*¹⁵ trial was a pilot, with only seven patients per arm.

One new trial has been published since the last appraisal by NICE: Bruttomesso *et al.*¹⁶ This trial recruited 42 patients already well controlled on the pump (mean HbA_{1c} 7.4% at randomisation) and randomised them to continuing pump therapy, or to MDI with lispro and glargine. The aim was to see if the need for pump therapy was reduced by the arrival of the analogue insulins. Patients had only 4 months on MDI. Three patients withdrew shortly after starting MDI because of poorer glycaemic control. After 4 months the patients switched to the other treatment arm. The primary outcome was glucose variability, as assessed by SMBG. HbA_{1c} during the study was 7.3% in both arms. There was no difference in the frequency of severe hypoglycaemia, but moderate hypoglycaemia was about 23% less frequent on pump therapy, although the definition of this is not stated in the published study. Glucose variability was 5–12% less on pump therapy, depending on time of day and method used. At the study end, patients could choose between

TABLE 1 Previous trials of pump vs. MDI: adults only, T1DM only, excluding pregnancy studies

Trial	Year of publication	n of participants	Design	Pump	MDI	Duration on pump
Bak <i>et al.</i> , 1987 ³²	1987	20	Crossover	Actrapid ^a	Actrapid and NPH	6 months
Bode <i>et al.</i> , 1996 ³³	1996	55	Crossover	Soluble		12 months
Bolli <i>et al.</i> , 2009 ¹⁷	2009	43	Parallel	Lispro ^b	Lispro t.i.d., glargine once	24 weeks
Bruttomesso <i>et al.</i> , 2008 ¹⁶ – incorporates Maran <i>et al.</i> , 2005 ³⁴	2008, 2005	42	Crossover	Lispro	Lispro, glargine	4 months on each
Chiasson <i>et al.</i> , 1984 ³⁵	1984, 1985	12	Crossover	Regular	Regular and Ultralente	3 months on each
DeVries <i>et al.</i> , 2002 ³⁶	2002	55 completed of 79 starters	Started as crossover but reduced to parallel	Aspart	Aspart and NPH	16 weeks
Düsseldorf Study group (Ziegler <i>et al.</i> , 1990 ³⁷)	1990	96	Parallel	Not specified	Mixture of b.i.d. and MDI with regular and NPH	2 years
Haakens <i>et al.</i> , 1990 ³⁸	1990	52 started, 35 completed	Crossover	Soluble	Soluble, Ultralente, isophane	6 months
Hanaire-BROUTIN <i>et al.</i> , 2000 ³⁹	2000	40	Crossover	Lispro	Lispro and NPH	4 months on each
Hirsch <i>et al.</i> , 2005 ⁴⁰	2005	100	Crossover	Aspart	Aspart and glargine	4 weeks
Home <i>et al.</i> , 1982 ⁴¹	1982	10	Crossover	Actrapid	Actrapid, Ultralente	10 weeks
Hoogma <i>et al.</i> , 2006 ^{42,43}	2006	256	Crossover	Lispro	Lispro and NPH	6 months on each
Lepore <i>et al.</i> , 2003 ⁴⁴	2003	32	Parallel	Lispro	Lispro and NPH	12 months
Nathan <i>et al.</i> , 1982 ⁴⁵	1982	5	Crossover	Soluble	NPH and regular	8–12 weeks
Nosadini <i>et al.</i> , 1988 ⁴⁶	1988	44	Parallel	Soluble	Soluble t.i.d. and NPH	1 year
Oslo, 1988, ⁴⁷ 1986 ⁴⁸	1985–92	30	Parallel	Velosulin ^a	Regular porcine and NPH	4 years
Saubrey <i>et al.</i> , 1988 ⁴⁹	1988	21	Crossover	Actrapid	Actrapid (NovoPen [®]) and NPH	10 weeks
Schiffrin and Belmonte, 1982 ⁵⁰	1982	16	Crossover	Soluble	Three soluble, one NPH	6 months
Schmitz <i>et al.</i> , 1989 ⁵¹	1989	10	Crossover	Velosulin, porcine regular	Velosulin and Insulatard [®] NPH	6 months on each
Schottenfeld-Naor <i>et al.</i> , 1985 ⁵²	1985	9	Crossover	Velosulin	Velosulin and Insulatard	4 months on each
Thomas <i>et al.</i> , 2007 ¹⁵	2007	14	Parallel	Lispro	Lispro and glargine	24 weeks
Tsui <i>et al.</i> , 2001 ⁵³	2001	27	Parallel	Lispro	Lispro and NPH	9 months

b.i.d., twice a day; t.i.d., three times a day.

a Novo Nordisk, Gatwick, UK.

b Eli Lilly, Basingstoke, UK.

pump therapy and glargine-based MDI. Thirty patients chose pump, five chose MDI and four opted for summer MDI and winter pump. The study was supported by Disetronic and one author worked for the company.¹⁶

The Bolli *et al.*¹⁷ trial (see *Table 1*) was published in 2009 but had been available in abstract form for the last assessment report.

Overall, therefore, there was still a poor evidence base with only one new trial, and that being of short duration (4 months on each arm) and limited sample size (only 39 patients).

Observational studies

Bacon *et al.*⁵⁵ reported 10-year follow-up data on 197 patients on pump therapy. The main indications for the pump were recurrent hypoglycaemia and poor control. HbA_{1c} improved by about 0.7% and the number of severe hypoglycaemic episodes by about 80%. Only about 5% discontinued pump therapy.

Beato-Vibora *et al.*,⁵⁶ from King's College Hospital, looked back over 12 years of pump therapy in 327 patients, with a mean duration of 4.3 years on the pump. An initial reduction in HbA_{1c} of 8 mmol/mol or 0.7% was partially maintained with reduction at year 5 of 0.4%. The proportion of people having frequent mild-to-moderate hypoglycaemia fell from 29% to 12% and the frequency of severe hypoglycaemia was halved.

Bruttomesso *et al.*,⁵⁷ from the Veneto region of Italy, provide a retrospective study of all patients in their region who started pump therapy. Of 138 patients, 20 stopped pump therapy, although mostly in the earlier years. Strict eligibility criteria had to be met, including 'the technical, physical and intellectual abilities', plus motivation, stable personality and realistic expectations of pump therapy. All were familiar with MDI and received extra education. HbA_{1c} was 9.3% when starting pump therapy, fell to 7.9 by end of year 1 and was largely sustained there for 7 years.

Carlsson *et al.*,⁵⁸ from Sweden, reported results of 272 patients with at least 5.5 years of follow-up. They compared their results with a much larger group on MDI. HbA_{1c} was reduced by 0.42% at 1 year and 0.43% at 2 years, but some of the effect was lost by 5 years when the reduction compared with the MDI group was only 0.2%.⁵⁸ A later paper⁵⁹ reported that the reduction in HbA_{1c} varied by baseline levels, with a small reduction of 0.29% (85% CI 0.11% to 0.47%) in those with baseline HbA_{1c} of 7%, a reduction of 0.39% (85% CI 0.27% to 0.52%) in those with baseline HbA_{1c} of 8% and a larger reduction of 0.50% (85% CI 0.36% to 0.67%) in those with baseline HbA_{1c} of 9%, which would take them nowhere near target.

Cohen *et al.*⁶⁰ compared two cohorts from Melbourne in a non-randomised comparison. One group received pump therapy and the other received intensified MDI. Both were previously on analogue MDI. Among 126 patients on the pump, HbA_{1c} fell by 0.64% at 6 months, but then rose again, with a reduction of about 0.4% at 2 years and about 0.2% at 5 years. The reduction in HbA_{1c} on intensified MDI was smaller: 0.15% at 6 months. This was despite a similar programme of education, based on DAFNE but shorter, in both pump and MDI groups.

Lepore *et al.*,⁶¹ from three Italian centres, compared results in two matched groups of 110 patients on pump therapy and 110 on MDI, followed for 3 years. HbA_{1c} fell by 0.7% in the pump group and this reduction persisted for the 3 years. HbA_{1c} fell by 0.3% in the MDI group at 3 years.

Nixon *et al.*⁶² reported a study of 35 patients on pump therapy. There was an initial fall of 1.7% in HbA_{1c} but by 5 years the reduction was only 0.9%. However, this reflected a mix of results, with one-third of patients reducing HbA_{1c} by 2.2% and maintaining it there, whereas others had no change on the pump or had an initial reduction not sustained.

Orr *et al.*,⁶³ from Ontario, report results among 235 patients on pump therapy. The overall baseline HbA_{1c} was 8.7%, which was reduced to 7.5% after 6 months on the pump, after which it drifted up again to 8.2% in years 3–10. In 39 patients who were followed for 10–15 years, the mean HbA_{1c} was 8.03%. However, two groups of patients who started with high baselines (8.5–10% and > 10%) reduced their HbA_{1c} to about 8% by 8–10 years.

Quiros *et al.*,⁶⁴ from Barcelona, followed 151 patients on pump therapy for 5 years. Overall, HbA_{1c} was reduced from a mean of 8.0% at baseline to 7.8% at 5 years. However, in the 61% of patients who started pump therapy because of poor glycaemic control, HbA_{1c} fell from 8.4% at baseline to 8.0% at 5 years. There was a marked reduction in severe hypoglycaemia.⁶⁴

Rosenlund *et al.*⁶⁵ from Denmark looked at the effects of 4 years of pump therapy on albuminuria compared with an unmatched group on MDI. On pump therapy, HbA_{1c} fell from 8.4% to 7.8%, maintained to 4 years.⁶⁵

Steineck *et al.*⁶⁶ from Sweden reported mortality data from a cohort of 18,168 people with T1DM in Sweden, of whom 13% were on pump therapy. Total mortality at 7 years was 6% in the pump group and 8% in the MDI group. There were many small differences that would increase the risk in the MDI group – more hypertension, more on lipid-lowering drugs, more with low physical activity, more smokers and more with low education levels. Steineck *et al.*⁶⁶ used propensity matching to adjust for the differences, and concluded that those on pump therapy had a 0.73 hazard ratio for total mortality. However, there could have been confounding factors for which they could not allow.

Most long-term studies show a disappointing waning of the initial HbA_{1c} improvement. Perhaps there is a case for educational updates. In a small trial with only 23 patients, Carlone *et al.*⁶⁷ randomised patients on long-standing pump therapy to standard care or to six educational weekly group meetings on advanced features of the pump, carbohydrate counting and other aspects of diet. After 6 months, the intervention group had reduced their HbA_{1c} by 1%. The control group did not change.

New developments

The main developments in pump therapy have been the use in combination with CGM systems, of which there are two forms that are now relevant to the pump. The first is when the CGM device is integrated with the pump, which means that it sends glucose results to the pump every 5 minutes or so, from a sensor just under the skin. Strictly speaking this means that the glucose result is for the level in interstitial tissue, not in the bloodstream, but the two are closely related. With the integrated CGM system, the pump can send alarms to the user, following which they can take action. This helps users to avoid hypoglycaemic episodes, but some find the alarms to be a nuisance and may disable the alarms. False alarms are not uncommon.

Four trials of CGM compared the pump with CGM against MDI with SMBG, which confounds things [Hermanides *et al.* (Eurythmic trial),⁶⁸ Lee *et al.*,⁶⁹ Peyrot and Rubin,⁷⁰ Bergenstal *et al.* (STAR-3)⁷¹]. The durations of these trials were only 6, 3.5, 3.7 and 12 months, respectively.

Continuous glucose monitoring would have implications for the use of pump therapy rather than MDI if the effectiveness of CGM differed between the two forms of treatment. Garg *et al.*⁷² found that the effects of real-time CGM in reducing HbA_{1c} and hypoglycaemia were similar in two matched groups on MDI and pump.

More recently, the Medtronic Veo (Medtronic, Watford, UK) has been introduced, which has a facility to link with a CGM system and suspend insulin infusion (the LGS facility) if the glucose level goes too low, for up to 2 hours. This means that the pump can take action. In practice, most suspensions are for much less than 2 hours because the wearer takes action. However, at night when the wearer is asleep, this may not happen.⁷³

There have been two trials of the Veo suspend pump. In the ASPIRE (Automation to Simulate Pancreatic Insulin Response) trial⁷⁴ in the USA and Canada, the recruits were familiar with pump therapy. They had a 2-week run-in period and were selected for the trial if they had nocturnal hypoglycaemia (defined as plasma glucose < 3.7 mmol/l) at least twice in that period. They also had to be prepared to wear the sensors at least 80% of the time. They were randomised to the Veo with its LGS facility, or to the Medtronic Paradigm Revel, which has integrated CGM but no LGS action. The trial was sponsored by Medtronic, and Medtronic staff were involved in data analysis and editorial assistance.⁷⁴ The trial showed no difference in HbA_{1c} after 3 months, perhaps not surprisingly because the baseline HbA_{1c} was very good at 7.2% or 55 mmol/mol. There was reduced hypoglycaemia, especially nocturnal. In the Veo group, 111 of 121 patients had at least one nocturnal suspension on the pump that lasted 2 hours. A 2-hour suspension does not lead to significant ketosis. QoL measures, EuroQol-5 Dimensions (EQ-5D) and the Hypoglycaemia Fear Survey (HFS) score, showed no difference between the arms of the trial. There were only four severe hypoglycaemic episodes, none in the Veo arm.

So the main benefit of the Veo LGS over the integrated CGM pump system is reduction of nocturnal hypoglycaemia. There is quite a large extra capital cost for the device (£2692) with an annual cost, including consumables, of £4862. This will make it difficult to prove cost-effectiveness. The group in which the Veo is most likely to be cost-effective will be patients with recurrent severe hypoglycaemia, but that group is covered by existing NICE guidance on the pump and is not recruited to the REPOSE Trial.

The other trial of the Veo was by Ly *et al.*⁷⁵ in Australia. This trial recruited mainly children and adolescents, with only 31% aged > 18 years. Patients were selected on the basis of impaired awareness of hypoglycaemia. They had been on pump therapy for an average of 4 years. They were randomised to the Veo suspend pump or to stay on their previous pump and use SMBG – not CGM. This immediately raises a problem because the Veo arm has both the LGS facility and CGM. It would have been better to have CGM in both arms. A more serious problem with the study is that, despite reasonable numbers (49 to pump plus SMBG, 45 to the Veo) and randomisation, there was a very marked baseline mismatch in previous severe (defined as seizure or coma) and moderate (defined as requiring assistance) hypoglycaemia, with a rate of 130 per 100 patient-months [95% confidence interval (CI) 111 to 150 patient-months] in the Veo group, but only 21 per 100 patient-months in the control arm (95% CI 14 to 30 patient-months). At study end after 6 months, the rate of moderate and severe hypoglycaemic episodes was 28.4 in the Veo group and 11.9 in the control arm. However, these figures were reversed when the authors adjusted for baseline rates, from 28.4 to 9.5, and from 11.9 to 34.2, all per 100 patient-months. There were no significant changes in HbA_{1c}, but both groups started with quite reasonable levels of 7.6% and 7.4%.

The analysis by Ly *et al.*⁷⁵ has been strongly criticised by the German Institute for Quality and Efficiency in Healthcare [Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)], as reported by Heinemann and Hermanns.⁷⁶

The Veo has been appraised by the NICE Diagnostics Assessment Programme. Their guidance is shown in *Box 1*.

The patient group in which it has been recommended is different from that in the REPOSE Trial, and so the arrival of the Veo and its LGS facility has no implications for the implementations of the results of the REPOSE Trial.

Findings: structured education

The DAFNE course has changed little since the original trial published in 2002.² A programme of work has included a trial comparing the 5-day course in 1 week with 1 day a week for 5 weeks, which found little difference in outcomes.⁷⁸

One finding from the DAFNE research programme has been that many patients doing the DAFNE course, in preparation for going on to pump therapy, no longer need to progress to a pump after completing

BOX 1 National Institute for Health and Care Excellence guidance on the MiniMed Veo insulin pump⁷⁷

1.1 The MiniMed Paradigm Veo system is recommended as an option for managing blood glucose levels in people with type 1 diabetes only if:

- they have episodes of disabling hypoglycaemia despite optimal management with continuous subcutaneous insulin infusion and
- the company arranges to collect, analyse and publish data on the use of the MiniMed Paradigm Veo system (see section 7.1).

1.2 The MiniMed Paradigm Veo system should be used under the supervision of a trained multidisciplinary team who are experienced in continuous subcutaneous insulin infusion and continuous glucose monitoring for managing type 1 diabetes only if the person or their carer:

- agrees to use the sensors for at least 70% of the time
- understands how to use it and is physically able to use the system and
- agrees to use the system while having a structured education programme on diet and lifestyle, and counselling.

1.3 People who start to use the MiniMed Paradigm Veo system should only continue to use it if they have a decrease in the number of hypoglycaemic episodes that is sustained. Appropriate targets for such improvements should be set.

1.4 The Vibe and G4 PLATINUM CGM system shows promise but there is currently insufficient evidence to support its routine adoption in the NHS for managing blood glucose levels in people with type 1 diabetes. Robust evidence is needed to show the clinical effectiveness of using the technology in practice.

1.5 People with type 1 diabetes who are currently provided with the MiniMed Paradigm Veo system or the Vibe and G4 PLATINUM CGM system by the NHS for clinical indications that are not recommended in this NICE guidance should be able to continue using them until they and their NHS clinician consider it appropriate to stop.

Reproduced with permission from NICE. © National Institute for Health and Care Excellence 2016. *Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system)*. Available from: www.nice.org.uk/guidance/dg21. NICE guidance is prepared for the NHS in England, and is subject to regular review and may be updated or withdrawn. NICE has not checked the use of its content in this article to confirm that it accurately reflects the NICE publication from which it is taken.

the course. Ray *et al.*²⁴ reported that after DAFNE education, 69% of patients previously being considered for pump therapy could remain on MDI.

However, another study from the programme (Mansell *et al.*⁷⁹) found that some patients who had been through DAFNE education still benefited from pump therapy in terms of a reduction in stress [measured by the PAID (Problem Areas in Diabetes Questionnaire) score] and improved glycaemic control at 12 months of follow-up. This may have been because individuals who progress to the pump after doing a DAFNE course have higher pre-course stress levels.⁸⁰

Conversely, attendance at DAFNE courses sometimes identifies individuals for whom pump therapy is indicated because of a troublesome dawn phenomenon.

Research into DAFNE education has also been undertaken by the Irish DAFNE group.⁸¹ They carried out a large randomised trial of group follow-up compared with individual clinic visits for patients who had

completed the DAFNE course. The intervention group received group education at 6 and 12 months after DAFNE, following a semistructured curriculum, whereas the control group had individual clinic appointments with doctor, nurse or dietitian. The additional education conferred no benefit over individual clinic visits.

The Irish DAFNE group also carried out a qualitative study to identify factors that influenced how well DAFNE graduates incorporated what they had learned into long-term daily living.⁸² They identified four themes:

1. Being empowered, and feeling able to manage their diabetes, which some people did not manage to do.
2. Embedded knowledge, which increased over time, for example as patients got better at carbohydrate counting.
3. Maintaining motivation, including coping with uncertainty. The researchers commented that this was most marked at 6 months but improved later. Reducing the risk of complications was a strong motivation factor.
4. Continued support from health-care professionals.

The Australian OzDAFNE group⁸³ also looked at psychological changes after the DAFNE course, and found increases in what they called 'mastery/control' and a reduction in diabetes-related distress. One of their key points was that the mean duration of diabetes in their participants was 18 years, but they had low self-assessment of their ability to manage their diabetes, so they recommended that referral to DAFNE courses should not be restricted to recently diagnosed patients.

Findings: new insulins

Some new basal insulins have been introduced, including degludec (Tresiba, Novo Nordisk, Gatwick, UK) and glargine 300 (Toujeo, Sanofi-Aventis, Guildford, UK). However, these are very long-acting basal insulins, and may not have the flexibility in dosing that is needed in MDI for T1DM, and with no data to date about how these might be used effectively in patients with T1DM who are undergoing structured education.

Newer short-acting insulins include 'fast aspart', which, in pump therapy, is reported to have a faster glucose-lowering effect but with the same effect overall. The implications for glycaemic control and hypoglycaemia were not reported by Zijlstra *et al.*⁸⁴

Findings: quality of life

Past reviews found a disappointingly low amount of evidence on QoL. This has implications for cost-effectiveness analysis. The Thomas *et al.*¹⁵ pilot trial of pump therapy versus analogue MDI reported QoL as measured by the Diabetes Quality of Life questionnaire (DQOL) but found no difference. With only seven patients in each arm this may not be surprising. The 2008 health technology assessment (HTA)⁹ for NICE identified 48 observational studies of pump therapy, but only one reported QoL in adults, and it was a before-and-after study in which patients switched to the pump from conventional insulin therapy, not analogue MDI.

One observational study⁸⁵ published since then has compared QoL. This study⁸⁵ by the EQuality1 Study Group from Italy, has both strengths and weaknesses. It was a very large case-control study, with 1341 people with T1DM from 62 clinics, with 481 on the pump and 860 on MDI. The MDI patients came from centres both with and without pump services. Reliable instruments were used: the diabetes-specific quality of life scale (DSQOL) for QoL, Diabetes Treatment Satisfaction Questionnaire (DTSQ) for treatment satisfaction and Short Form questionnaire-36 items (SF-36) for health status. Eighty-four per cent of patients on the pump had been on it for > 1 year; 90% of the MDI group were on glargine-based MDI with the rest using NPH. All of the MDI patients had been on at least four insulin injections a day for > 6 months. The pump and MDI groups were well matched on some variables, but there were striking differences in carbohydrate counting (56% of pump group vs. 40% on MDI) and self-adjustment of insulin doses (80.5% vs. 66.5%), suggesting a marked educational imbalance.

Some DSQOL results were slightly better among the pump group, but this was statistically significant only for diet restrictions (65.5 vs. 60.8; $p = 0.0003$). DTSQ scores were better on pump (30.2 vs. 26.2; $p < 0.0001$). SF-36 scores were better on MDI, but in most domains, not statistically significantly so. However, the authors report that multiple regression analysis (details not provided, but adjusted for clinical factors including complications, which were more common in the pump group) showed that the pump group had significantly better scores in DSQOL diet, daily hassles and fear of hypoglycaemia. No differences were found between NPH and glargine-based MDI. The study was supported by Medtronic.

The lack of difference between the QoL effects of NPH and glargine-based MDI may not apply to detemir (Levemir, Novo Nordisk, Gatwick, UK)-based MDI, because detemir given twice daily may provide a more flexible lifestyle than once-daily glargine.

The Five Nations Study⁴³ was a good-quality trial completed before long-acting analogues became available. It compared pump therapy with lispro and NPH-based MDI, but, unusually, the NPH insulin could be given up to four times a day and only 41% of patients had it once daily, with 32% getting it twice a day and 23% thrice daily. The study reported QoL using DQOL and Short Form questionnaire-12 items (SF-12). With SF-12 there was no difference in physical state but the pump group did better on mental health. The end of trial DQOL was 75 on pump and 71 on MDI, a small but statistically significant difference ($p < 0.001$). The difference reflected gains in treatment satisfaction, flexibility of eating and lifestyle, and reduced worry.

Conclusions

The evidence base for pump therapy compared with modern MDI is still quite sparse, and REPOSE has more participants than in all of the previous trials put together, even if we include the Hirsch *et al.* trial⁴⁰ with its 100 patients on very short duration of 4 weeks on each therapy. If we exclude the Hirsch *et al.* trial,⁴⁰ REPOSE has more than double the number in the other three trials, which had a total of 99 patients.^{15–17} It also recruited a different group of patients from most previous trials, as it excluded those who met the NICE criteria for pump therapy. So it recruited patients in a band of need below those for whom the pump has been approved by NICE.

Chapter 3 Methods

Methods for the randomised controlled trial

The trial protocol was published in a separate paper.⁸⁶

Study design

The REPOSE Trial was a pragmatic, multicentre, parallel-group, open-label, confirmatory cluster RCT. Participants were allocated a place on a week-long DAFNE course, depending on their availability to attend the course. The course (cluster element) groups were then randomly allocated in pairs to either pump or MDI treatment, with allocation concealed. A cluster design was chosen because of the impracticality of randomising individuals and then finding suitable times for that participant to attend a course of the correct allocation.²³ Such an approach was more likely to have resulted in significantly higher attrition rates pre course. Following the course, participants received the trial treatment for 2 years and outcome measures were collected at 6, 12 and 24 months post course. Outcome measurement was not blinded (see *Data collection*).

Approvals obtained

The protocol was approved by the Research Ethics Committee (REC) North West, Liverpool East, on 26 April 2011 (REC reference number 11/H1002/10). Each participating centre gave UK NHS Research and Development (R&D) approval (see *Appendix 2*). The protocol received Medicines and Healthcare products Regulatory Agency (MHRA) clinical trials authorisation on 26 May 2011 [European Union Drug Regulating Authorities Clinical Trials (EudraCT) reference no: 2010-023198-21].

Setting

The trial was conducted in eight secondary care diabetes centres in Sheffield, Cambridge, Dumfries and Galloway, Edinburgh, Glasgow, Harrogate, London and Nottingham (see *Table 11*). Participating centres all had experience in delivering high-quality structured education using DAFNE and had variable levels of experience delivering pump therapy; most were established pump centres but some were relatively new to pump therapy. Nottingham was a reserve centre, activated midway through the trial. The seven centres involved from the outset were asked to recruit 40 participants to three pump and three MDI courses (5–8 patients on each course) over 11 months. Owing to a higher than anticipated dropout rate prior to the DAFNE courses we then recruited to an additional pair of courses at Harrogate, and a pair of courses at the reserve centre, Nottingham.

Participants

Participants were eligible for the trial if they met the following inclusion criteria:

1. were aged ≥ 18 years
2. had T1DM for at least 12 months at the time of the DAFNE course
3. were fluent in speaking, reading and understanding English
4. were willing to undertake intensive insulin therapy with SMBG, carbohydrate counting and insulin self-adjustment
5. had no preference for either pump or MDI, and were happy to be randomised
6. were currently using, or willing to switch to, insulin detemir
7. had a need for structured education to optimise diabetes control.

Furthermore, participants were excluded if they met any of the following criteria:

1. had already completed a diabetes education course
2. used a pump in the previous 3 years (defined as > 2 weeks' use in the last 3 years) or had strong clinical indications for pump therapy in the view of the investigator
3. had renal impairment with a chance of needing renal replacement therapy within the next 2 years (enrolment staff to check that creatinine levels not > 200 µmol/l).
4. had uncontrolled hypertension (diastolic blood pressure of > 100 mmHg and/or sustained systolic level of > 160 mmHg)
5. had a history of heart disease within the past 3 months
6. had severe needle phobia (severity of phobia assessed, considering if the phobia might preclude full participation in either treatment arm or influence the participant's preference for pump therapy)
7. had a current history of alcohol or drug abuse
8. had serious or unstable medical or psychological conditions that are active enough to preclude the participant safely taking part in the trial (based on investigatory judgement)
9. had recurrent episodes of skin infections
10. were pregnant or planning to become pregnant within the next 2 years
11. had taken part in any other investigational clinical trial during the 4 months prior to screening
12. had any other issue that might have precluded them from satisfactory participation in the study based on investigatory judgement
13. were unable to give informed consent.

Interventions

Dose Adjustment For Normal Eating with multiple daily injection

Participants on the MDI arm attended a standard DAFNE structured education course, described in detail elsewhere.² Courses are conducted over 5 consecutive days, providing an average of 38 hours of structured education, delivered to groups of 5–8 adults, aged ≥ 18 years, in an outpatient setting. Courses are delivered by diabetes specialist nurses and dietitians who attend an educator training course, the DAFNE education programme, a seven-part programme consisting of 105 hours of structured training.

The DAFNE curriculum uses a progressive modular-based structure to improve self-management in a variety of medical and social situations. Content is designed to deliver key learning topics at the appropriate time during the week. In this way, knowledge and skills are built up throughout the course with active participant involvement and problem-solving as key methods of learning. The key modules are: 'What is diabetes?', 'Food and diabetes', 'Insulin management', 'Management of hypoglycaemia' and 'Sick day rules'. Lesson plans give guidance on timing and a student activity section serves to give an idea of expected responses. Each meal and snack during the course is used as an opportunity to practise carbohydrate estimation and insulin dose adjustment.

Dose Adjustment For Normal Eating with pump

Participants on the pump arm attended a modified DAFNE course, which had been tested in a pilot study, previously published.²⁷ The 5-day structure of the standard adult DAFNE course was maintained while incorporating the additional skills and learning outcomes that were considered necessary to use pumps successfully. The principles of insulin dose adjustment taught on the standard adult course were maintained.²³ The need to introduce 'pump skills' required the addition of a pre-course group session, delivered 1–3 weeks before the DAFNE course. This session gave participants the opportunity to learn about the basics of insulin pump therapy, including how to set up the pump, so that they could practise using it with saline before starting on insulin at the beginning of the course. The session included the theory of pump therapy, understanding cannulas and infusion sets, skin care, pump maintenance and the advantages and disadvantages of the insulin pump. Participants switched to insulin on the evening before the DAFNE course or on the first day of the course.

Ongoing treatment

After attending the DAFNE course, participants received the trial treatment for 2 years from the secondary care service. All of the participants in both groups were invited to an additional DAFNE follow-up group session at 6 weeks post course, which is standard for DAFNE course attendees.

Multiple daily injection participants used a combination of quick-acting insulin analogues and twice-daily injections of insulin detemir. Pump participants used a Medtronic Paradigm® Veo™ insulin pump (Model X54) with short-acting analogue insulin, as in a meta-analysis⁸⁷ this was shown to lower HbA_{1c} to a greater extent than traditional soluble insulin. As insulin is already marketed and licensed for use, and as the participants were already accessing insulin through prescription on a regular basis, there was no need to change how the insulin was accessed for the trial – participants collected insulin from their pharmacist as normal.

The insulin pumps include, as standard, a Medtronic Bolus Wizard (Medtronic, Watford UK) to aid calculation of insulin doses. In order to reduce any potential bias, MDI participants were also given access to a bolus calculator (Accu-Chek Aviva Expert Bolus Advisor System, Roche Diagnostics Ltd, Burgess Hill, UK).

Fidelity testing (FT) of pump courses was undertaken in order to assess whether or not courses were delivered in accordance with DAFNE philosophy and principles, and that the educators had the necessary skills to deliver these principles. The results of the FT are reported in *Chapter 5*. Standard DAFNE courses were not tested, as there is a rigorous quality assurance programme of MDI courses in standard care.

Treatment was changed (pump to MDI or MDI to pump) at the discretion of the local principal investigator (PI) if self-management of diabetes had become ineffective and was considered a risk to the individual. If the participant failed to attend the pump course then they were withdrawn from pump treatment.

Primary outcomes

The main primary end point was the change in HbA_{1c} at 24 months, in those participants whose baseline HbA_{1c} was $\geq 7.5\%$ (58 mmol/mol). The key secondary end point was the proportion of participants reaching the NICE target of a HbA_{1c} level of $\leq 7.5\%$ (58 mmol/mol) at 24 months (of all participants).

Glycated haemoglobin is the accepted gold standard measure of glycaemic control and provides a measure of efficacy. Most health economic models of T1DM estimate the cost-effectiveness by primarily modifying HbA_{1c} levels, which subsequently affect the risk of diabetic complications.⁸⁸ However, it is important to note that HbA_{1c} may not have fallen in patients who entered the trial with low baseline levels of HbA_{1c}, but who might have been experiencing frequent hypoglycaemia or wished to increase dietary freedom. Success for such individuals would be a HbA_{1c} level that is maintained, or even rises slightly, with a reduction in the frequency of hypoglycaemia.²³ We included such patients as they could provide important information about QoL and the potential of pump therapy to reduce rates of hypoglycaemia. However, as their glycaemic control may not alter, including their HbA_{1c} data would have reduced our statistical power to establish improvement in our primary end point. We therefore powered the trial on the number of participants with a baseline HbA_{1c} of $\geq 7.5\%$ (58 mmol/mol) and in whom a fall would reflect a worthwhile improvement in glycaemic control. We ensured standardisation by testing HbA_{1c} in a central laboratory.

Exploratory outcomes on the primary end points

The primary outcome and key secondary outcome were also evaluated at 6 and 12 months in order to explore the short- and medium-term effects of the intervention.

Secondary outcomes

Secondary outcomes were evaluated in all participants and were measured at 6, 12 and 24 months. Blood and urine samples for secondary outcomes were tested in local laboratories.

Hypoglycaemia

We recorded episodes of both moderate and severe hypoglycaemia and specifically recorded episodes at night (those occurring between 23.00 and 07.00). We used a standard definition of severe hypoglycaemia,^{89,90} being 'an episode leading to cognitive impairment sufficient to cause either coma or requiring the assistance of another person to recover'. The number of severe episodes are reliably recorded by patients for up to 1 year.⁹¹

During the last NICE appraisal of pump therapy, the question of the impact of moderate hypoglycaemia was raised.¹³ The modelling had included only severe hypoglycaemia, and the point was made that moderate hypoglycaemia, sufficient to interrupt activities of daily living, might, because of greater frequency, have a more cumulative effect on QoL than severe hypoglycaemia. We therefore also recorded rates of moderate hypoglycaemia in an attempt to increase power and identify the ability of pumps to reduce rates of hypoglycaemia. With no standard definition of moderate hypoglycaemia, the Trial Management Group (TMG) agreed to define these as 'any episodes which could be treated by that individual, but where hypoglycaemia caused significant interruption of current activity, such as having caused impaired performance or embarrassment or having been woken during nocturnal sleep'. As these episodes are more frequent, reliable recall of such events is unlikely to be sustained for more than a few weeks. We therefore asked participants to record the number and timing of moderate episodes over the 4 weeks prior to each follow-up visit. We used this approach successfully to record the frequency of mild episodes in a recent epidemiological study of hypoglycaemic burden in diabetes.⁸⁹

Insulin dose and body weight

Pump treatment may result in the use of less insulin, leading to a favourable effect on body weight. We recorded total insulin dose at each time point and calculated units per kilogram of body weight.

Lipids and proteinuria

A recent study⁶¹ reported little difference in HbA_{1c} on pump therapy compared with MDI but found less progression to microalbuminuria in the pump group, and also lower cholesterol levels. We measured high-density lipoprotein (HDL) cholesterol and total cholesterol (TC). Proteinuria was measured using the albumin-to-creatinine ratio (ACR).

Diabetic ketoacidosis

Diabetic ketoacidosis was measured throughout the trial through the assessment of serious adverse events (SAEs).²³ As all significant episodes of ketosis require hospital admission, we were confident in capturing all of the relevant episodes.

Quantitative psychosocial outcomes

The quantitative psychosocial outcomes are described later (see *Outcomes*).

Sample size

It is generally accepted that a difference of 0.5% (5.5 mmol/mol) in HbA_{1c} is clinically worthwhile. To detect this difference with a standard deviation (SD) of 1% at 80% power and 5% two-sided significance using a *t*-test requires 64 patients per group, for subjects > 7.5% HbA_{1c}. To allow for a clustering effect of the educators, with an average of seven patients per DAFNE group and a within-course intraclass correlation coefficient (ICC) of 0.05, common in diabetes care, the sample size increases to 84. Allowing for a 10% dropout over 24 months, the sample size per group becomes 93. Audit of the DAFNE database showed us that 75% of subjects had a HbA_{1c} of $\geq 7.5\%$, therefore requiring 124 subjects per group and 248 in total. We planned to recruit 280 subjects, which increased the power to 85% but allowed for some variation in dropout rates and the proportion of patients with HbA_{1c} $\geq 7.5\%$. However, monitoring of baseline data showed that the actual proportion of participants with HbA_{1c} $\geq 7.5\%$ was around 90% rather than 75%. A modelling exercise undertaken during recruitment, with conservative estimates of 85% (HbA_{1c} $\geq 7.5\%$) and dropout rate of 15%, suggested that the trial would require at least 240 participants with primary outcome data at 2 years in order to preserve power of at least 85%.²³

Recruitment

A number of methods were used to approach potential participants:

- PIs or educators identified people from DAFNE waiting lists. They then telephoned or wrote to potentially eligible individuals.
- Individuals attending a clinic appointment with a trial PI or educator were offered the option of a future or immediate consultation regarding the trial.
- Clinicians [general practitioner (GP), dietitian, nurse] provided information to patients and referred them to PIs to be screened and enrolled.
- Details of the trial were advertised through the use of posters and leaflets in clinics (diabetes outpatient, dietetic, GP surgery).
- Reception staff in diabetes clinics were informed about the trial and provided with leaflets to give to patients who expressed an interest.
- Participant identification centres were used at some research centres to assist in the identification of suitable participants.

Interested individuals were given the opportunity to discuss the trial with the PI or educator. Those who were still interested in taking part were screened for eligibility. Those who were eligible were either invited to attend a local information meeting, at which the trial was discussed in detail and questions answered, or were provided with a patient information sheet and consent form and given the opportunity to ask further questions. Individuals who were still wanting to take part consented to the trial by one of three methods: (1) by returning a completed consent form (see *Appendix 3*) in the post, (2) by completing the form with the PI or educator or (3) by completing the form at a local information meeting. The participants' contact details, GP details and ethnicity were also collected.

Allocation to Dose Adjustment For Normal Eating courses and randomisation

Following consent, participants were allocated to a REPOSE DAFNE course, depending on the participants' availability.²³ Up to eight participants were allocated to each course, with a minimum of five preferable. Courses were randomised, in pairs, to either DAFNE with pump or DAFNE with MDI.²³ Participant allocation to courses was finalised for each course pair before randomisation took place, no less than 6 weeks prior to the date of the first DAFNE course in that pair. For the first seven centres, a simple randomisation procedure in block size of '2', stratified by centre, was used for courses 1–4. Courses 5 onwards were allocated in pairs using minimisation of the overall and number of participants, with most recent baseline HbA_{1c} value of $\geq 7.5\%$ or $< 7.5\%$ between the treatment groups. Any additional courses were allocated using minimisation. Known dropouts prior to the DAFNE course were excluded from the minimisation algorithm for future course allocation. A validated user-written Stata[®] 13 (StataCorp LP, College Station, TX, USA) code was produced to generate the allocation by a statistician within Sheffield Clinical Trials Research Unit (CTRU), who implemented the randomisation. The trial co-ordinator revealed the allocation to study centres.²³

Blinding of the course allocation was not possible because of the nature of the treatment. Course allocations were revealed to centres 4–6 weeks prior to the date of the first course to allow sufficient preparation time. Participants were informed of the allocation of their DAFNE course no earlier than 4 weeks prior to that course. At this point they were asked to keep a record of any new episodes of moderate hypoglycaemia, which would be collected at the baseline assessment. If the course was a pump course, the participant was booked into a pre-course pump session, up to 3 weeks prior to the course date, in addition to the baseline assessment, which had to take place before the pump session.

If, for any reason, participants were unable to take part in the course at short notice, they could be allocated to a later course date, but only in the same trial arm as in the course to which they were originally allocated. Centres could also keep a list of reserve participants for courses, agreed prior to the time when the course allocation had been revealed to the educators. In the case of participants dropping out, the next person on the reserve list would be invited to participate in that course.

Data collection

Study visits took place at the participants' diabetes centre. A data collection form (DCF) (see *Appendix 4*) was completed by the educator with the participant. Blood and urine samples were taken and analysed at local laboratories. Two blood samples were taken for measurement of the primary outcome (HbA_{1c}). One of these was analysed at a central laboratory as the primary measure and the second was tested at the local laboratory as a back-up. DCF data were entered at local centres on to the in-house Prospect web-based electronic data capture system, managed by the CTRU.

Baseline assessments took place up to 3 weeks prior to the DAFNE course. The educator completed the DCF with the participant and handed him/her the self-complete psychosocial questionnaire, asking for return of the completed questionnaire at the forthcoming DAFNE course. Additional demographic data collected at baseline were date of birth, sex, qualifications (highest qualification obtained) and current occupation. Participants were also handed a SAE contact card to aid in contacting their diabetes centre in the event of an AE.

At the DAFNE course, an attendance form was completed, detailing any missed sessions. The completed baseline psychosocial questionnaire was collected and the baseline DCF moderate hypoglycaemic episodes section was updated so that a full 4 weeks of hypoglycaemic episodes were recorded. At all time points, psychosocial questionnaires were posted from centres to Sheffield CTRU and entered on to Prospect by Sheffield CTRU clerical staff.

Participants were followed up at 6, 12 and 24 months after the DAFNE course. Participants were sent the blood glucose diary (see *Appendix 5*) and instructions for recording moderate hypoglycaemic episodes 4 weeks prior to each visit. Additionally, participants were posted the self-complete psychosocial questionnaire pack prior to the visit and asked to bring their completed questionnaire to the appointment, along with the blood glucose diary and record of moderate hypoglycaemic episodes.

Severe hypoglycaemic episodes or SAEs were collected from participants if reported over the telephone or in clinic. Any additional diabetes-related contacts (DRCs) were also recorded (see *Appendix 6* for ongoing data collection booklet).

Blinding of outcome measures was considered impractical because of the intervention-specific nature of outcome measures and the necessity of a local diabetes nurse to collect the data. However, use of an objective outcome (HbA_{1c}) measured in a central laboratory will have minimised bias on the primary end point.

Trial completion

Participants were deemed to have completed the study if they had trial data recorded at baseline and 24 months. Participants were withdrawn from the study if:

- The participant asked to fully withdraw from the trial. On requesting withdrawal from the trial, participants were able to consent to continue to have their routine HbA_{1c} results recorded.
- The participant died.

Participants who were changing treatment continued in the trial unless formally withdrawn. Participants were deemed lost to follow-up if they failed to attend the baseline visit, DAFNE course or 24-month follow-up.

Research governance

The trial sponsor was Sheffield Teaching Hospitals NHS Foundation Trust. The trial was conducted in accordance with Good Clinical Practice (GCP) and the Medicines for Human Use (Clinical Trials) Regulations 2004.⁹² All staff recruiting participants to the trial had undertaken GCP training. In line with the three-level categorisation of clinical trial risk in the Medical Research Council/Department of Health

(DH)/MHRA report on risk-adapted approaches to the management of clinical trials of investigational medicinal products⁹³ (based on the classification by Brosteanu *et al.*⁹⁴), the REPOSE Trial was classified as a Type A study: no higher than the risk of standard medical care. The trial treatment in REPOSE was licensed and administered according to its market authorisation. Trial-specific labelling was not used. Given the lack of criticality of the investigational medicinal product (IMP) with the data analysis and trial results, and the design of the trial being equivalent to standard care, there was no IMP tracking and accountability undertaken.

Three committees were established to govern the conduct of the study: an independent Trial Steering Committee (TSC), an independent Data Monitoring and Ethics Committee (DMEC) and a TMG. Full membership of the TSC and DMEC are listed at the end of this report. The committees functioned in accordance with Sheffield CTRU standard operating procedures (SOPs). The TSC was responsible for overall supervision and monitoring of the trial; it considered any recommendations from the DMEC and provided advice on any actions to be taken. The DMEC operated within a charter agreed by all members and was responsible for monitoring efficacy and safety data. Any concerns were reported to the TSC with recommendations. The TMG was responsible for supporting the implementation of the trial.

Reporting of adverse events

Adverse events were defined as any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences that are not necessarily caused by or related to that product. SAEs were defined as any AE that results in death; is life-threatening (subject at immediate risk of death); requires inpatient hospitalisation or prolonging existing hospitalisation; results in persistent or significant disability or incapacity, or consists of congenital anomaly or birth defect; or is another important medical event that may jeopardise the participant. Pregnancy was also recorded as a SAE, so that any AEs could be identified if and when the child was born.

Included as AEs were an increase in frequency of hypoglycaemia, a blood glucose reading > 30 mmol/l, unexplained constantly raised blood glucose readings, suspicion of pump malfunction and pump site infection. Excluded as AEs were non-serious episodes of hypoglycaemia and ketonuria.

Details of AEs were collected during follow-up appointments. Participants were also provided with a contact card and encouraged to get in touch with their diabetes team if they had experienced any adverse health events. SAEs were reported in accordance with the Sheffield CTRU and REPOSE SAE SOPs. SAEs were assessed by the local PI and reported to Sheffield CTRU within 24 hours of becoming aware of the event, with the exception of events that had been stated as exempt from immediate reporting, for which 28 days was 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, when applicable, relationship to pump. The Summary of Product Characteristics for NovoRapid and Levemir (Novo Nordisk, Gatwick, UK) were kept on file as the reference safety information for the assessment of events. AEs were reviewed at regular intervals by the three study oversight committees. The chief investigator and DMEC chairperson were notified of all SAEs on the event being reported.

Reporting of protocol non-compliances

Protocol non-compliances were reported and assessed in accordance with the Sheffield CTRU and REPOSE non-compliances SOPs. A non-compliance was defined as 'a departure from the protocol or GCP that has been identified retrospectively'. Non-compliances were addressed with staff training or, when appropriate, an amendment to the protocol. In line with MHRA guidance, deliberate prospective protocol non-compliances or 'waivers' were deemed to be unacceptable. A prospective list of exemptions from reporting and of pre-specified major and minor non-compliances was drawn up by the CTRU, the chief investigator and the sponsor.

Trial monitoring

Responsibility for monitoring was delegated to the CTRU and conducted in accordance with CTRU SOPs. Both on-site and central monitoring methods were adopted. Onsite monitoring visits took place at all centres at study set-up, prior to delivery of the first DAFNE course, post delivery of DAFNE course 2 and at study closeout. A further monitoring visit took place during follow-up at seven centres. At each visit, the study site file and key essential logs were reviewed for completeness. Source data verification was conducted for 100% of consent and SAE forms. Patient hospital records were reviewed to substantiate participant existence and eligibility (for which criteria were verifiable from hospital records). Monitoring reports were issued after each visit detailing any remedial actions required. Central monitoring tasks included point of entry validation, verification of data and post-entry validation checks. One participant per DAFNE course per centre was randomly selected for verification. Case report forms at all data collection time points were reviewed for completeness and quality, and verified to monitor data entry. Source data verification also took place for 100% of central laboratory HbA_{1c} results. Feedback on verification was provided and additional verification was undertaken when concerns were identified.

Statistical methods

All statistical analyses were performed in Stata 13 onwards. The MDI is the reference group for all treatment comparisons.

Analysis populations

The intention-to-treat (ITT) data set includes all participants who were randomised according to randomised treatment assignments (ignoring any occurrences post randomisation, such as protocol or treatment non-compliance and withdrawals) with at least one HbA_{1c} assessment measure after baseline. Sensitivity analysis of the ITT primary outcome set was performed using six additional analysis sets, as described later in this section.

The per-protocol group is a subset of the ITT group who complied with the protocol. Protocol compliance was defined as adhering to both the DAFNE course and to pump/MDI. Compliance was reviewed and assessed on a case-by-case basis with the following general considerations applied:

- 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 he/she adhered to the pump/MDI for the full 2 years (excluding any reasonable temporary interruptions of around 2 weeks).

A review group (SH and JE), 'blinded' to patient outcome data, convened to decide any contentious cases for treatment interruptions with the help of the trial statistician (EL).

The complete-case group is a subset of the ITT group who had outcome measurements at a specific follow-up time.

An additional four analysis sets were performed to examine the sensitivity of primary results to multiple imputation and exclusions, as described later in this section.

Data completeness

A CONSORT (Consolidated Standards Of Reporting Trials) flow diagram was used to display data completeness and patient throughput from first contact to final follow-up.

Baseline characteristics

The baseline participant characteristics, diabetes history and laboratory tests were summarised and assessed for comparability between the intervention and control group. No statistical significance testing was carried out to test baseline imbalances between the arms, but any noted differences are reported descriptively.

Primary effectiveness analysis

The primary end point for this study is the change in HbA_{1c} after 2 years in participants whose baseline HbA_{1c} was $\geq 7.5\%$ (58 mmol/mol). The mean change in HbA_{1c} at 24 months post DAFNE course was compared between participants allocated to pump and participants allocated to MDI using a mixed-effects model. The model was adjusted for clustering by DAFNE course (random effects), centre and baseline HbA_{1c} as a continuous covariate (fixed effects).

The mean (SD) HbA_{1c} change from baseline for the pump and MDI groups, and the number in each group, are displayed. The efficacy of the intervention is reported as mean difference (MD) in HbA_{1c} change at 2 years, with its associated 95% CI and *p*-value, adjusted for the factors stated above.

Multiple imputation of missing data

Multiple imputation was used to impute missing data on the primary outcome in order to fulfil the ITT principle and for sensitivity analysis. Multiple imputation was used to impute 24-month HbA_{1c} data for patients with at least one assessment after randomisation (i.e. at 6 or 12 months), but without 24-month primary outcome data. Participants' baseline characteristics were summarised and compared between completers and non-completers. Data were imputed using chained equations (regression) with 50 imputations using baseline, 6- and 12-month HbA_{1c} measurements, DAFNE course, centre, age, sex and HFS behaviour as covariates in the imputation equation. Initially, 10 imputation replicates were planned; however, this was increased to 50 in order to produce a stable and reliable estimate of variability.

The following sensitivity analyses were undertaken on the primary outcome and displayed alongside the ITT results:

1. per-protocol cases (subset of ITT who did not deviate from the protocol)
2. complete cases (subset of ITT including only participants with complete HbA_{1c} data at 24 months)
3. multiple imputation of all missing cases (including those without any follow-up data who are excluded from the ITT analysis)
4. horizontal mean value imputation of all missing cases
5. excluding participants who withdrew from the study because of pregnancy
6. excluding participants with measurements outside a time window of 6 weeks before and after the 24-month follow-up.

A sensitivity analysis on the primary outcome – adjusted for duration of diabetes, number of moderate hypoglycaemic episodes and number of severe hypoglycaemic episodes – was to be performed if notable baseline imbalances were observed; however, none was observed.

An exploratory analysis (on available data) to assess whether or not there were differences in primary outcome between DAFNE lead course educators was conducted using a multilevel model with three levels – patients nested in DAFNE course, which, in turn, are nested within the course lead. Baseline HbA_{1c}, treatment group and centre were treated as fixed effects in the model. The ICCs from this model are presented.

The effect of centre was explored using a mixed-effects regression model. The primary outcome was regressed against treatment, centre (fixed effects) and an interaction term between treatment and centre, and it was also adjusted for course (random effects). The *p*-value for the interaction between treatment and centre is presented. The MDs between treatment groups with associated 95% CIs, estimated from the mixed-effects model, are presented by centre with the aid of forest plots.

Key secondary effectiveness analysis

The key secondary end point is the proportion of patients reaching the NICE target of a HbA_{1c} level of $\leq 7.5\%$ (58 mmol/mol) at 2 years (including all participants regardless of baseline HbA_{1c} value). The treatment effect was investigated using a mixed-effects logistic regression model adjusted for baseline

HbA_{1c}, centre (fixed effect), and a random effect around DAFNE course. The proportion of patients with HbA_{1c} of $\leq 7.5\%$ is presented by treatment group alongside the odds ratio (OR) of HbA_{1c} $\leq 7.5\%$ on pump compared with HbA_{1c} $\leq 7.5\%$ on MDI and its associated 95% CI and *p*-value.

Secondary effectiveness analysis

Glycated haemoglobin at 6 and 12 months

Secondary analyses on the primary outcome and key secondary outcome were repeated for HbA_{1c} at 6 and 12 months to explore the short- and medium-term effects of the intervention:

- the change in HbA_{1c} at 6 and 12 months in participants whose baseline HbA_{1c} was $\geq 7.5\%$ (58 mmol/mol)
- the proportion of participants reaching the NICE target of HbA_{1c} level of $\leq 7.5\%$ (58 mmol/mol) at 6 and 12 months.

These outcomes were analysed using statistical models as for the primary and key secondary outcome.

Episodes of severe and moderate hypoglycaemia

The number of episodes of moderate hypoglycaemia reported in the 4-week period prior to the 6-, 12- and 24-month visits were compared between treatment groups using a mixed-effects negative binomial linear regression model, with centre and baseline continuous HbA_{1c} included as fixed effects and course as a random effect. The occurrence of at least one moderate hypoglycaemic episode in the 4 weeks prior to starting the DAFNE course was also included as a covariate.

Each episode of moderate hypoglycaemia was classed as 'confirmed' or 'unconfirmed' by an educator and the blood glucose level was recorded by the participant. The following outcomes were analysed:

1. all recorded episodes
2. confirmed episodes, defined as episodes that were confirmed and for which the blood glucose level (if recorded) was < 3.5 mmol/l
3. confirmed episodes (US definition), defined as episodes that were both confirmed and for which the blood glucose level (if recorded) was < 4 mmol/l.

Severe hypoglycaemic episodes were collected on an ongoing basis. The number of episodes recorded post baseline was analysed in a similar manner to moderate hypoglycaemic episodes, but with the addition of study follow-up time as the exposure. A sensitivity analysis was conducted in the same manner by excluding the first 6 months of data in order to explore any effect of a 'settling in' period on the pump.

The incidence rates of moderate hypoglycaemic episodes in the 4 weeks before each time point are displayed by treatment group, and the treatment effect is reported as an adjusted incidence rate ratio (IRR) with its associated 95% CI and *p*-value. The incidence rates of severe hypoglycaemic episodes over the study duration are displayed as episodes per patient-year and are reported alongside the IRR, its associated 95% CI and *p*-value.

The overall change in the rate of episodes of severe hypoglycaemia was estimated for the treatment groups combined using a mixed-effects negative binomial linear regression model. The numbers of episodes were compared pre and post baseline, using participant as the random effect, adjusted for treatment, time by treatment interaction, baseline HbA_{1c} and centre. Length of follow-up was included as the exposure variable. Length of follow-up before baseline was set at 365 days, as participants recorded a 12-month history of severe hypoglycaemic episodes at baseline.

The proportions of participants who experienced at least one moderate hypoglycaemic episode at 6, 12 and 24 months were compared between treatment groups using a mixed-effects logistic regression model adjusted for DAFNE course (random effect), centre, presence of at least one episode before baseline and

baseline HbA_{1c} (fixed effects). The proportion of patients who experienced at least one episode of severe hypoglycaemia during the study period was compared between groups using a mixed-effects logistic regression adjusted for DAFNE course, centre and baseline HbA_{1c}. Presence of at least one severe episode before baseline was not used as a covariate in the logistic regression model as all participants with at least one episode before baseline experienced at least one episode post baseline. The proportion of patients reporting hypoglycaemic episodes is presented by treatment group alongside the adjusted OR and its associated 95% CI and *p*-value.

Insulin dose, body weight and lipids

Insulin dose was calculated as:

$$\text{Insulin dose (pump)} = \frac{24\text{-hour basal dose} + \text{typical daily bolus total}}{\text{body weight (kg)}};$$

$$\text{Insulin dose (MDI)} = \frac{\text{typical daily dose of background insulin} + \text{typical daily dose of quick-acting insulin}}{\text{body weight (kg)}}.$$
(1)

In the calculation of insulin dose, weight was taken as the value on the same visit the dose was recorded. If weight was not recorded, it was estimated from other study visits as follows:

- If 24-month weight was missing, 12-month weight was used.
- If 12-month weight was missing, it was imputed as the time-weighted average of 6- and 24-month weight or as 6- or 24-month weight if only one observation was available.
- If 6-month weight was missing, it was imputed as the average of baseline and 12-month data, or imputed as baseline or 12-month data if only one observation was available.
- In all other situations the missing data were left blank.

The analysis of weight was based on available data only.

The mean change from baseline in insulin dose, weight, TC and 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 HbA_{1c} (fixed effects). The MD between the groups in change from baseline is displayed with its associated 95% CI and *p*-value.

Proteinuria

Proteinuria was defined from the ACR at each visit. At each visit a patient was defined as:

- macroalbuminuria – if ACR ≥ 30
- microalbuminuria – if 3 ≤ ACR < 30
- normal – if ACR < 3.

If ACR was missing at a time point, proteinuria status was imputed, based on data from recorded conditions at the same time point.

Proteinuria was analysed using mixed-effects ordered logistic regression adjusted for clustering by DAFNE course (random effect), centre and baseline HbA_{1c} (fixed effects). The OR of being in a higher category (for which macroalbuminuria is the highest category) compared with a lower category is displayed with its associated 95% CI and *p*-value.

Blood glucose testing

The self-reported number of blood glucose tests performed in the 2 weeks prior to 24-month follow-up was compared between treatment groups, in a post hoc analysis, using a mixed-effects model adjusted for

clustering by DAFNE course (random effect), centre and baseline number of blood glucose tests (fixed effects). For both treatment groups combined, the change in the number of tests performed at 24 months compared with baseline was analysed using a paired *t*-test. Blood glucose testing is presented as number of tests per day, taken as an average over the 2 weeks reported.

Psychosocial questionnaires

Methods for the analysis of questionnaire data are described later (see *Methods for the psychosocial evaluation*).

Subgroup analysis

Pre-planned subgroup analyses were undertaken and regarded as exploratory; significant results from the analysis were interpreted with caution, as recommended for subgroup analyses.⁹⁵ The following subgroups were investigated:

- baseline HbA_{1c} (< 7.5% or 58 mmol/mol, ≥ 7.5% to < 8.5% or 69 mmol/mol, ≥ 8.5%)
- duration of diabetes (< 15 years, ≥ 15 years)
- symptoms of hypoglycaemia (do not feel symptoms or < 3 mmol/l, ≥ 3 mmol/l)
- self-reported use of the bolus advisor over the study duration (never or rarely, sometimes, often or always)
- age (< 35, 35–49, ≥ 50 years)
- sex
- body mass index (BMI) (normal, < 25 kg/m²; overweight, 25–29.9 kg/m²; obese, ≥ 30 kg/m²)
- level of education [up to Advanced level (A-level) equivalent, vocational/beyond A-level]
- occupational status (Office for National Statistics levels 1–4)
- socioeconomic status as defined by the Office for National Statistics Index of Multiple Deprivation (above/below median in England, and above/below median in Scotland)
- insulin dose at start of therapy (< 0.7 or ≥ 0.7 IU/weight)
- frequency of moderate hypoglycaemic episodes within the 4 weeks prior to baseline (none, 1, 2 or 3, 4–9, 10+)
- experience of lead DAFNE course educator {'less experienced' [six courses or fewer within previous 3 years or completed the DAFNE Educator Programme (DEP) within previous year] vs. 'higher-level experience [seven or more courses within previous 3 years or had continuous 'educator' status for > 6 years]}.

The subgroup analysis used mixed-effects linear regression modelling with the primary outcome, change in HbA_{1c} (%), as the response. The model included main effects of the treatment group and subgroup, an interaction term between treatment and subgroup, and covariates of centre (fixed effect) and DAFNE course (random effect). Treatment effect estimates and 95% CIs are presented within each subgroup category. We used a statistical test for interaction between the randomised intervention group and the subgroup to examine the evidence for treatment effect varying between subgroup; the *p*-value for this interaction is reported unadjusted for multiple testing. Subgroup analyses were also summarised visually using forest plots.

Safety and harms analysis

Serious adverse events and AEs were summarised and assessed for similarity between the treatment groups. Both SAEs and AEs are reported on an ITT basis (i.e. according to the group to which the participants was randomised), but the number occurring following a treatment switch are highlighted.

Patient and public involvement

As part of our recent work funded by a NIHR programme grant (PGfAR),²⁷ 15 DAFNE graduates were recruited to act as a 'user group' and contribute to different aspects of the work. We invited two members

to join both the steering group and other investigator meetings. In addition, one of the project team is a pump user. They provided input to the trial design, implementation and dissemination, including all participant materials.²³ The work supported by the programme grant included qualitative studies in which the barriers to self-management in T1DM were explored. This work led to the development of a pilot study within the PGfAR work, in which a modified DAFNE course incorporating a pump curriculum was developed and piloted in three centres.

Methods of the fidelity assessment

Aim

To ensure that there was consistency in:

1. the delivery of the 5-day DAFNE pump curriculum
2. the timing and content of pump pre-assessment/setting up on pump session.

Multiple daily injection courses were not included in the FT, as there exists a rigorous quality assurance programme of MDI courses in standard care, and trial centres are routinely audited.

Methods

An experienced DAFNE educator and peer reviewer from Sheffield Teaching Hospitals NHS Foundation Trust was employed as the fidelity assessor (FA); this educator was not directly involved in the delivery of REPOSE courses. The FA assessed whether or not the pump courses delivered the correct DAFNE content and philosophy. The FA visited each centre to observe the 'Wednesday' of the pump DAFNE course. Wednesday was chosen as pump curriculum sessions that incorporated key differences to MDI would be delivered by DAFNE educators from both dietetic and nursing specialties. In addition, patients on the course should have settled into the course, be more relaxed and be starting to establish patterns and adjustments to their regimen by the third day. It was planned that the FT take place on the first or second pump course at each centre.

Experienced educators who devised the pump curriculum and the national director of the DAFNE programme discussed which sessions differed most between the pump and MDI DAFNE curricula and, thus, warranted observation. These sessions were decided as follows:

- daily goals, blood glucose results and insulin doses
- insulin dose adjustment theory, basal rate testing
- dose adjustment practice – reducing and increasing insulin
- setting up Bolus Wizard
- sick day rules
- alcohol
- exercise.

All but one session was scheduled for observation on the FT visit, as it was not possible to timetable all sessions that differed between the MDI and pump courses on 1 day. In lieu of observation, the FA reviewed the lesson plan for the sick day rules session.

The following data and documents were requested to be made available for the FT visit:

- pre-course pump session details including patient attendance, session timings and lesson plan
- pump course timetable
- list of course participants and details
- lesson plan for all observed sessions and the sick day rules lesson plan.

A DEP peer support learning outcomes form was completed for each session observed. This form listed the essential learning outcomes for each session and the FA evaluated whether or not these were met (or partially met). For each learning outcome, the FA provided evidence for its achievement. A template report was devised and used to collate the data collected from the FT visit.

Once the FA had completed the assessment, feedback was given immediately so that educators could resolve any problems. The report was completed within 3 days of the visit and sent to the trial management office.

Methods for the economic evaluation

Setting and perspective

The health economic analyses are designed to inform UK decision-makers within the UK NHS on the potential resource implications of choosing to use pump therapy with DAFNE structured education (pump + DAFNE) or MDI with DAFNE structured education (MDI + DAFNE) for the group of adults with T1DM in the REPOSE Trial, comprising adults with T1DM who are naive to pump therapy.

To ensure that all economic analyses were applicable to the UK decision-making setting, all economic analyses took the NHS and Personal Social Services perspective in line with (NICE) guidance.²²

Two approaches: economic evaluation alongside the clinical trial and long-term cost-effectiveness modelling

The cost-effectiveness of 'pump + DAFNE' compared with 'MDI + DAFNE' was assessed using an Economic Evaluation Alongside Clinical Trials (EEACT) and long-term modelling exercise. The EEACT took a 2-year time horizon and the long-term modelling took a lifetime horizon. As the long-term modelling takes a lifetime time horizon, and includes all clinically important complications of diabetes, this should be considered as the primary analysis.

Price year and discounting

All costs are reported in 2013–14 prices; if costs were obtained from a previous financial year they were inflated to 2013–14 prices using the Hospital and Community Health Services Pay and Prices index.⁹⁶ All costs and QALYs were discounted at a rate of 3.5% in line with NICE guidance.²² All costs and QALYs were assumed to fall at the end of the year, apart from the cost of the structured education courses, which were assumed to occur at the start of the first year.

Population and subgroups for analysis

The individuals in the REPOSE Trial were adults with T1DM who were eligible to receive a structured education course. Furthermore, all individuals were naive to insulin pump therapy and did not have a preference to receive the pump. The average age of participants was 40.4 years and their mean duration of their diabetes was 18.0 years. Data were collected from individuals at baseline and at 6 months, 1 and 2 years post randomisation. In the MDI + DAFNE arm, 6, 3 and 5 individuals out of 135 were lost to follow-up at 6 months, 1 and 2 years, respectively. A further individual in the MDI + DAFNE arm withdrew from the trial at 6 months. In the pump + DAFNE arm, 0, 1 and 2 individuals out of 132 were lost to follow-up at 6 months, 1 and 2 years, respectively. A further individual in the pump + DAFNE arm withdrew from the trial at 1 year.

The data collected in the REPOSE Trial were considered to be the only relevant evidence on the relative effectiveness of pump + DAFNE compared with MDI + DAFNE. This is because REPOSE is the only large study in a UK setting in which adults with T1DM in both trial arms have received equivalent diabetes education in both the pump and MDI trial arms.

There are two populations in the REPOSE Trial: (1) the ITT population and (2) the per-protocol population. The ITT population includes all individuals who graduated their DAFNE course and had follow-up data for at least one data collection period. In the ITT population, individuals were assigned to their randomised treatment irrespective of whether or not they switched to the other insulin delivery mechanism. The per-protocol population includes all of the individuals who were in the ITT population and adhered to their insulin delivery mechanism (either pump or MDI). Unless otherwise stated, all analyses of the REPOSE Trial data to inform the health economic analyses were conducted in the ITT population.

The population analysed in the primary health economic analyses is all individuals in the REPOSE Trial, regardless of whether or not the individual's baseline HbA_{1c} was ≥ 58 mmol/mol (7.5%). The analysis population differs from the population used in the primary clinical end point statistical analysis, as the base-case health economic analysis focuses on the whole trial population rather than those individuals with a HbA_{1c} of < 58 mmol/mol (7.5%). For the health economic analyses, it is important to assess the cost-effectiveness of pump + DAFNE compared with MDI + DAFNE for all adults with T1DM who would be potentially eligible to receive either treatment if they were adopted as standard practice.

Subgroup analyses 1–6 were conducted in the long-term modelling only, because of concerns about the reduction in sample size potentially producing spurious results in the EEACT. However, subgroup analysis 7 was conducted in the EEACT, as this was an important subgroup analysis for the estimation of treatment effect of HbA_{1c} (see *Statistical methods*). The subgroup analyses were conducted in following subgroups of the REPOSE Trial participants:

1. baseline HbA_{1c} ≥ 58 mmol/mol (7.5%)
2. baseline HbA_{1c} ≥ 58 mmol/mol (7.5%) and < 69 mmol/mol (8.5%)
3. baseline HbA_{1c} ≥ 69 mmol/mol (8.5%) and < 80 mmol/mol (9.5%)
4. baseline HbA_{1c} ≥ 80 mmol/mol (9.5%)
5. baseline HbA_{1c} < 69 mmol/mol (8.5%)
6. baseline HbA_{1c} ≥ 69 mmol/mol (8.5%)
7. all individuals in the per-protocol population.

Cost of the Dose Adjustment For Normal Eating course

A detailed within-trial costing of the DAFNE courses was not undertaken because DAFNE is an already established intervention within the NHS. The cost of DAFNE training for adults with T1DM using MDI has been calculated by DAFNE UK as being £359.10 per course attendee in 2012–13 prices (£363.10 in 2013–14 prices).⁹⁷

Based on discussion with experts involved in the REPOSE Trial, including a Professor of Clinical Diabetes and Honorary Consultant Physician, and a Professor in Public Health and Health Technology Assessment, it was assumed that the cost of a DAFNE course in the pump + DAFNE arm is identical to the cost of a DAFNE course in the MDI + DAFNE arm, except for the cost of staff time spent conducting an additional pre-course pump-fitting session.

Data were collected on the time spent delivering a pre-course fitting session for pump + DAFNE participants in the FT process. The FT process was conducted for one pump + DAFNE course at each trial centre to ensure that the pump + DAFNE course taught the principles of insulin adjustment in a similar fashion to the MDI + DAFNE course. These data were utilised to estimate the additional cost of the pre-course pump fitting session in the pump + DAFNE arm. Expert advice was sought from two centres in which it was unclear whether reported time use as part of the FT referred to the educator time spent or the total time individuals spent at the venue (which could include non-contact waiting time). To ensure consistency between the estimated costs of a MDI + DAFNE course and a pump + DAFNE course, the cost of staff time was obtained from the estimated cost of staff time for the MDI + DAFNE course. The cost of the pre-course fitting session was estimated to be £28.82 per adult with T1DM.

Economic analysis alongside the clinical trial of pump + Dose Adjustment For Normal Eating versus multiple daily injection + Dose Adjustment For Normal Eating

Resource use by individuals in the REPOSE Trial over the 2-year follow-up period

Resource use was collected either on an ongoing basis or was self-reported by the individuals in the trial at baseline or at a follow-up period (6 months, 1 and 2 years post randomisation). All unit costs used to value the reported resource use in the EEACT, apart from the costs associated with insulin use, are presented later (see *Table 3*). The unit costs associated with insulin use are reported separately later (see *Table 4*).

Diabetes-related contacts were collected using two methods in the REPOSE Trial. Patient's self-reported number and type (either face to face or not face to face) of diabetes-related contacts since the last REPOSE visit (or in the year prior to baseline) were collected in each of the REPOSE DCFs (baseline, 6, 12 and 24 months). Ongoing information was collected from the sites on the number of visits, the type of visit and the time spent at each visit. The self-reported contacts were used in the health economic analysis for two reasons: (1) this method was consistent with the method used to collect information on the baseline number of contacts; and (2) national-level commissioning information provides only a cost per outpatient appointment (rather than for a specified time for a specific health-care professional to conduct an appointment), so from a costing perspective it is the number of contacts that is important rather than the time spent at each contact.

Table 2 shows that numbers of diabetes-related contacts were higher in the CSII + DAFNE arm of the REPOSE Trial than the MDI + DAFNE arm in the first year of the trial. However, most of these differences disappear in the second year of the trial. It should also be noted that the average time spent delivering diabetes-related contacts is higher for pump + DAFNE individuals than MDI + DAFNE individuals, except for telephone contacts delivered between 12 and 24 months post randomisation. This indicates that there are important differences in the number and time spent at diabetes-related contacts for MDI and pump users in the NHS.

The unit costs used to estimate the total cost diabetes-related contacts are presented in *Table 3*.

The individual's self-reported resource use was collected on whether they were using lipid-lowering, antiplatelet or depression medication at the time of each REPOSE visit. No information was collected on the type of drug or the quantity used. It was assumed that, if an individual reported use of medication received medication, they had been receiving that specific medication since the last REPOSE visit. The average quarterly cost of each type of medication is reported in *Table 3*.

Data were collected on an ongoing basis for all inpatient hospitalisations that were not scheduled to treat a pre-existing condition. Therefore, the only missing data were for individuals who were lost to follow-up or withdrew from the trial. At each admission, information was collected on the cause. The possible causes for each admission were DKA, myocardial infarction (MI), severe hypoglycaemia, ischaemic heart disease, unstable angina, heart failure (HF), foot ulcer and renal disease. If the admission was not due to one of these causes, the reason was recorded. This occurred for only one inpatient admission in the REPOSE Trial. The *NHS Reference Costs 2013–14*⁹⁸ (and all previous years used to inform the unit costs) present the cost of non-elective inpatient stays as short stays, excess bed-days and long stays. The cost of inpatient stays were estimated as the cost of a short stay if the length of stay was ≤ 1 day. If the length of stay was ≥ 2 days then the cost of the visit was estimated using the following formula:

$$\begin{aligned} \text{Cost of stay} = & \text{cost of an inpatient short stay} + \text{cost of an inpatient excess bed-day} & (2) \\ & \times (\text{number of days in hospital} - 1). \end{aligned}$$

TABLE 2 Differences in the number of diabetes-related contacts in the MDI + DAFNE and pump + DAFNE arms of the REPOSE Trial

Diabetes-related contacts		Year prior to baseline		Months post randomisation					
				0–6		6–12		12–24	
		Face to face	Not face to face	Face to face	Not face to face	Face to face	Not face to face	Face to face	Not face to face
MDI + DAFNE									
Ongoing data collection (n = 95)	<i>n</i> , mean (SD)	–	–	0.432 (1.048)	0.474 (1.590)	0.621 (0.947)	0.516 (2.178)	1.295 (2.539)	1.263 (5.260)
	Time (minutes), mean (SD)	–	–	16.47 (52.89)	5.47 (23.90)	26.17 (44.23)	7.68 (48.05)	46.58 (90.73)	13.32 (53.99)
Self-reported (n = 128)	<i>n</i> , mean (SD)	4.125 (7.374)	1.242 (3.089)	1.531 (2.159)	0.477 (2.230)	1.156 (1.492)	0.336 (1.642)	2.875 (4.719)	1.094 (3.852)
Pump + DAFNE									
Ongoing data collection (n = 118)	<i>n</i> , mean (SD)	–	–	0.814 (1.402)	1.220 (1.913)	0.924 (1.334)	0.788 (2.095)	1.576 (2.878)	0.703 (1.458)
	Time (minutes), mean (SD)	–	–	39.03 (76.63)	15.89 (28.24)	37.37 (68.36)	10.26 (28.66)	60.13 (155.82)	9.32 (21.22)
Self-reported (n = 132)	<i>n</i> , mean (SD)	4.197 (6.211)	2.167 (4.489)	1.795 (2.436)	1.076 (2.092)	1.242 (1.564)	0.962 (2.813)	2.787 (4.199)	0.576 (1.393)

At baseline, self-reported data were collected on the number of diabetes-related admissions in the past year, days spent in hospital and the reason for admission. The possible causes included DKA, hypoglycaemia, MI, ischaemic heart disease, unstable angina, HF, foot ulcer and renal disease. It was possible that individuals had missing information on the number of days that they were in hospital or the reason for the admission. Mean value imputation was used to impute the number of missing days. All of the admissions for which the reason was missing were treated as an 'other cause inpatient stay'.

Data were also collected on an ongoing basis for individual's severe hypoglycaemic events. Severe hypoglycaemia was defined in the REPOSE Trial as been any hypoglycaemic episode that an individual was unable to treat themselves. Information was collected on whether each severe hypoglycaemic event required either a paramedic call-out and/or an inpatient admission. If it was reported that an individual did not have an inpatient admission or a paramedic call-out then it was assumed that a friend or family member provided aid to the individual, which meant that no admission or paramedic call-out was required. This had no implications for NHS resource use, so these episodes of severe hypoglycaemia were assumed to have no monetary cost to the NHS in the EEACTION. The unit costs for a paramedic call-out or an inpatient admission for severe hypoglycaemia are presented in *Table 3*.

Information was collected for all individuals in the REPOSE Trial (at baseline, 6, 12 and 24 months post randomisation) on their current insulin regimen (including type of insulin used), the typical daily insulin dose in the week preceding data collection, the number of injections per day, the type of insulin used by the individual and the method of insulin delivery. As information on insulin type was available, the cost of insulin and insulin pens was estimated separately for each insulin type.

The unit costs associated with insulin use are presented separately from the rest of the unit costs in *Table 4*. The daily cost of insulin was multiplied by the number of days between each data collection period (6 months,

TABLE 3 Unit costs used in the within-trial analysis of the REPOSE data

Costs used in the within-trial analyses	Cost (2013–14, £)	Notes
DAFNE courses		
Cost of a DAFNE course	363.10	DAFNE fact sheet 6 ⁹⁷
Cost of a pre-course pump fitting session	28.82	REPOSE Trial data and DAFNE fact sheet 6 ⁹⁷
Hypoglycaemia		
Cost of hypoglycaemia admission	446.73	<i>NHS Reference Costs 2013–14</i> . ⁹⁸ Non-elective inpatient short stay. FCE weighted average of the currency codes: KB01C, KB01D, KB01E, KB01F, KB02G, KB02H, KB02J, KB02K
Paramedic cost per case	233.58	Elliot <i>et al.</i> 2014, ⁹⁹ table 5
Cost of inpatient admissions		
DKA		
Cost of the first day	527.78	<i>NHS Reference Costs 2012–13</i> . ¹⁰⁰ Non-elective inpatient short stay. Currency code PA67Z
Cost of subsequent days	284.42	<i>NHS Reference Costs 2012–13</i> . ¹⁰⁰ Non-elective inpatients excess bed-days. Currency code PA67Z
Renal hospitalisation		
Cost of the first day	471.70	<i>NHS Reference Costs 2013–14</i> . ⁹⁸ Non-elective inpatients short stay. Weighted average of the currency codes: LA09J, LA09K, LA09L, LA09M, LA09N, LA09P, LA09Q
Cost of subsequent days	257.87	<i>NHS Reference Costs 2013–14</i> . ⁹⁸ Non-elective inpatients excess bed-days. Currency codes: LA09J, LA09K, LA09L, LA09M, LA09N, LA09P, LA09Q
MI		
Cost of the first day	560.60	<i>NHS Reference Costs 2013–14</i> . ⁹⁸ Non-elective inpatients short stay. Weighted average of the currency codes: EB10A, EB10B, EB10C, EB10D, EB10E
Cost of subsequent days	248.89	<i>NHS Reference Costs 2013–14</i> . ⁹⁸ Non-elective inpatients excess bed-days. Currency codes: EB10A, EB10B, EB10C, EB10D, EB10E
Foot ulcer		
Cost of the first day	509.39	<i>NHS Reference Costs 2012–13</i> . ¹⁰⁰ Non-elective inpatient short stay. Currency codes: KB03C, KB03D, KB03E
Cost of subsequent days	156.34	<i>NHS Reference Costs 2012–13</i> . ¹⁰⁰ Non-elective inpatient short stay day. Currency codes: KB03C, KB03D, KB03E
Other inpatient stays		
Cost of the first day	755.44	<i>NHS Reference Costs 2012–13</i> . ¹⁰⁰ Non-elective inpatient short stay. Currency code PA68Z
Cost of subsequent days	335.81	<i>NHS Reference Costs 2012–13</i> . ¹⁰⁰ Non-elective inpatient excess bed-day. Currency code PA68Z
Medication costs (per quarter)		
Cost of lipid medication	9.27	Prescription Cost Analysis: England 2011 (BNF, ¹⁰¹ chapter 2, section 12)
Cost of antiplatelet medication	1.87	Prescription Cost Analysis: England 2011 (BNF, ¹⁰¹ chapter 2, section 9)
Cost of depression medication	6.08	Prescription Cost Analysis: England 2011 (BNF, ¹⁰¹ chapter 4, section 3)

TABLE 3 Unit costs used in the within-trial analysis of the REPOSE data (*continued*)

Costs used in the within-trial analyses	Cost (2013–14, £)	Notes
Cost of diabetes-related contacts		
Cost of a face-to-face clinic	105.49	<i>NHS Reference Costs 2013–14.</i> ⁹⁸ Non-consultant-led outpatient attendance. Non-admitted face-to-face follow-up. Service description: Diabetic Medicine
Cost of a telephone contact	75.80	<i>NHS Reference Costs 2013–14.</i> ⁹⁸ Non-consultant-led outpatient attendance. Non-admitted non-face-to-face follow-up. Service description: Diabetic Medicine

BNF, *British National Formulary*; FCE, finished consultant episode.

TABLE 4 Unit costs of insulin

Item	Average unit cost (£)	Number of units	Cost per unit (£)	Associated yearly cost of an insulin pen (£)	Source
Consumables related to MDI					
Cost of an insulin needle	0.11	N/A	N/A	N/A	HSCIC ¹⁰²
Cost of an insulin syringe	0.13	N/A	N/A	N/A	HSCIC ¹⁰²
Quick-acting insulin					
Human insulin					
Vial	9.87	1000	0.01	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	18.97	1500	0.01	8.78	
Animal insulin					
Vial	26.15	1000	0.03	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	38.29	1500	0.03	5.97	
Insulin aspart (NovoRapid)					
Vial	14.08	1000	0.01	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	28.31	1500	0.02	9.59	
Disposable pen	30.63	1500	0.02	N/A	
Insulin lispro (Humalog)					
Vial	16.61	1000	0.02	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	28.31	1500	0.02	8.86	
Disposable pen	28.31	1500	0.02	N/A	
Insulin glulisine (Apidra)					
Vial	16.00	1000	0.02	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	28.30	1500	0.02	7.86	
Disposable pen	28.30	1500	0.02	N/A	
Background insulin					
Human insulin					
Vial	10.41	988	0.01	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	21.52	1500	0.01	9.30	
Disposable pen	21.05	1500	0.01	N/A	

continued

TABLE 4 Unit costs of insulin (continued)

Item	Average unit cost (£)	Number of units	Cost per unit (£)	Associated yearly cost of an insulin pen (£)	Source
Animal insulin					
Vial	26.17	1000	0.03	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	38.32	1500	0.03	9.57	
Insulin detemir (Levemir)					
Cartridges for a reusable pen	42.00	1500	0.03	9.59	BNF, ¹⁰¹ HSCIC ¹⁰²
Disposable pen	42.10	1500	0.03	N/A	
Insulin glargine (Lantus)					
Vial	30.68	1000	0.03	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	41.50	1500	0.03	7.86	
Disposable pen	41.50	1500	0.03	N/A	
Mixed insulin					
<i>Biphasic isophane insulin</i>					
Animal insulin					
Vial	25.20	1000	0.03	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	37.80	1500	0.03	5.97	
Human insulin					
Vial	15.43	987	0.02	N/A	BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridges for a reusable pen	18.94	1500	0.01	7.74	
Disposable pen	21.43	1500	0.01	N/A	
<i>Biphasic insulin aspart</i>					
Cartridges for a reusable pen	28.79	28.79	0.02	9.59	BNF, ¹⁰¹ HSCIC ¹⁰²
Disposable pen	29.89	29.89	0.02		
<i>Biphasic insulin lispro</i>					
Vial	16.61	1000	0.02		BNF, ¹⁰¹ HSCIC ¹⁰²
Cartridge for reusable pen	29.03	1500	0.02	8.93	
Disposable pen	30.13	1500	0.02		
BNF, <i>British National Formulary</i> ; HSCIC, <i>Health and Social Care Information Centre</i> ; N/A, <i>not applicable</i> .					

1 and 2 years) to calculate the cost of insulin in the first and second year. If an individual was receiving insulin pump therapy then the cost of needles, insulin pens and syringes were not applied, as these were already included in the estimates of the cost of insulin pump consumables. From this information a cost of insulin for each individual in the REPOSE Trial was calculated.

Cost of the insulin pumps and consumables

The annual cost of an insulin pump and insulin pump consumables was estimated using a survey, which was conducted in all of the trial centres. This survey obtained information on the unit costs and the quantities of insulin pumps and insulin pump consumables purchased by centres in routine clinical practice. Information was also collected on the insulin pump consumables used by participants in the REPOSE Trial. Data were collected over a 6-month period for the insulin pump consumables and a 12-month period for the insulin pumps. The Scottish centres purchased insulin pumps and insulin pump consumables through

the Scottish Government. Instead of completing the survey, information was obtained on the average price that the Scottish Government paid for insulin pumps and consumables.

One centre did not report any price information and two centres did not report the quantities of insulin pump consumables used by REPOSE participants. This missingness was addressed by using the mean price and mean resource use at the other trial centres to calculate the cost of insulin pumps and consumables.

For some centres, data collection on individuals' use of consumables was for a period that was somewhat shorter than 6 months and we estimated their consumables use for 12 months assuming a pro rata uplift. The cost of insulin pumps and insulin pump consumables during the trial duration was estimated by multiplying the annual cost of insulin pumps and consumables by the fraction of each year that each individual spent on insulin pump therapy.

The annual cost of an insulin pump was calculated assuming a pump lifetime of 4.5 years, based on the clinical expert opinion of a diabetes specialist nurse. The annualised cost was multiplied by the number of days that an individual spent on an insulin pump to give the total cost of insulin pump therapy in the trial period.

The effect of a price reduction of insulin pumps and insulin pump consumables of 25% and 50% from the pump costing survey prices was tested in scenario analyses. A further scenario analysis was conducted by using a cost of £2002 per annum for a Medtronic pump and consumables reported in Riemsma *et al.*⁸ Riemsma *et al.*⁸ conducted an appraisal of integrated sensor-augmented pump therapy systems for managing blood glucose levels compared with stand-alone insulin pumps with a separate CGM system in the UK for NICE's diagnostics advisory committee. One of the comparators in this appraisal was stand-alone insulin pumps with an additional continuous blood glucose monitoring system. As such, this cost for a Medtronic insulin pump was obtained from the estimated cost of a stand-alone insulin pump estimated in this study. The costs were obtained from the stated prices of an insulin pump from the London New Drugs Group in November 2014.¹⁰³

Treatment switching

During the REPOSE Trial, it was possible for individuals to switch from insulin delivery mechanism to the other, that is to switch from insulin pump therapy to MDI and vice versa. It is important to include treatment switching in a health economic analysis, as it is unreasonable to assume that (1) people who switch treatment will use the same resources over a lifetime as someone who does not use a pump and (2) someone still receiving an insulin pump has the same benefit from treatment as someone who has switched to using MDI. As a consequence of including treatment switching in the long-term model, the mean cost and QALY gain per patient in the pump + DAFNE arm is more likely to represent the true lifetime costs and QALYs than an analysis that ignored treatment switching.

It was possible to switch treatment twice, and two individuals did so in the REPOSE Trial. The data in the REPOSE Trial were analysed to assess the number of people with diabetes who switched treatment. The estimated cost of insulin and insulin pumps was adjusted to reflect the fact that individuals switch treatments. As the EFACT uses a microcosting approach to estimate costs and obtains QALY data from the self-reported EQ-5D data to calculate QALYs, all other cost and QALY effects due to switching are included in the analysis.

The cost of insulin was adjusted for treatment switching by using the data on an individual's insulin use. If an individual switched treatment once, insulin use between the last follow-up period and the treatment switching date was estimated using the reported insulin use at his/her last follow-up period (individuals were followed up at 6 months, 1 and 2 years post randomisation). Similarly, insulin use between his/her treatment switching date and the next follow-up period was estimated using the data observed in the next follow-up period. For example, if an individual switched treatment 11 months post randomisation, his/her insulin use reported at 6-month follow-up would be used to estimate the cost of insulin between 6 and

11 months, and insulin use at 1-year follow-up would be used to estimate insulin use between 11 months and 1 year. If an individual switched between the baseline and the 6-month follow-up period then his/her data were treated as missing, as no information was available on insulin use when using his/her randomised treatment allocation, after receiving DAFNE education. Furthermore, if an individual switched treatment twice ($n = 2$) then the individual was excluded from the EEACT analysis population. This was because individuals both switched and switched back to their original treatment within the time period between two consecutive follow-up periods. Therefore, no information was available on their resource use when they received the other treatment.

The cost of an individual's use of insulin pumps and consumables in each year was calculated by multiplying the fraction of the year for which they used insulin pumps by the associated yearly cost of insulin pumps and insulin pump consumables.

Estimating the within-trial cost effects

The total cost for each individual consisted of the cost of the following components: inpatient admissions; paramedic call-outs for severe hypoglycaemia; the cost of a pump fitting session for individuals who received pump + DAFNE; the cost of pump-fitting session for individuals who switched from MDI to insulin pump therapy and insulin; annual cost of an insulin pump; annual cost of insulin pump consumables; and the cost of DAFNE course.

In the base-case analysis, complete cost information was used in the EEACT. Complete total cost information was available for 98%, 90% and 92% of individuals in the ITT population at baseline, 1 and 2 years, respectively.

In a scenario analysis, missing cost data were imputed for those individuals who attended at least one REPOSE Trial follow-up visit. Total discounted cost data were imputed using chained equations (predictive mean matching), utilising baseline HbA_{1c}, treatment allocation, age at baseline and baseline cost values as covariates in the imputation equations. Ten different imputed values were calculated for each individual with missing data.

Estimating within-trial quality-adjusted life-year effects using the EuroQol-5 Dimensions and the Short Form questionnaire-12 items

To generate QALY measures over the 2-year trial follow-up, information was collected on an individual's utility using two different instruments: the EQ-5D and the SF-12. The EQ-5D and SF-12 questionnaires were completed by individuals at baseline and all follow-up visits (6, 12 and 24 months).

In the base-case within-trial analysis, the utility values measured by the EuroQol-5 Dimensions, 3-level version (EQ-5D-3L) were used to calculate QALYs using an area-under-the-curve analysis. EQ-5D utility scores were used in the base case because they are NICE's preferred utility measure.¹ In a scenario analysis, utility values measured using the Short Form questionnaire-6 Dimensions (SF-6D) (a measure derived from the SF-12) were used to calculate QALY values.¹⁰⁴

In the base case, only individuals with complete QALY data were included in the analysis. Utilities, as measured by the EQ-5D-3L, were completed by 99%, 93%, 88% and 90% of individuals at baseline, 6, 12 and 24 months, respectively. If an individual had a missing 6-month utility value, then it was assumed that the 6-month utility value would be the average of the baseline and 1-year utility values. If an individual had a missing utility score at 12 or 24 months, then they were excluded from the base-case analysis. The 6-month utility values of individuals with missing utility data at 12 or 24 months were similar in both model arms. The individuals in the pump + DAFNE arm, who did not have 1- or 2-year EQ-5D-3L data, had a mean EQ-5D-3L utility score of 0.8177 [standard error (SE) 0.0602] at 6-month follow-up. The individuals in the pump + DAFNE arm, who did not have 1- or 2-year EQ-5D-3L data, had a mean EQ-5D-3L utility score of 0.904 (SE 0.0256) at 6-month follow-up. The hypothesis that the difference between these two distributions was equal to zero could not be rejected using a two-sided *t*-test with equal variances at

the 10% significance level. Therefore, there is no indication that excluding these individuals from the base case would bias the results.

In a scenario analysis, multiple imputation was used to impute missing QALY values for individuals with assessment data for least one follow-up point. Data were imputed using chained equations (predictive mean matching), utilising baseline HbA_{1c}, treatment allocation, age at baseline and baseline cost or QALY values as covariates in the imputation equations. Ten imputed values were calculated for each individual, with missing data in the analyses using imputed data.

Statistical model used for the within-trial analysis

A seemingly unrelated regression model was used to estimate the costs and QALYs in the EEACT. A seemingly unrelated regression is a type of statistical model that allows for multiple outcome variables to be modelled simultaneously.¹⁰⁵ This approach is advantageous, as any covariances between covariates across the different outcome variables are estimated. One seemingly unrelated regression was fitted to four outcome variables: (1) total discounted costs in year 1, (2) total discounted costs in year 2, (3) total discounted QALYs in year 1 and (4) total discounted QALYs in year 2, using the 'mysureg' command in the 'ml_ado' package in Stata version 13.1. For the QALY outcome variables, baseline HbA_{1c}, treatment allocation and baseline utility were included as covariates, and clustering was controlled for in each DAFNE course. Baseline utility was included as a covariate to estimate QALYs so that any baseline differences in health between the two treatment arms was controlled for.¹⁰⁶ For the cost outcome variables, baseline HbA_{1c}, centre, treatment allocation and baseline resource use were included as covariates, and clustering was controlled for in each DAFNE course.

A scenario analysis was conducted in which both missing cost and QALY data were imputed for individuals with at least one assessment during the REPOSE Trial follow-up period. A regression was conducted in each imputed data set and combined using Rubin's rules.¹⁰⁷ Details of the imputation procedures used in this scenario analysis are given in *Estimating the within-trial cost effects and Estimating within-trial quality-adjusted life-year effects using the EuroQol-5 Dimensions and the Short Form questionnaire-12 items*.

The impact of treatment allocation on total costs was calculated by adding the treatment allocation parameters relating to the cost outcomes in years 1 and 2. Likewise, the impact of treatment allocation on total QALYs was calculated by adding the treatment allocation parameters relating to the QALY outcomes in years 1 and 2. CIs around the effect of treatment allocation on total costs and total QALYs were calculated using the formula for calculating the variance of a variable that is a sum of correlated variables. The variances and covariance used in this calculation were obtained from the variance–covariance matrix of the seemingly unrelated regression.

Analysis

The key measure of cost-effectiveness in the EEACT was the ICER base on the mean incremental effect of pump + DAFNE compared with MDI + DAFNE on total costs and total QALYs. The CIs around these effects were estimated from the variance–covariance matrix of the regression model. The results were presented on a cost-effectiveness plane and the uncertainty around the mean effect was presented using a confidence ellipse.

Long-term cost-effectiveness

The Sheffield Type 1 Diabetes Policy Model Overview

The Sheffield Type 1 Diabetes Policy Model (henceforth, the Model) was used to estimate the lifetime costs and QALYs for individuals receiving MDI + DAFNE and pump + DAFNE. The Model has been developed and used over several years, and a detailed description is provided in a journal article¹⁰⁸ and a detailed report to the NIHR on the DAFNE programme grant research.²⁷ In this analysis, we have updated some aspects of the evidence used within the Model. We term the version used here as 'The Sheffield Type 1 Diabetes Policy Model version 1.3'.

The Model is an individual-level simulation model, which consists of a series of submodels that simulate the progression of diabetic complications (microvascular and macrovascular), SAEs (severe hypoglycaemia and DKA) and mortality in a given population with T1DM. Each of the modelled microvascular (nephropathy, neuropathy, retinopathy and macular oedema) and macrovascular complications (MI, stroke, HF and angina) are included in the model as separate Markov submodels with an annual time cycle. Short-term AEs (severe hypoglycaemia and DKA) are modelled as the annual incidence of these complications, dependent on each patient's characteristics. The Model structure is also presented in *Figure 1*. The Model attaches utilities and ongoing costs to health states and one-off costs to events (the move to another health state in a submodel). These costs and utilities are combined with the length of time that a patient spends in a health state to estimate lifetime costs and QALYs. The Model estimates patient's disease progression over their lifetime.

The disease progression parameters in the Model were not updated in these analyses. However, the costs and utilities associated with health states and events were updated. A full probabilistic sensitivity analysis (PSA) was conducted with 500 probabilistic runs, each with 5000 individuals in each Model arm. All Model runs were conducted using the SIMUL8 2010 professional (Simul8 Corporation, Boston, MA, USA) programme.

Microvascular events and disease progression

For each microvascular complication (retinopathy, neuropathy and nephropathy), individuals progress to the more severe health states within each annual time cycle according to the probabilities reported in table 29 of Heller *et al.*²⁷ The health states included for retinopathy include no retinopathy, background retinopathy, proliferative retinopathy and blindness. The health states included for neuropathy include no neuropathy, clinical neuropathy, clinically confirmed neuropathy, diabetic foot syndrome and peripheral arterial disease (PAD) with amputation. The health states included for nephropathy include no nephropathy, microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD) and death from ESRD.

Macrovascular events and disease progression

The risks of fatal and non-fatal macrovascular complications (MI, stroke, HF and angina) are modelled in three stages. First, the annual probability of experiencing any cardiovascular event is estimated based on individual characteristics, as per the 5-year cardiovascular risk model of Cederholm *et al.*¹⁰⁹ Second, if the individual is deemed to experience a cardiovascular event, the type of event (MI, stroke, HF or angina) is determined using methods outlined in Palmer,¹¹⁰ based on data from the Diabetes Control and Complications Trial (DCCT) Epidemiology of Diabetes Interventions and Complications study.¹¹¹ Third, is the issue of fatality. If the event experienced is a MI, stroke or HF, it is determined whether or not the event is fatal using methods outlined in Palmer¹¹⁰ and as shown in table 31 of Heller *et al.*²⁷

Individuals can also die from other causes; this other-cause mortality is modelled based on UK life tables from 2012–14, adjusted to exclude the causes either attributed to diabetes mellitus (either type 1, type 2 or unspecified) or modelled directly in the microvascular and macrovascular disease components (deaths due to ESRD, MI, stroke and HF).

Utilities: health-related quality of life for health states in the long-term model

Heller *et al.*²⁷ (pp. 108–9) detail the utility analyses undertaken to inform version 1.2 of the model. Since that report, further analysis has taken place in the course of peer-reviewed journal publication, and the utilities presented in this analysis are based primarily on those revised analyses, which are now published in Peasgood *et al.*¹¹² The main change in this analysis is that the preferred statistical model to estimate utility values in the publication is a random-effects model rather than a Tobit model. Riemsma *et al.*⁸ conducted the independent economic analysis for NICE on the cost-effectiveness of integrate CGM and insulin pump therapy. For the independent analysis, a systematic review of utilities in type 2 diabetes mellitus published in 2014 by Beaudet *et al.*¹¹³ was used for many of the health states of their economic model. The utilities presented in version 1.2 of the model were considered for updating by the new information presented in Peasgood *et al.*¹¹² and Beaudet *et al.*¹¹³

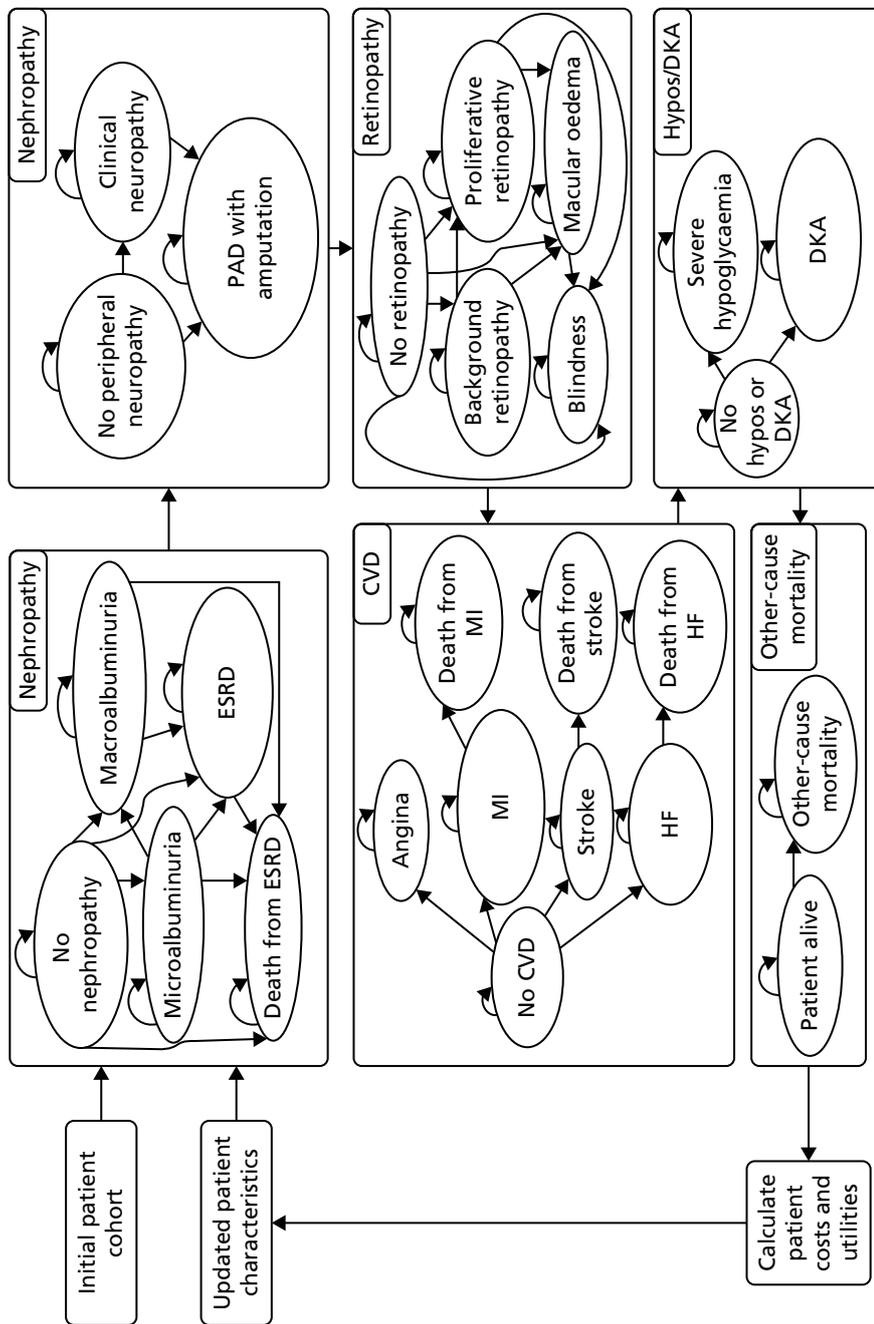


FIGURE 1 The structure of the Sheffield Type 1 Diabetes Policy Model (from Thokala et al.¹⁰⁸ with permission from John Wiley & Sons, Inc.). CVD, cardiovascular disease; ESRD, end-stage renal disease; hypos, hypoglycaemic episodes; PAD, peripheral arterial disease.

The following criteria were applied to decide if a utility value should be updated. Utility values estimated in a population with T1DM were preferred to values estimated in a population with type 2 diabetes mellitus. If multiple values were available in a T1DM population, utility values that were estimated using the EQ-5D were preferred to other utility values. If a paper presented more than one parameter value, the parameter from the best-fitting model was the preferred source. If two papers analysed the same data source then the most recent paper was the preferred source. The utility parameters used in the Model version 1.3 base-case analyses, and the distributions used in the PSA, are given in *Table 5*.

Unit costs for health states in the long-term model

The base case unit costs, which are presented in Heller *et al.*,²⁷ were inflated to 2013–14 prices using the Hospital and Community Health Services Index.² The base-case health-state costs used, and the distributions used in the PSA, are given in *Table 6*.

Pre-specified subgroup analyses

A series of subgroup analyses were conducted in the long-term modelling. The same subgroup analyses were not conducted in the within-trial analysis, as conducting analyses in these subgroups would lead to a reduced sample size and increase the chance that a spurious result would be found. The cost-effectiveness of pump + DAFNE against MDI + DAFNE was compared for subgroups:

1. baseline HbA_{1c} \geq 7.5% (58 mmol/mol)
2. baseline HbA_{1c} \geq 7.5% (58 mmol/mol) and $<$ 8.5% (69 mmol/mol)
3. baseline HbA_{1c} \geq 8.5% (69 mmol/mol) and $<$ 9.5% (80 mmol/mol)
4. baseline HbA_{1c} \geq 9.5% (80 mmol/mol)
5. baseline HbA_{1c} $<$ 8.5% (69 mmol/mol)
6. baseline HbA_{1c} \geq 8.5% (69 mmol/mol)
7. all individuals in the per-protocol population.

For people with a baseline HbA_{1c} of $<$ 7.5% (58 mmol/mol), there were insufficient numbers ($n = 12$ people in the MDI + DAFNE arm, $n = 13$ in the pump + DAFNE arm) to conduct a subgroup analysis.

The subgroup analyses were conducted by changing only the individual characteristics that were inputted into the model. All of the other parameters and assumptions in the model were identical to those in the base case.

Modelled cohort of 5000 simulated individuals

Individual characteristics were drawn from the baseline characteristics of all individuals, irrespective of treatment arm, in the ITT population. The variables included in the baseline individual characteristics are HbA_{1c}, age, diabetes duration, triglycerides, TC, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, systolic blood pressure, baseline cost of insulin, baseline cost of diabetes-related contacts, sex, physical activity (measured as being either low, medium or high, based on the time spent walking, fast walking or running per week), smoking status, ethnicity, history of nephropathy, history of neuropathy, history of retinopathy, history of MI, history of stroke, history of HF and history of angina.

The observed characteristics (including missing values) of the REPOSE Trial individuals were sampled with replacement to generate a cohort of 5000 individuals to be used in the economic model. After the cohort of 5000 individuals was obtained, missing data values were observed for TC, HDL cholesterol, LDL cholesterol, systolic blood pressure and sex. To obtain the missing data, these values were imputed. The data were imputed in the cohort of 5000 individuals, rather than for the individuals in the trial data set, as this allowed the missing data to vary across different replications of an individual with missing data. If the data were imputed before the sampling, then the missing data would take on a fixed value in the cohort of 5000 individuals rather than being uncertain.

TABLE 5 Base-case utility parameters

Health state for event	Utility	SE	Beta distribution		Source
			Alpha	Beta	
Baseline utility value					
Male with T1DM and no complications	0.866	0.010	947.789	146.898	Peasgood <i>et al.</i> 2016 ¹¹²
			Gamma distribution		
	Disutility		Alpha	Beta	
Complications or covariates					
Female with T1DM and no complications	0.0236	0.008	8.703	0.003	^a Peasgood <i>et al.</i> 2016 ¹¹²
Nephropathy					
Microalbuminuria	0				Assumption
Microalbuminuria	-0.017	0.01	2.89	0.006	Coffey <i>et al.</i> 2002 ¹¹⁴
ESRD	-0.078	0.026	9	0.009	Coffey <i>et al.</i> 2002 ¹¹⁴
Neuropathy					
Clinical neuropathy	-0.055	0.01	30.25	0.002	Coffey <i>et al.</i> 2002 ¹¹⁴
Clinically confirmed neuropathy	-0.055	0.01	30.25	0.002	Coffey <i>et al.</i> 2002 ¹¹⁴
Diabetic foot syndrome	-0.1042	-0.119	0.767	0.136	Peasgood <i>et al.</i> 2016 ¹¹²
PAD with amputation	-0.1172	-0.055	4.541	0.026	^a Peasgood <i>et al.</i> 2016 ¹¹²
Retinopathy					
Background retinopathy	-0.0544	-0.023	5.594	0.010	Peasgood <i>et al.</i> 2016 ¹¹²
Proliferative retinopathy	-0.0288	-0.026	1.227	0.023	Peasgood <i>et al.</i> 2016 ¹¹²
Blindness	-0.208	0.013	256	0.001	Coffey <i>et al.</i> 2002 ¹¹⁴
Cardiovascular					
MI (first year)	-0.065	0.03	4.694	0.014	Alva <i>et al.</i> 2014 ¹¹⁵
MI (subsequent years)	-0.057	0.03	3.61	0.016	Alva <i>et al.</i> 2014 ¹¹⁵
HF	-0.101	0.032	9.962	0.010	Alva <i>et al.</i> 2014 ¹¹⁵
Stroke	-0.165	0.035	22.224	0.007	Alva <i>et al.</i> 2014 ¹¹⁵
Angina	-0.09	0.018	25	0.004	^b Clarke <i>et al.</i> 2002 ¹¹⁶
AEs					
Hypoglycaemia episode unable to treat yourself	-0.002	-0.002	1	0.002	Peasgood <i>et al.</i> 2016 ¹¹²
DKA	-0.0091	-0.01	0.828	0.011	^a Peasgood <i>et al.</i> 2016 ¹¹²

a A parameter value was not available in the author's preferred statistical model.

b Value is presented later (see Table 7) as ischaemic heart disease.

TABLE 6 Base-case health state and transition costs

Health state	Mean cost (£)	SE	Gamma distribution		Source
			Alpha	Beta	
Microalbuminuria (ongoing)	36	3.56	100	0.36	BNF 2012, ¹¹⁷ McEwan <i>et al.</i> 2007 ¹¹⁸
Microalbuminuria (ongoing)	36	3.56	100	0.36	
ESRD (ongoing)	24,436	2444	100	244.36	<i>NHS Reference Costs 2011</i> ¹¹⁹ (activity-weighted average of LD01A, LD02A, LD03A, LD04A, LD05A, LD06A, LD07A, LD08A, LD09A, LD010A and LD011A and LD012A)
Death due to ESRD	0	0	0	0.00	Assumption
Clinically confirmed neuropathy	271	27.14	100	2.71	Currie <i>et al.</i> 2007 ¹²⁰
Clinical neuropathy	271	27.14	100	2.71	Assumed equal to clinically confirmed neuropathy
Diabetic foot syndrome	2848	285	100	28.48	<i>NHS Reference Costs 2011</i> ¹¹⁹ [activity-weighted average of 'Non-Elective Inpatient (Long Stay)', 'Non-Elective Inpatient (Long Stay) Excess Bed-day' and 'Non-Elective Inpatient (Short Stay)' for currency code QZ17B]
PAD with amputation (year 1)	7221	722	100	72.21	<i>NHS Reference Costs 2011</i> ¹¹⁹ [activity-weighted average of 'Non-Elective Inpatient (Long Stay)', 'Non-Elective Inpatient (Long Stay) Excess Bed-day' and 'Non-Elective Inpatient (Short Stay)' for currency codes QZ12Z and QZ11B]
PAD with amputation (ongoing)	439	43.93	100	4.39	McEwan <i>et al.</i> 2007 ¹¹⁸
Background retinopathy	145	14.47	100	1.45	
Proliferative retinopathy	661	66.11	100	6.61	
Macular oedema	661	66.11	100	6.61	Assumed equal to proliferative retinopathy
Blindness (year 1)	1584	158	100	15.84	Clarke <i>et al.</i> 2003 ¹²¹
Blindness (ongoing)	519	51.88	100	5.19	
First MI (year 1)	6788	679	100	67.88	Clarke <i>et al.</i> 2003 ¹²¹
Second MI	6788	679	100	67.88	
Final MI	6788	679	100	67.88	
MI (ongoing)	904	90.43	100	9.04	
Fatal MI	2101	210	100	21.01	
First stroke (year 1)	4361	436	100	43.61	
Second stroke	4361	436	100	43.61	
First stroke (ongoing)	559	55.90	100	5.59	
Fatal stroke	5684	568.45	100	56.84	
HF (year 1)	3818	382	100	38.18	
HF (ongoing)	1173	117	100	11.73	
Fatal HF	3818	382	100	38.18	

TABLE 6 Base-case health state and transition costs (*continued*)

Health state	Mean cost (£)	SE	Gamma distribution		Source
			Alpha	Beta	
Angina (year 1)	3397	340	100	33.97	
Angina (ongoing)	951	95.09	100	9.51	
Hypoglycaemia	187	18.69	100	1.87	Previous calculation (weighted average of the following HRG codes, with activities obtained from the hypoglycaemia rates observed before and after DAFNE: KB02D, KB02E, KB02F, KB02D, KB02E, KB02F, KB01B, KB01B, KB01A, KB01A, PS13A, PS13B, PS13C, VB09Z, VB09Z)
DKA with hospitalisation	1399	140	100	13.99	<i>NHS Reference Costs 2011</i> ¹¹⁹ [activity-weighted average of 'Non-Elective Inpatient (Long Stay)', 'Non-Elective Inpatient (Long Stay) Excess Bed-day' and 'Non-Elective Inpatient (Short Stay)' for currency codes KB01B and PA67Z, respectively]

BNF, *British National Formulary*; HRG, *Healthcare Resource Group*.

The imputation procedure depended on whether the missing value was a continuous or a categorical variable. TC, HDL cholesterol, LDL cholesterol and systolic blood pressure were imputed using chained equations, utilising the truncated regression procedure. Sex was imputed separately from TC, HDL cholesterol and systolic blood pressure, using the Poisson procedure. In both sets of imputation models, all of the complete individual characteristics were included as predictive covariates. LDL cholesterol was calculated using the imputed data for TC and HDL cholesterol, using the following formula:

$$\text{LDL cholesterol} = \text{total plasma cholesterol (cholesterol)} - \text{HDL cholesterol} - (\text{triglycerides}/2.19).^{122} \quad (3)$$

All of the imputations were performed using single imputation. The reason for using one imputed value was that as more imputations were performed, the average value of these imputations would converge for the different replications of an individual from the trial population. Therefore, the uncertainty in the values of the missing data would not be fully reflected in the model cohort.

Summaries of the baseline characteristics of the 5000 simulated individuals for the base-case cohort and the 260 individuals sampled from the REPOSE Trial are given in *Table 7*. The summary of baseline characteristics for the 5000 simulated individuals for each of the pre-specified subgroup analyses is provided in *Appendix 7*.

Incorporating estimated clinical effectiveness from the REPOSE Trial: glycated haemoglobin

The probability of switching treatment, changes in HbA_{1c}, the probability of a severe hypoglycaemic event and the probability of the DKA were based on data from the REPOSE Trial. These four clinical effects have been included in the health economic model, as they all would impact on the costs of treatment and QALYs gained by people if either option were to be adopted in routine clinical practice. HbA_{1c} has been included as it is the key driver of all modelled diabetic complications in the Model. Changes in HbA_{1c} were estimated using a beta regression. The probability of severe hypoglycaemia and DKA have been included, so that any benefits of either arm in reducing the incidence of these events is included in the economic

TABLE 7 The baseline characteristics of REPOSE participants and the simulated cohort

Characteristic	REPOSE ITT population (N = 260)	Simulated cohort (N = 5000)
Continuous variables, mean (SD)		
Baseline HbA _{1c} (mmol/mol)	76.0 (18.6)	76.1 (18.8)
Age (years)	40.4 (13.4)	40.3 (13.3)
Diabetes duration (years)	18.0 (12.5)	18.0 (12.5)
Triglycerides (mmol/mol)	1.4 (1.0)	1.3 (1.0)
TC (mmol/mol)	4.9 (0.9)	4.9 (0.9)
HDL cholesterol (mmol/mol)	1.6 (0.4)	1.6 (0.4)
LDL cholesterol (mmol/mol)	2.8 (0.9)	2.8 (0.9)
Systolic blood pressure	131.4 (16.4)	131.3 (16.3)
Baseline cost of insulin (£)	357.24 (147.65)	360.39 (157.92)
Baseline cost of diabetes-related contacts (£)	561.61 (885.92)	571.63 (928.92)
Categorical variables n/N (%)		
Sex		
Female	104/260 (40.0)	2050/5000 (41.0)
Male	152/260 (58.5)	2950/5000 (59.0)
Missing	4/260 (1.5)	0/5000 (0.0)
Physical activity		
Low	67/260 (25.8)	1245/5000 (24.9)
Medium	128/260 (49.2)	2440/5000 (48.8)
High	65/260 (25.0)	1320/5000 (26.4)
Smoking status		
Current	50/260 (19.2)	960/5000 (19.2)
Former	67/260 (25.8)	1315/5000 (26.3)
Never	143/260 (55.0)	2725/5000 (54.5)
Ethnicity		
White	258/260 (99.2)	4955/5000 (99.1)
Black	2/260 (0.8)	45/5000 (0.9)
Nephropathy		
No complications	239/260 (91.9)	4645/5000 (92.9)
Microalbuminuria	13/260 (5.0)	235/5000 (4.7)
Macroalbuminuria	7/260 (2.7)	135/5000 (2.7)
Dialysis or transplant	1/260 (0.4)	20/5000 (0.4)
Neuropathy		
No complications	238/260 (91.5)	4535/5000 (90.7)
Neuropathy or ulcers	22/260 (8.5)	465/5000 (9.3)

TABLE 7 The baseline characteristics of REPOSE participants and the simulated cohort (*continued*)

Characteristic	REPOSE ITT population (N = 260)	Simulated cohort (N = 5000)
Retinopathy		
No complications	145/260 (55.8)	2800/5000 (56.0)
Background diabetic retinopathy	91/260 (35.0)	1740/5000 (34.8)
Proliferative diabetic retinopathy	24/260 (9.2)	465/5000 (9.3)
MI		
No complications	255/260 (98.1)	4890/5000 (97.8)
MI	5/260 (1.9)	110/5000 (2.2)
Stroke		
No complications	259/260 (99.6)	4985/5000 (99.7)
Stroke	1/260 (0.4)	15/5000 (0.3)
HF		
No complications	259/260 (99.6)	4970/5000 (99.4)
HF	1/260 (0.4)	30/5000 (0.6)
Angina		
No complications	257/260 (98.9)	4940/5000 (98.8)
Angina	3/260 (1.2)	60/5000 (1.2)

model. The probability of severe hypoglycaemia and DKA were estimated using negative binomial models. Treatment switching has been included, as it is expected that when an individual switched treatment from pump to MDI or from MDI to pump that the cost of managing their diabetes and their clinical outcomes would change. The probability of switching treatment was estimated using parametric survival curves, using treatment switching as the event of interest.

Incorporating treatment switching

During REPOSE, individuals in both trial arms could switch their insulin delivery mechanism; because of effects on both costs and clinical outcomes, it was important to incorporate treatment switching into the model. A total of 17 of 132 (12.88%) individuals, initially randomised to the pump, switched once to MDI to deliver their insulin. A further two individuals, initially randomised to the pump, switched from pump to MDI and then switched again from MDI back to pump. A total of 8 of 128 (6.25%) individuals, initially randomised to MDI, switched to pump.

Kaplan–Meier curves were fitted to individual-level data using treatment switching as the event. Parametric survival curves were fitted to the data with HbA_{1c} prior to switching, number of DKAs and number of severe hypoglycaemic events in the year prior to switching (or 2 years' follow-up if no switching occurred) included as covariates. The SEs of the parametric models were adjusted for clustering within each course. Separate models were fitted to individuals initially randomised to insulin pump therapy and MDI, so no assumption of proportion hazards or accelerated failure time was made. Exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma distributions for the parametric curves were considered. The goodness of fit of the different curves was assessed using visual assessment of the Kaplan–Meier plots and the Akaike information criterion (AIC) and the Bayesian information criterion (BIC).

Based on expert clinical opinion of a Professor of Clinical Diabetes and Honorary Consultant Physician, and a Professor in Public Health and Health Technology Assessment, it was assumed, in the base case, that if an individual was on an insulin pump after 2 years then they would remain on the pump; this assumption was made, as, in their experience, once an adult with T1DM was successfully using an insulin pump then they were unlikely to change the method of insulin delivery.

In the model, treatment switching impacted on HbA_{1c} and the cost of pumps, diabetes-related contacts and insulin. Details on how the HbA_{1c} of patients who switched are given later (see *Estimation of each individual's glycated haemoglobin*); details on how the costs of treatment were updated for people who switched are also given later (see *Cost of insulin, diabetes-related contacts and insulin pumps*). No explicit inclusion of treatment switching on the risk of DKA and severe hypoglycaemia was included in the model because of the relatively small numbers of these events in each trial arm (see *Table 7*). However, the risk of DKA and severe hypoglycaemia does depend on the HbA_{1c} of the individual in the model; therefore, there are differences in the risk of DKA and severe hypoglycaemia between those who switched treatment and those who did not.

Estimation of each individual's glycated haemoglobin

To develop the method to incorporate HbA_{1c} treatment effect evidence into the model, several factors were considered. Data were collected on each individual's HbA_{1c} at each follow-up visit. As HbA_{1c} is the key predictor of clinical events in the model, it is important that the distribution of HbA_{1c} is reflective of what was observed in the REPOSE Trial. Because 5000 replicated individuals are included in the model from the $n = 260$ sample, we are able to incorporate heterogeneity of individual outcomes into the cost-effectiveness analysis using statistical modelling of the REPOSE data set. A clinical expert (Senior Clinical Lecturer/Honorary Consultant) commented that few adults with T1DM were able to sustain a HbA_{1c} level of < 31 mmol/mol (5%) for a full year, and that, in the expert's experience, no adult with T1DM had a HbA_{1c} of > 200 mmol/mol (20.5%). A final consideration was that the lowest HbA_{1c} observed in the DAFNE research database was 30 mmol/mol (4.9%).²⁷

The effect of pump + DAFNE treatment compared with MDI + DAFNE treatment on HbA_{1c} was estimated using a beta regression.¹²³ Beta regressions estimate outcome parameters, which are bound by, but do include, a range of 0–1. HbA_{1c} from the trial data was transformed so that a HbA_{1c} level of 29 mmol/mol (4.8%) was equal to zero. The upper limit of HbA_{1c} was taken to be 201 mmol/mol (20.5%). A beta regression estimates two parameters of interest for simulating each individual's HbA_{1c} response to pump + DAFNE in the model, the mean effect (μ) and a dispersion parameter (ϕ). The expectation and the variance of each individual's outcome, y_i , are estimated using the following formulae:

$$E(y_i) = \hat{\mu}_i$$

$$Var(y_i) = \frac{\hat{\mu}_i \times (1 - \hat{\mu}_i)}{1 + \hat{\phi}_i}. \quad (4)$$

To estimate the mean effect on 1-year HbA_{1c}, treatment allocation, baseline HbA_{1c} and centre were included as covariates. To estimate the dispersion parameter in the 1-year HbA_{1c} regression, only baseline HbA_{1c} was included as a covariate. All of the parameters that were included in the mean effect regression were tested as covariates, but were not statistically significant at the 5% level.

To estimate the mean effect on 2-year HbA_{1c}, all of the covariates used to estimate the mean effect on 1-year HbA_{1c} were used, and 1-year HbA_{1c} was included as an additional covariate. To estimate the dispersion parameter, HbA_{1c} at 1 year was used. All of the parameters that were included in the mean effect regression were tested as covariates, but were not statistically significant at the 5% level.

The uncertainty in each individual's outcome was parameterised using a beta distribution, which was individualised, based on their covariates. Independent beta distributions were fitted to 1- and 2-year HbA_{1c} outcomes, as they had different expectations of the mean effect and the variance in the mean effect in the first and second year. For each individual, two independent random draws were taken: one from their individualised beta distribution for 1-year HbA_{1c} and the other from their individualised beta distribution for 2-year HbA_{1c}, to determine their HbA_{1c} at 1 and 2 years, respectively.

In the base case, it was assumed that if an individual switched treatments then they had a change in HbA_{1c} equal to the difference between the predicted mean effect on HbA_{1c} in their randomised treatment arm and the predicted mean effect on HbA_{1c} in their non-randomised treatment arm. The mean effects were obtained from their individualised outcomes from the beta regressions. In the base case, the estimates of changes in HbA_{1c} were obtained from the per-protocol population, as individuals who switched insulin delivery mechanism were not included in this population. Therefore, treatment effect parameters in this population reflect the relative effectiveness of pump + DAFNE versus MDI + DAFNE for those individuals who did not switch insulin delivery mechanism.

The Model is designed to use a mean HbA_{1c} value, using the DCCT% scale, for each individual in each yearly time cycle. In the base-case analysis, an individual's HbA_{1c} for the first model cycle (0–1 years) is given by their baseline HbA_{1c}, an individual's HbA_{1c} for the second model cycle (1–2 years) is given by their 1-year HbA_{1c} sampled from their individualised beta distribution for 1-year HbA_{1c} and an individual's HbA_{1c} for the third model cycle (2–3 years) is given by their 2-year HbA_{1c} sampled from their individualised beta distribution for 2-year HbA_{1c}. These sampled values of HbA_{1c} on the beta scale were then transformed on to the DCCT% scale for use in the long-term modelling.

The trial population – used to estimate HbA_{1c} effect, changes to HbA_{1c} on treatment switching and the timing of changes in HbA_{1c} – was tested in three deterministic scenario analyses. In the first scenario analysis, the treatment effect was estimated in the ITT population, and when an individual switched insulin delivery mechanism his/her HbA_{1c} still changed so that it was reflective of the other trial arm of REPOSE. In the second, the treatment effect was estimated in the ITT population, but there was no variation in HbA_{1c} changes for those individuals who switched. This scenario was conducted as in the ITT analysis population: individuals who switched insulin delivery mechanism remained in the arm to which they were originally randomised. In the third scenario analysis, HbA_{1c} effects were modelled as occurring one model cycle earlier than they did in the base case. For example, an individual's 2-year HbA_{1c} was used as their modelled HbA_{1c} value in the second model cycle in the scenario analysis rather than the third model cycle in the base case.

Estimating severe hypoglycaemic events and diabetic ketoacidosis events

To develop the method to incorporate severe hypoglycaemic events and DKA treatment effect evidence into the model, several factors were considered. Data on severe hypoglycaemic events and DKA were collected on an ongoing basis throughout the trial. A summary of the numbers of DKAs and severe hypoglycaemic events is given in *Table 8*. It can be seen that the number of DKAs and severe hypoglycaemic events declines in the second year on every measure except self-reported DKAs in the MDI + DAFNE arm, where the number of events was the same in both years. As such, the statistical models used in the economic data estimated the incidence of severe hypoglycaemia and DKA in the first and second years separately.

Negative binomial regressions were used to predict the number of DKAs and severe hypoglycaemic events in years 1 and 2 for each outcome separately. When the outcome variable was the number of hypoglycaemic events in year 1, year-1 HbA_{1c} and treatment group were included as covariates. When the outcome variable was the number of hypoglycaemic events in year 2, year-2 HbA_{1c} and treatment group were included as covariates. When the outcome variable was the number of DKAs in year 1, year-1 HbA_{1c} and treatment group were included as covariates. When the outcome variable was the number of DKAs in year 2, year-2 HbA_{1c} and treatment group were included as covariates. The possibility of using the number of events in the previous year, baseline events for the 1-year outcomes and year-1 events for the 2-year outcomes, as a covariate was explored. However, because of the low number of events, the negative binomial models often did not converge when this was included as a covariate.

The statistical models did not converge for DKAs reported as SAEs in the first year. This was not the case for self-reported DKAs and there were more self-reported cases of DKA than were picked up through the reporting of SAEs. Therefore, the rates of DKA were estimated using self-reported DKAs as the outcome measure.

TABLE 8 Summary of the observed incidence of DKA and severe hypoglycaemia in the ITT population

AE	Year 1			Year 2			Total		
	Pump + DAFNE (n = 132)	MDI + DAFNE (n = 128)	Total (n = 260)	Pump + DAFNE (n = 132)	MDI + DAFNE (n = 128)	Total (n = 260)	Pump + DAFNE (n = 132)	MDI + DAFNE (n = 128)	Total (n = 260)
DKAs: SAEs									
Number of (%) participants with ≥ 1 DKA	15 (11.4)	1 (0.8)	16 (6.2)	4 (3.0)	2 (1.5)	6 (2.2)	17 (12.9)	3 (2.3)	20 (7.7)
Number of hospital admissions	16	5	21	5	4	9	21	9	30
DKAs: self-reported admissions									
Number of (%) participants with ≥ 1 DKA	17 (12.9)	6 (4.7)	23 (8.8)	6 (4.5)	5 (3.7)	11 (4.1)	18 (13.6)	8 (6.3)	26 (10.0)
Number of self-reported DKAs	24	11	35	7	11	18	26 ^a	13 ^a	39 ^a
Severe hypoglycaemia									
Number of (%) participants with ≥ 1 severe hypoglycaemic event	10 (7.6)	9 (7.0)	19 (7.3)	4 (3.0)	7 (5.5)	11 (4.2)	14 (10.6)	11 (8.6)	25 (9.6)
Number of severe hypoglycaemic events	21	12	33	4	12	16	25	24	49

^a These values are not the sums of the 1- and 2-year follow-up, as individuals had missing information in either year.

The statistical models were fitted using the Zelig package in R version 3.2.0 (The R Foundation for Statistical Computing, Vienna, Austria) and using specifications described above; it was used to simulate the predicted number of severe hypoglycaemia and DKA events in each trial arm 10,000 times. The simulations were separately in each trial arm and for HbA_{1c} values every 0.1% between 4% and 20.5%. The number of events observed in the simulations was truncated at 20 events per year to reduce the effect of extreme values in the simulation on the cost-effectiveness results. These simulations were then used to determine the probability that an individual would suffer a given number of severe hypoglycaemic events and DKA events in 1 year, dependent on their HbA_{1c} that year and the trial arm to which they were allocated. The probability that an individual would suffer a given number of events was a fixed parameter in the PSA; therefore, any differences in the rates of DKA or severe hypoglycaemia for an individual between any two model runs will solely be due to differences in their HbA_{1c}.

In the base case, the statistical models fitted to the incidence of severe hypoglycaemia and DKA in years 1 and 2 were used in the first and second model cycles, respectively, to predict the incidence of severe hypoglycaemia and DKA. The statistical models for year 2 were also used in all subsequent model years because we assumed that year 1 models might not be representative of ongoing event rates because of 'teething problems' with treatments given, which are in a sense 'ironed out' by year 2. This assumption was based on the clinical opinion of the clinical members of the REPOSE TMG, including honorary consultants in diabetes and diabetes nurse specialists.

In a scenario analysis, individuals in both model arms returned to their baseline rate of severe hypoglycaemia and DKA after the second year. Self-reported information was collected at baseline on the number of severe hypoglycaemic events and DKAs experienced by the individuals in the 12 months prior to baseline data collection. The baseline incidence of these events was estimated using the same methods used to estimate the probability of experiencing these events in year 1 or year 2; however, treatment allocation was not included as covariate. This is because all of the events in the baseline rate models occurred prior to an individual's randomisation in the REPOSE Trial.

Cost of insulin, diabetes-related contacts and insulin pumps

The cost of insulin, diabetes-related contacts and insulin pumps (including consumables) in the long-term model was estimated based on resource use data from the REPOSE Trial data and the unit costs used in the EEACT (see *Resource use by individuals in the REPOSE Trial over the 2-year follow-up period*). Statistical models were fitted to these subcomponents of total cost in the EEACT, as it is expected that the covariates that predict the cost of insulin in year 1 may be correlated with the covariates that predict the cost of insulin in year 2. It is also expected that this may be true for the cost of diabetes-related contacts and the cost of insulin pumps (including consumables). Therefore, instead of fitting six independent regression models, three seemingly unrelated regressions were fitted [one seemingly unrelated regression for the cost of insulin, another for the cost of diabetes-related contacts and, finally, one for the cost of insulin pumps (including consumables)].

In the 'cost insulin seemingly unrelated regression model', the cost of insulin in year 1 and the cost of insulin in year 2 were used as the outcome variables for the seemingly unrelated regression model. Baseline cost of insulin, baseline HbA_{1c}, treatment allocation, whether or not the individual switched from MDI to insulin pump infusion in year 1 and whether or not the individual switched from insulin pump infusion to MDI in year 1 were included as covariates to predict the cost of insulin in year 1. Baseline cost of insulin, baseline HbA_{1c}, the actual method of insulin delivery that an individual was using at the end of the first year, whether or not the individual switched from MDI to insulin pump infusion in year 2 and whether or not the individual switched from insulin pump infusion to MDI in year 2 were included as covariates to predict the cost of insulin in year 2. The SEs were adjusted for clustering in each DAFNE course. For each individual in the model, their baseline cost of using insulin, their HbA_{1c}, their treatment at the start of the year and whether or not they switched treatment were used with the parameter values from the regression to predict their cost of insulin.

In the 'cost of diabetes-related contacts seemingly unrelated regression model', the cost of diabetes-related contacts in year 1 and year 2 were used as the outcome variables for the seemingly unrelated regression model. Baseline cost of diabetes-related contacts, baseline HbA_{1c}, and treatment allocation – whether or not the individual switched from MDI to insulin pump infusion in year 1 and whether or not the individual switched from insulin pump infusion to MDI in year 1 – were included as covariates to predict the cost of insulin in year 1. Baseline cost of diabetes-related contacts, baseline HbA_{1c}, the actual method of insulin delivery that an individual was using at the end of the first year, whether or not the individual switched from MDI to insulin pump infusion in year 2 and whether or not the individual switched from insulin pump infusion to MDI in year 2 were included as covariates to predict the cost of insulin in year 2. The SEs were adjusted for clustering in each DAFNE course. For each individual in the model, their baseline cost of diabetes-related contact resource use, their HbA_{1c}, their treatment at the start of the year and whether or not they switched treatment were used with the parameter values from the regression to predict their cost of insulin pump therapy.

In the 'cost of insulin pump seemingly unrelated regression model', the cost of insulin pumps and consumables in year 1 and the cost of insulin pumps and consumables in year 2 were the two outcome variables used in the model. No control was made for baseline resource use or baseline HbA_{1c} for either outcome variable, as no individual in the REPOSE Trial had a previous history of using an insulin pump. The individual's randomised treatment arm, whether or not they switched from pump to MDI in the first year and whether or not they switched from MDI to pump in the first year were included as covariates to predict the cost of insulin pumps and consumables in year 1. An individual's actual treatment at the end of the first year, whether or not they switched from pump to MDI in year 2 and whether or not they switched from MDI to pump in year 2 were included as covariates to predict the cost of insulin pumps and consumables in year 2. For each individual in the model, their HbA_{1c}, their treatment at the start of the year and whether or not they switched treatment were used with the parameter values from the regression to predict their cost of insulin pump therapy.

Duration of treatment effectiveness beyond the trial period

A key parameter for the long-term cost-effectiveness modelling is the duration of effectiveness of the two interventions and, in particular, the length of time that HbA_{1c} improvements last. The REPOSE Trial provides data only up to 2 years after randomisation. Therefore, the available literature on the long-term duration of treatment effectiveness for MDI individuals taking a DAFNE course and pump + DAFNE individuals needs to be assessed to determine the assumptions to be used for HbA_{1c} progression beyond the 2-year trial period.

A literature search was conducted for studies on the duration of HbA_{1c} improvements for MDI + DAFNE individuals and insulin pump therapy individuals. Seven potentially relevant studies were identified. Two studies^{124,125} were identified as being potentially relevant for MDI + DAFNE individuals. Five studies^{56–59,63} were identified as being potentially relevant for insulin pump therapy individuals. Two studies^{56,59} were excluded: Beato-Vibora *et al.*⁵⁶ was not included because fewer than one-quarter of the individuals in the initial sample had follow-up data for any given year; Clements *et al.*⁵⁹ was excluded because it was a subgroup analysis of the data presented by Carlsson *et al.*⁵⁸ As such, if Carlsson *et al.*⁵⁸ was included to estimate the long-term duration of treatment effect of pump therapy, the effect estimated from Clements *et al.*⁵⁹ would be given double the weight of the other studies because of a published subgroup analysis being available.

For the five included studies^{56–59,63} (two studies for adults receiving MDI + DAFNE and three studies for adults receiving pump + DAFNE), the average yearly increase in HbA_{1c} was estimated, pragmatically, using data from the point of largest reduction in HbA_{1c} and the last observation in which the sample size was greater than one-quarter of the initial sample size. A weighted average of these studies' evidence (using the initial sample size) calculated the mean yearly HbA_{1c} increase for both trial arms (*Table 9*). The weighted average yearly HbA_{1c} increase for insulin pump therapy individuals was 0.052% per annum. The weighted average yearly HbA_{1c} increase for MDI + DAFNE individuals was 0.054% per annum.

TABLE 9 A summary of the observed changes in HbA_{1c} over time for pump and MDI

Study	Treatment group				
	Pump			MDI	
	^a Orr <i>et al.</i> , 2015 ⁶³	Carlsson <i>et al.</i> , 2013 ⁵⁸	Bruttomesso <i>et al.</i> , 2002 ⁵⁷	Gunn and Mansell, 2012 ¹²⁵	Speight <i>et al.</i> , 2010 ¹²⁴
Initial sample size	200	272	138	111	104
Baseline HbA _{1c} , %	8.68	8.39	9.30	8.6	9.3
Peak HbA _{1c} improvement, %	-1.18	-0.43	-1.34	-0.5	-0.6
Time of peak HbA _{1c} improvement, years	0.5	2	1	1	1
Last observed HbA _{1c} improvement with $n \geq 25\%$ the initial sample size, %	-0.49	-0.20	-1.31	-0.37	-0.4
Time of last HbA _{1c} improvement	9 years	5 years	10 years	7 years	44 months
Average yearly HbA _{1c} increase (from peak to last observed value)	0.08	0.06	0.00	0.03	0.08
Implied time to baseline (years from baseline)	9.9	8.5	408.6 (lifetime effect)	19.0	8.2
Funding	None stated	Region of Gotland in Sweden	None stated	NIHR	Diabetes UK and DAFNE collaborative

^a Data are assumed to be observed in the middle of a follow-up period for the analysis.

The uncertainty in these long-term changes was parameterised using a normal distribution in the PSA. There was no SD for the mean HbA_{1c} increases across the studies in each model arm; data were obtained from the REPOSE Trial on the SD of the mean change in HbA_{1c} between years 1 and 2. The mean observed change in HbA_{1c} between years 1 and 2 for individuals receiving MDI + DAFNE was -0.08%, with a SD of 0.84%. The mean observed change in HbA_{1c} between years 1 and 2 for individuals receiving pump + DAFNE was -0.09%, with a SD of 0.98%. To estimate the SE for each trial arm, the SD associated with each trial arm was divided by the combined sample size of the studies used to estimate the long-term changes in HbA_{1c}. The estimated mean effect and the estimated SE for each model arm were used to parameterise a normal distribution for the PSA.

In the base-case analysis, data from the studies on the HbA_{1c} increases for MDI + DAFNE individuals and pump individuals were used for each individual's lifetime. To ensure that each individual could not have implausibly high or low HbA_{1c} values, their HbA_{1c} was constrained so that it could not fall below 4.8% or go above 20.5%.

In addition to these five studies, the cost-effectiveness model used by Riemsma *et al.*⁸ used an annual progression of 0.045% per annum derived from the DCCT trial. This was assumed to apply equally to all comparators analysed in the study. In a further sensitivity analysis it was assumed that individuals would return to their baseline HbA_{1c} at the end of the third year in the model with no further progression of their HbA_{1c}.

Threshold analysis

A two-way price and effectiveness threshold analysis was conducted to assess the HbA_{1c} reduction and/or annual cost reduction necessary to potentially make CSII cost-effective in the UK for the whole UK population of adults with T1DM who are eligible to receive a structured education course, are naive to pump therapy and do not have a preference to receive the pump. A conservative assumption was made, in that all HbA_{1c} changes did not apply to 1-year HbA_{1c}, but did apply to all future years. The treatment effect associated with pump + DAFNE compared with MDI + DAFNE was varied between HbA_{1c} changes of -0.3% and -1.2%, in -0.1% increments.

There were two methods used for estimating the change in HbA_{1c} due to receiving pump therapy. In the first method, the following steps were taken: (1) all individuals' HbA_{1c} values were estimated as if they were a MDI + DAFNE recipient and then (2) a treatment effect (HbA_{1c} change) of pump + DAFNE versus MDI + DAFNE was inputted into the model. In the second method (1) the reduction in HbA_{1c} was applied to the individual's mean effect in the beta regression; (2) this reduction in HbA_{1c} resulted in a different variance to an equivalent MDI patient as their mean effect was lower; and (3) HbA_{1c} was sampled from the individualised beta distribution, which reflected the mean effect and variance parameters. The second method of conducting the threshold analysis will help future investigators to understand the effect of including heterogeneity in an individual's response to CSII on the HbA_{1c} reductions that are required to make CSII cost-effective. However, it should be noted that this method assumes that the heterogeneity is defined by the equations estimated from the REPOSE Trial and, as such, may not be valid if CSII were to be clinically more effective.

In both scenario analyses, the cost of insulin pumps and insulin pump consumables was changed from 100% of the mean cost obtained from the pump costing survey to 50% of the mean price observed at REPOSE sites in 5% price reduction increments. Deterministic model runs were used to produce all of the results in the threshold analysis.

It should be noted that other than the method used to estimate HbA_{1c}, all of the other parameters were the same, and assumptions were the same as were used in the base case. As all assumptions were the same as those presented for the base-case analysis, all individuals who switched from MDI + DAFNE to pump + DAFNE received the HbA_{1c} associated with pump + DAFNE, and the individuals who switched from pump + DAFNE to MDI + DAFNE received their HbA_{1c} associated with MDI + DAFNE. This means that the modelled HbA_{1c} reductions are equivalent to per-protocol analysis (treatment switchers removed) rather than an ITT analysis (treatment switchers included in their originally randomised groups) of any future study of pump + DAFNE versus MDI + DAFNE.

As no study other than REPOSE has been conducted to assess the cost-effectiveness of pump + DAFNE versus MDI + DAFNE for adults in the UK with T1DM, the results should be indicative of the HbA_{1c} reductions that pump + DAFNE would need to achieve if it were to be deemed cost-effective compared with MDI + DAFNE.

Methods for the psychosocial evaluation

Aims and objectives

As noted in *Chapter 2*, evidence on QoL effects of the pump has been inconsistent, with some studies reporting no difference between the pump and MDI groups, and others reporting improved QoL on the pump. A previous HTA report identified some gains in QoL that could be described as 'social related' rather than 'health related'.¹⁴ These included flexibility of lifestyle and fewer problems dealing with variations in daily life, such as timing of meals. For this reason, we included a range of psychosocial measures alongside embedded qualitative research in the REPOSE Trial.

The psychosocial study employed a mixed-methods quantitative (questionnaires) and qualitative (interviews) approach to:

1. establish whether or not, and why, there were any differences in QoL and other psychological or psychosocial outcomes between participants using pump and MDI regimens
2. examine whether or not, and why, QoL and other outcomes changed over time
3. understand and explore the added benefit (if any) of pump technology over MDI from participants' and educators' perspectives
4. explore why some patients may do better than others using the pump
5. examine acceptability of, and reasons for, discontinuing (pump) treatment
6. enhance understanding and assist in the interpretation of trial outcomes.

Quantitative methods

Validated and reliable questionnaires were used to assess generic and health-specific QoL, treatment satisfaction, fear of hypoglycaemia, hypoglycaemia unawareness, self-efficacy, social support, adherence to treatment, emotional well-being and acceptability of technology. A repeated-measures longitudinal questionnaire study explored both differences in outcomes between the two trial arms and the short- and long-term predictors and mediators of outcomes. Outcomes were measured at baseline and at 6, 12 and 24 months after the DAFNE course. These time points were selected to capture both short- and long-term post-treatment changes in psychosocial outcomes. Questionnaires were posted to participants and self-completed within 6 weeks of the specified time point.

Outcomes

Quantitative psychosocial end points were measured via participant self-completed questionnaires, which included items assessing QoL (generic and diabetes specific), fear of hypoglycaemia, treatment satisfaction and emotional well-being. There has been limited examination of the impact of pump therapy on these areas, on how and why these may change over time, and why individuals are able or unable to use pump therapy to improve glycaemic control. Rubin and Peyrot¹²⁶ reviewed the evidence on 'patient-reported outcomes' and concluded that, at present, there is little evidence that pump therapy improves them.

Diabetes-specific QoL was assessed using the DSQOL, a reliable and valid measure.¹²⁷ Specifically designed for the German study on which UK DAFNE is based, it was included to facilitate important comparisons between the UK and German studies. In addition, generic measures of QoL, the World Health Organization Quality of Life Abbreviated Questionnaire (WHOQOL-BREF)¹²⁸ and functional health status using the SF-12¹²⁹ and EQ-5D¹³⁰ were used. The SF-12 was used to facilitate comparison with 'healthy controls' and other long-term conditions.

The HFS¹³¹ is a well-validated psychometric tool assessing participants' fear of hypoglycaemia, both overall and separately, for behaviour and worry. A specific benefit to the survey is that it may be able to identify participants who are likely to maintain high blood glucose levels, thus aiding understanding of potential reasons for poor glycaemic control. A study by Nixon and Pickup,¹³² in people who had been using a pump for an average of 5 years, found that fear of hypoglycaemic episodes remained a problem.

The DTSQ¹³³ has proven to be highly sensitive in clinical trials.¹³⁴ Treatment satisfaction refers to an individual's subjective appraisal of their experience of treatment, including ease of use, side effects and efficacy. Improvements in satisfaction are not necessarily accompanied by improvements in QoL; treatment satisfaction can be high despite diabetes having a negative impact on QoL, which is why it is important to measure both separately.

The Hospital Anxiety and Depression Scale (HADS)¹³⁵ measures anxiety on one subscale and depression on another through the use of seven questions for each characteristic. It was important to measure emotional well-being in the trial, as participants may find it easier to manage their condition after DAFNE education or with one of the treatments. This could have a substantial effect on their emotional well-being, which the QoL measures are not sensitive enough to pick up.

The DAFNE Principles Questionnaire was completed at 24 months only. This questionnaire (12 items) assesses the impact of the DAFNE course on self-management behaviours, such as bolus and basal rate changes, correction dose practices, timing of injections/bolus doses and review of blood glucose data. It was included partly in order to establish if there were differences in self-management practices between participants in the pump and MDI arms, to aid interpretation of the final trial findings. The DAFNE Principles Questionnaire was administered to all of the participants irrespective of treatment group. This measure was previously used in DAFNE.⁷⁸

Statistical power was calculated for the primary outcome of HbA_{1c}, thus the psychosocial outcomes are either over- or underpowered, depending on the underlying effect size. Statistically significant results are considered in combination with qualitative data in order to answer the key psychosocial research aims.

Statistical analysis of questionnaire data

Short Form questionnaire-12 items

The Physical Component Summary was calculated using physical functioning, body pain, role physical and general health domain scores. The Mental Component Summary was calculated using vitality, social functioning, role emotional and mental health domain scores. When the questionnaires were only partially completed, missing items were imputed using a single imputation procedure based on the mean calculated from complete items on that domain.¹³⁶ The scores were standardised and scaled to range from 0 to 100, with higher scores representing better outcomes.^{129,137}

Diabetes-specific quality of life

The DSQOL domain scores (social relations, leisure time restrictions and flexibility, physical complaints, worries about the future, daily hassle or functions, diet restrictions) and DSQOL total score were calculated if at least 80% of the items from the domain were complete, using the following formula:

$$\text{Domain score} = \text{sum of at least 80\% items} \times \frac{\text{number of items on domain}}{\text{number of non missing items}} \quad (5)$$

Preference-weighted treatment satisfaction was calculated by multiplying the various treatment goals with the corresponding degree of satisfaction (scores of $-2.5 =$ totally dissatisfied to $2.5 =$ extremely satisfied) and summing the results.

Finally, all DSQOL scores were converted to a 0–100 scale, in which a higher value means worse outcome (more burden) on all scores.

World Health Organization Quality of Life Abbreviated Questionnaire

Four subdomains of WHOQOL-BREF were calculated (physical health, psychological, social relationships and environment) if at least 80% of the questions in that domain were present. The domains were scored by calculating the mean of the items within each domain, and scaling to range from 0 to 100,¹³⁸ with higher scores representing better outcomes.

Hypoglycaemia Fear Survey

The HFS behaviour and worry scores were calculated if at least 80% of items within that domain were complete, using *Equation 5* (see *Diabetes-specific quality of life*).¹³¹

The HFS behaviour score ranges from 10 to 50 and the HFS worry score ranges from 17 to 85; in both cases, higher scores represent more fear.

Diabetes Treatment Satisfaction Questionnaire

The DTSQ, which measured satisfaction with diabetes treatment, was administered at baseline and 6- and 24-month follow-up. The DTSQc [Diabetes Treatment Satisfaction Questionnaire (change)], which measures change in satisfaction from pre-trial treatment, was administered at 12 months' follow-up.

Treatment satisfaction (DTSQ) and treatment satisfaction change (DTSQc) were calculated if at least five of the six items were complete using the following formula:

$$\text{Treatment satisfaction (change)} = \text{sum of at least five items} \times \frac{6}{\text{number of non-missing items}} \quad (6)$$

For the treatment satisfaction domain, higher scores represent higher satisfaction (range 0 to 36 on DTSQ and -18 to 18 on DTSQc). Two further domains, perceived frequency (change) in hyperglycaemia and perceived frequency (change) in hypoglycaemia, were calculated based on single items. Only complete

data were used for these scores and low scores represent good perceived blood glucose control (scoring ranges of 0 to 6 in DTSQ, and -3 to 3 in DTSQc).

Hospital Anxiety and Depression Scale

Anxiety and depression domain scores were calculated by summing the items in the respective domains. Mean value imputation based on the other six items of a domain was used to impute missing data if a single item was missing. If more than one item was missing then the domain score was not calculated. The HADS scores range from 0 to 21, with higher scores indicating more anxiety/depression (scoring: normal is 0–7; borderline abnormal 8–10; 11–21 abnormal).¹³⁵

EuroQol-5 Dimensions

The EQ-5D-3L tariff was derived from five three-level questions using UK norms. The tariff was calculated only if all five questions were answered. It is measured on a scale from -0.56 to 1.00 (good health).

The availability of questionnaire outcome data was summarised for each time point.

The DTSQ domains at 6, 12 and 24 months post course were compared between the treatment groups using a non-parametric Wilcoxon–Mann–Whitney *U*-test. The median and interquartile range (IQR) of change from baseline for the DTSQ domains at 6 and 24 months, and the median and IQR score for the DTSQc domains at 12 months, are displayed by treatment group. The differences between groups post course are displayed as the median difference (in change from baseline for DTSQ scores) with its associated 95% CI, which was calculated as described in the study by Newson.¹³⁹

Other QoL outcomes (DSQOL, SF-12, WHOQOL-BREF, HFS, EQ-5D, HADS) at 6 months post course are compared between the treatment groups using a mixed-effects linear regression model of change from baseline adjusted for DAFNE course (random effect), baseline HbA_{1c}, baseline score and centre. The means and SDs for the treatment and control groups with adjusted MDs and associated CIs and *p*-values (unadjusted for multiple testing) are reported. This analysis is repeated for the 12- and 24-month outcomes. A complementary sensitivity analysis, in which the analysis described above was repeated only including patients with complete data, was performed.

Qualitative methods

Study design

An inductive, thematic approach was used, informed by the principles of Grounded Theory research.¹⁴⁰ This entailed concurrent data collection and analysis, allowing findings and themes arising from early phases of data collection to inform the areas explored in later phases, as well as sampling. In-depth interviews, informed by topic guides, were used as the main method of data collection, as these helped to ensure that the discussion remained relevant to areas under investigation, while affording the flexibility needed for participants to raise and discuss issues that they perceived as salient, including those unforeseen at the study's outset.^{141,142}

Patient participants, recruited from both trial arms, were interviewed at two time points: within 2 weeks of completing their DAFNE courses (round 1) and 6 months later (round 2). This longitudinal design permitted patients' initial understandings and experiences of using the pump and MDI regimens to be explored, and any continuities and changes in their diabetes self-management practices to be tracked and compared over time. Six months was selected as the time point for follow-up to coincide with collection of 6-month clinical and psychological data, and because previous experience of undertaking longitudinal qualitative research with DAFNE graduates had demonstrated that this allowed sufficient time to establish whether, and for what reasons, patients are able/unable to put their skills training into practice.^{143–146} In addition, cost considerations (including a request by the funder to reduce the costings for the qualitative component prior to the protocol being finalised) meant that it was not possible to do follow-up interviews with patients at later time points.

Educators were interviewed once, following completion of their centre's sixth REPOSE DAFNE course. This time point was chosen to avoid any risk of inadvertent contamination of the trial intervention by the qualitative questioning, and also because, at this point, it was anticipated that staff would have had considerable experience of trial recruitment and delivery on which they could reflect.

Recruitment and sampling

As per the original protocol, participants (patients and educators) were recruited from seven of the eight trial centres (with roughly equal numbers recruited from each centre); recruitment to the qualitative research was not undertaken in the eighth centre (Nottingham), as this centre came on board only in the later phases of the trial and recruited patients to only one set of courses.

When they were consented to take part in the trial, patient participants were asked whether or not they would be willing to be approached to take part in the qualitative research (see *Appendix 8*). Of the 317 patients who were randomised, 315 (99.37%) agreed to be approached. Participants who gave this agreement were purposively sampled so that both those randomised to pump and MDI arms of the trial were recruited and there was broad, and roughly equal, representation of ages, sex, diabetes duration and occupational/socioeconomic groups in the final sample.

It was initially planned that one nurse and one dietitian would be recruited and interviewed from each of the seven main trial centres. However, after initial interviews had been conducted and analysed, a decision was made to increase the number of nurse educators interviewed. This is because the initial interviews had made apparent that these staff members tended to have the greatest involvement in recruitment and notifying patients of the outcome of randomisation, and, as reported elsewhere,¹⁴⁷ these aspects of trial work proved to be particularly challenging for staff. Educators were sent recruitment packs and invited to 'opt in' to the study; all of those approached agreed to take part.

Recruitment of patients and educators continued until data saturation occurred, that is until no new findings or themes were identified in new data collected. All participants provided written consent prior to their interviews.

Data collection

Baseline interviews with patients were undertaken face to face to establish rapport and were conducted at a time and location convenient to them (mostly their own homes). Follow-up interviews were done by telephone (again at a time most convenient to the interviewee). There was no apparent difference in the quality and disclosure of information between interviews undertaken face to face and those done on the telephone. All staff opted to be interviewed by telephone.

Topic guides for the patient interviews were developed in light of literature reviews, course observations, inputs from the trial team and patient representatives, and revised in light of emerging findings. Full details of the topics explored in patients' round 1 and round 2 interviews are provided in *Appendix 9*. In brief, round 1 interviews explored patients' understandings of the trial and the pump, and their reasons for agreeing to take part; their views about the outcome of randomisation; and their early experiences of using a MDI or pump regimen to undertake diabetes self-management practices following course attendance and training in DAFNE principles. Round 2 interviews were used to explore whether or not, how and why patients' experiences of managing their diabetes had changed since their last interview (including reasons for adhering or not adhering to treatment recommendations, discontinuing treatment, etc.); how the use of their regimen (pump or MDI) had impacted on their perceptions of their diabetes, their confidence and perceived ability to undertake diabetes self-management practices; and their everyday (work and family) lives. Although broadly the same areas were explored in the follow-up interviews, each participant's round 1 interview account was reviewed before their round 2 interview was undertaken to enable follow-up of specific issues raised by particular individuals.

Staff interviews explored their experiences of recruiting into the REPOSE Trial, delivering the 5-day courses and undertaking patient follow-up as part of the trial; perceptions of patients' engagement with pump therapy compared with MDI during the trial; previous experiences (if any) of using insulin pumps in routine clinical practice; and views about the potential benefits of the pump compared with MDI regimens. In light of emerging findings, staff were also invited to reflect on whether or not their views about the potential benefits, and beneficiaries, of insulin pumps had changed in light of their experiences of delivering, and observing, patients during the REPOSE Trial. Full details of the areas explored in the staff interviews are also contained within *Appendix 9*.

Interviews with patients were conducted between June 2012 and June 2013, and those with staff between December 2012 and April 2013. All interviews averaged 1 hour, were digitally recorded and transcribed in full for in-depth analysis.

Data analysis

Data were analysed thematically using the method of constant comparison.¹⁴⁸ This entailed members of the qualitative research team reading patient and educator transcripts (which were treated as 'stand-alone' data sets) repeatedly before cross-comparing them to identify issues and experiences that cut across different patient and educator accounts. To address the study aims and objectives, a longitudinal analysis of the patient data was also undertaken. Each individual's round 1 and round 2 accounts were cross-compared and attention paid to continuities and changes in their experiences, views and diabetes self-management practices (using pump or MDI) over time, and the reasons for these. A key aspect of this analysis also focused on comparison of the (longitudinal) accounts of patients using pump and MDI regimens. This was done to better understand the impact of using pump (compared with MDI) regimens on patients' diabetes self-management practices, disease perceptions and everyday life.

Members of the qualitative team undertook their own independent analyses and wrote separate reports before meeting (both during and after data collection) to compare their interpretations, discuss discrepant cases, and reach agreement on recurrent themes and findings. For both patient and educator interviews, a final coding frame, which reflected the original study aims/questions and emergent themes, was developed once all of the data had been reviewed and consensus reached on key themes and findings. NVivo9 (Doncaster, VIC, Australia), a qualitative software package, was used to facilitate data coding and retrieval. Coded data sets were subjected to further analyses to allow for the identification of subthemes and illustrative quotations.

Confidentiality

To protect participants' identities, each individual was allocated a unique identifier and these identifiers are used in the reporting of interview data. In the case of staff, 'N' is used to refer to a nurse and 'D' to a dietitian. In the case of patients, data are tagged with the participant's treatment arm ('M' for MDI, 'P' for pump), identifying number and interview round (e.g. 'M7.2' refers to the second interview with MDI participant 7).

Chapter 4 Changes to the protocol

All study amendments are listed in *Appendix 10*. The most significant changes are explained below.

Inclusion/exclusion criteria

As NICE guidance advises that all patients who have poor diabetic control are considered for pump therapy, early concern was raised at the TMG regarding the potential for inclusion of individuals who had a definite need for pump therapy. Such participants were not the intended trial population for REPOSE. Prior to the start of recruitment, the inclusion and exclusion criteria were therefore changed in order to clarify that suitable participants were those who, in the opinion of the investigator, have a need for structured education to optimise their diabetes control, but do not have a clear indication for pump therapy. In the early stages of recruitment (January 2012), the criteria were clarified to exclude those who have a strong need for pump therapy. Further clarifications of the exclusion criteria for patients who have used pump therapy within the last 3 years were made in April 2012, defined as > 2 weeks' use within the last 3 years. Following early site monitoring visits in July 2012 some further minor clarifications were made to the exclusion criteria to confirm that a severe needle phobia must preclude full participation in either treatment arm or influence the participants' preference for pump therapy, and an unstable psychological condition must be active enough to preclude the participant safely taking part in the trial.

Recruitment target

The ITT population was defined as participants who consent to take part in the trial and who attend their DAFNE course at least in part. Although the trial was on course to meet the set recruitment target, it was noted that larger than anticipated numbers were withdrawing consent prior to the DAFNE course, resulting in lower than anticipated numbers eligible for the ITT analysis. The trial statistician undertook a review in August 2012 to determine the need for additional DAFNE courses and participants to maintain study power. Scenarios were modelled based on the current and predicted HbA_{1c} population prevalence of $\geq 7.5\%$, dropout rate (10% or 15%) and size of DAFNE course (four, five, six or seven participants). Assuming that these variables remained similar to those observed (as at August 2012), it was estimated that the trial would need to run an additional two to seven courses in order to maintain power for the primary outcome. Therefore, a reserve centre (Nottingham University Hospitals NHS Trust) was initiated. The target recruitment was increased to 'no more than 340 participants', with 280 expected to attend the DAFNE course (as originally planned).

Data collection procedures

The study power was calculated on a 90% retention rate at 24 months. Although in May 2013 the 6-month participant retention was high (95%), the trial team anticipated challenges in maintaining this rate at 24 months. To ensure that follow-up rates remained adequate, we added the option for site staff to collect appropriate data from participants over the telephone when participants had been unable to attend for follow-up. Furthermore, we included the possibility of obtaining outcome data from participants' medical records, for which participants had given consent. We also added an option for data to be collected at participants' homes or appropriate NHS location, if they had been unable to attend at their centre.

Diabetic ketoacidosis/illness letter to participants

Episodes of DKA were expected to occur in some REPOSE participants – as this is a known complication for individuals with T1DM – and were reported as SAEs. The TMG, TSC and DMEC regularly reviewed all SAEs and it was noted early in the trial that some centres were reporting an unexpectedly high number of DKA events. The DMEC reviewed the events and, although the numbers were not considered a major concern, recommended that a troubleshooting document be issued to participants as a precautionary measure, which was then agreed by the TSC. This provided written guidelines on how to manage illness. These were sent to all participants, following approval by the REC in August 2013. The pump troubleshooting document was based on a hand-out already issued to participants during the DAFNE education course and an equivalent version was provided to MDI participants (see *Appendix 11*). The letter also served as a reminder for participants to contact their diabetes team regarding any problems that they may be experiencing and to report any adverse health events that may have occurred.

The 24-month letter incorporating information about severe hypoglycaemia reporting

In October 2011 the UK Driver and Vehicle Licensing Agency released new medical standards for people with diabetes, containing stricter rules advising that people experiencing more than one severe episode of hypoglycaemia in 1 year should not drive. It was noted that reporting of severe hypoglycaemic events during the trial had been low and the TMG had concerns that patients may have been under-reporting events. The letter issued to all participants at 24 months – reminding them of their appointment and enclosing a copy of the psychosocial questionnaire for completion – was updated to reassure them that all of the information provided as part of the trial ‘is kept completely anonymous and not sent to any organisation where participants could be identified’ (see *Appendix 12*).

Bolus calculators letter

Participants on both arms of the trial were provided with bolus calculators. These devices help patients to calculate the correct pre-meal insulin dose to inject. Patients on MDI therapy would not always be provided with these devices; however, this was deemed necessary to reduce any potential bias, as pump participants had access to a bolus calculator via the pump. The qualitative research undertaken post course, and at 6 months, had indicated that some patients had become de-skilled and dependent on the devices, whereas others misunderstood the need to change the parameters, believing they had been pre-programmed during the DAFNE course. In some cases this could have been leading to ineffective management of their diabetes, potentially affecting their health. The issue was discussed with the trial DMEC, who suggested that a brief, light-touch intervention was administered to all of the participants in the trial, highlighting effective use of the devices. The TSC chairperson agreed with this action. Therefore, as a precautionary safety measure, in January 2014 we sent a document to *all* of the participants in the trial detailing appropriate use of the devices (see *Appendix 13*).

Chapter 5 Results of the randomised controlled trial

Trial recruitment

Participant recruitment initially took place at seven centres between November 2011 and December 2012. A review of recruitment and retention in August 2012 revealed higher than expected dropout rates prior to the DAFNE courses. The recruitment target was therefore increased to a maximum of 340, but with no more than 280 in the ITT population. In order to achieve this we facilitated an additional pair of DAFNE courses at an existing centre (Harrogate) and introduced a reserve centre (Nottingham) to facilitate a further two courses. Recruitment continued until April 2013. *Figure 2* illustrates recruitment and course attendance rates against targets. *Table 10* summarises course attendance by treatment group, with similar mean participant numbers per course. *Table 11* shows recruitment details by centre.

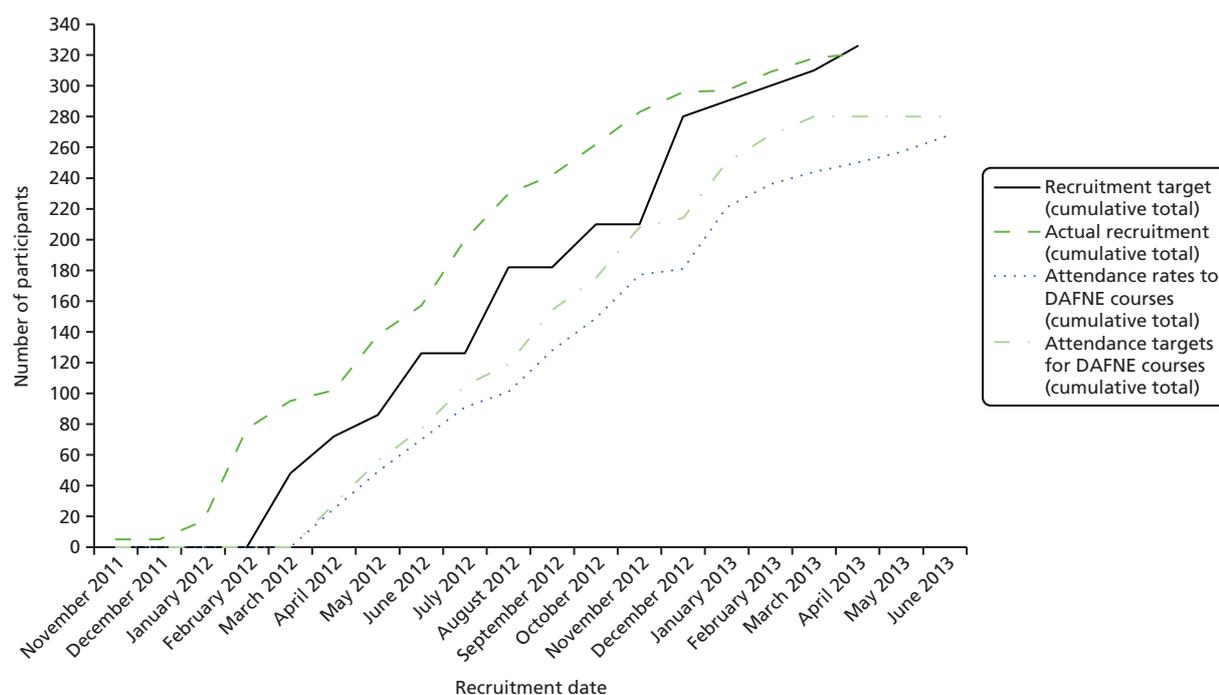


FIGURE 2 Participant recruitment and attendance targets and rates.

TABLE 10 Summary of course attendance

Summary of course attendance	Treatment group		
	MDI	Pump	Total
Mean number of participants (SD)	5.87 (1.39)	5.74 (1.39)	5.80 (1.38)
Median number of participants (IQR)	6 (5–7)	6 (5–7)	6 (5–7)
Minimum to maximum	3–8	3–8	3–8

TABLE 11 Recruitment by centre

Centres	Number of courses per centre	Number of participants attended
Sheffield Teaching Hospitals NHS Foundation Trust		
	Course 1: MDI	7
Total number of participants recruited: 41	Course 2: Pump	7
Recruited:	Course 3: MDI	5
First participant 10 January 2012	Course 4: Pump	4
Last participant 19 October 2012	Course 5: MDI	8
	Course 6: Pump	7
NHS Greater Glasgow and Clyde		
	Course 1: Pump	8
Total number of participants recruited: 45	Course 2: MDI	6
Recruited:	Course 3: Pump	7
First participant 1 February 2012	Course 4: MDI	8
Last participant 27 November 2012	Course 5: MDI	5
	Course 6: Pump	6
King's College Hospital NHS Trust		
	Course 1: Pump	5
Total number of participants recruited: 41	Course 2: MDI	6
Recruited:	Course 3: MDI	5
First participant 12 February 2012	Course 4: Pump	3
Last participant 5 December 2012	Course 5: Pump	6
	Course 6: MDI	4
Cambridge University Hospitals NHS Foundation Trust		
	Course 1: Pump	6
Total number of participants recruited: 43	Course 2: MDI	4
Recruited:	Course 3: MDI	7
First participant 23 November 2011	Course 4: Pump	5
Last participant 20 December 2012	Course 5: Pump	8
	Course 6: MDI	4
Harrogate and District NHS Foundation Trust		
	Course 1: Pump	6
Total number of participants recruited: 55	Course 2: MDI	7
Recruited:	Course 3: Pump	7
First participant 28 February 2012	Course 4: MDI	6
Last participant 10 April 2013	Course 5: MDI	7
	Course 6: Pump	5
	Course 7: Pump	7
	Course 8: MDI	6
NHS Dumfries and Galloway		
	Course 1: Pump	5
Total number of participants recruited: 41	Course 2: MDI	7

TABLE 11 Recruitment by centre (*continued*)

Centres	Number of courses per centre	Number of participants attended
Recruited:	Course 3: Pump	7
First participant 3 February 2012	Course 4: MDI	4
Last participant 2 October 2012	Course 5: MDI	3
	Course 6: Pump	4
NHS Lothian		
	Course 1: MDI	7
Total number of participants recruited: 43	Course 2: Pump	5
Recruited:	Course 3: Pump	6
First participant 8 May 2012	Course 4: MDI	6
Last participant 20 November 2012	Course 5: MDI	7
	Course 6: Pump	4
Nottingham University Hospitals NHS Trust		
	Course 1: MDI	6
Total number of participants recruited: 12	Course 2: Pump	4
Recruited:		
First participant 21 February 2013		
Last participant 15 March 2013		
Total recruited: 321	Total attendance	267

Participant flow

Figure 3 shows the CONSORT flow of participants through the trial. In total 1278 people were invited to take part, of which 885 responded. Of these responders, 362 were interested in taking part. Reasons given for non-participation are listed in Table 12. Of those interested, 334 were assessed as eligible and 321 of these consented to take part. Four of these dropped out prior to randomisation. Forty-six courses (23 course pairs) were randomised, comprising 317 participants (156 pump and 161 MDI). Fifty patients were excluded from the analysis: 40 patients withdrew before baseline data were collected and 10 withdrew before they attended a DAFNE course. All randomised courses were delivered.²³ One participant was deemed protocol non-compliant, as he/she had not adhered to the DAFNE course (as adjudicated by the course leader). Of the 267 participants (132 pump and 135 MDI) who were randomised, attended baseline visit and attended a DAFNE course, 260 (132 pump and 128 MDI) had HbA_{1c} data for at least one post-baseline follow-up visit and these make the ITT set. A total of 248 participants (128 pump and 120 MDI) had complete primary outcome data at 24 months' follow-up.²³

Baseline data

Table 13 shows the baseline demographics and characteristics of the trial population. Overall, eight centres recruited to the study contributing between 10 and 51 participants per centre. Patients were more likely to be male (60%) and were generally white British (91%). The average age of participants was 41 years.

Table 14 shows the history of diabetes among study participants at baseline. The median (IQR) duration of diabetes was 16 (8–26) years, 12% of the participants had an episode of severe hypoglycaemia in the 12 months prior to baseline and around half of the participants had a prior history of complications (55%).

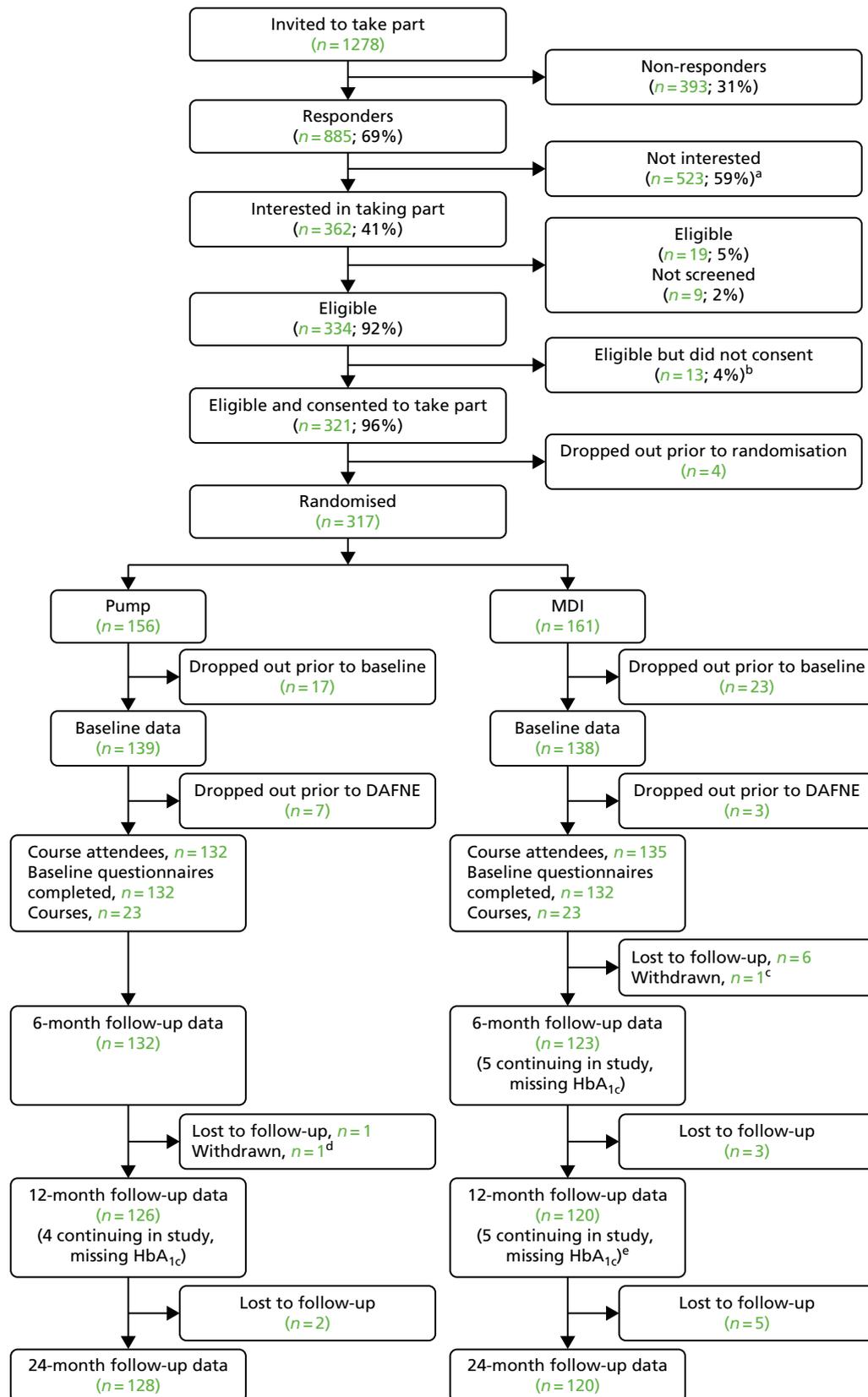


FIGURE 3 The CONSORT flow diagram. **Note:** for footnotes, see Table 12. Reproduced from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

TABLE 12 Reasons for non-participation (footnote to CONSORT flow diagram)

Reason	n (%)
(a) Most common reasons for non-participation based on 521 completed forms (multiple reasons per individual)	
Not interested in having a pump	189 (36)
Could not take week off work	123 (24)
Satisfied with my current treatment and management of diabetes	93 (18)
Lack of time	76 (15)
No reason documented/provided	29 (6)
Other	27 (5)
Does not meet eligibility criteria	26 (5)
Difficulty travelling to the course	21 (4)
Dependants at home	19 (4)
Moving/moved away from area/transferred care	16 (3)
Not willing to take part if not receiving a pump	13 (2)
Not interested in REPOSE	13 (2)
(b) Reasons for non-participation, based on seven completed forms (multiple reasons per individual)	
Not interested in having a pump	2 (29)
Lack of time	2 (29)
Could not take week off work	2 (29)
Other	1 (14)
Satisfied with my current treatment and management of diabetes	1 (14)
Not willing to take part if not receiving a pump	1 (14)
Medical reasons:	1 (14)
(c) Participant does not wish to continue because of personal/family issues	
(d) Participant does not wish to continue (switched from pump to MDI, did not like the practicalities of pump therapy)	
(e) Of the five participants continuing in study at 12 months – but without 12-month data – three had available 6-month data, two had no 6-month data	

TABLE 13 Demographics and characteristics of participants at baseline

Variable	Scoring	Treatment group		
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)
Recruitment centre, n (%)	London (King's College Hospital)	14 (10.6)	15 (11.1)	29 (10.9)
	Sheffield	18 (13.6)	20 (14.8)	38 (14.2)
	Glasgow	21 (15.9)	19 (14.1)	40 (15.0)
	Dumfries	16 (12.1)	14 (10.4)	30 (11.2)
	Cambridge	19 (14.4)	15 (11.1)	34 (12.7)
	Harrogate	25 (18.9)	26 (19.3)	51 (19.1)
	Edinburgh	15 (11.4)	20 (14.8)	35 (13.1)
	Nottingham	4 (3.0)	6 (4.4)	10 (3.7)

continued

TABLE 13 Demographics and characteristics of participants at baseline (continued)

Variable	Scoring	Treatment group			
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)	
Sex, n (%)	Male	78 (59.1)	82 (60.7)	160 (59.9)	
	Female	54 (40.9)	53 (39.3)	107 (40.1)	
Smoking status, n (%)	Smoker	23 (17.4)	30 (22.2)	53 (19.9)	
	Ex-smoker	42 (31.8)	27 (20.0)	69 (25.8)	
	Never smoker	67 (50.8)	78 (57.8)	145 (54.3)	
Ethnicity, n (%)	White British ^a	125 (94.7)	119 (88.1)	244 (91.4)	
	Irish	1 (0.8)	0 (0.0)	1 (0.4)	
	Any other white background	1 (0.8)	3 (2.2)	4 (1.5)	
	Indian	1 (0.8)	1 (0.7)	2 (0.7)	
	Chinese	0 (0.0)	1 (0.7)	1 (0.4)	
	African	0 (0.0)	1 (0.7)	1 (0.4)	
	Caribbean	0 (0.0)	1 (0.7)	1 (0.4)	
	Arab	0 (0.0)	1 (0.7)	1 (0.4)	
	Any other ethnic group	0 (0.0)	4 (3.0)	4 (1.5)	
	Prefer not to say	1 (0.8)	3 (2.2)	4 (1.5)	
	Missing	3 (2.3)	1 (0.7)	4 (1.5)	
	ONS occupational status, ^b n (%)	Level 1	32 (24.2)	24 (17.8)	56 (21.0)
		Level 2	37 (28.0)	43 (31.9)	80 (30.0)
Level 3		39 (29.5)	46 (34.1)	85 (31.8)	
Level 4		12 (9.1)	14 (10.4)	26 (9.7)	
Not classifiable		4 (3.0)	2 (1.5)	6 (2.2)	
Missing		8 (6.1)	6 (4.4)	14 (5.2)	
Highest qualification obtained, n (%)	No formal qualifications	7 (5.3)	8 (5.9)	15 (5.6)	
	GCSE level	24 (18.2)	26 (19.3)	50 (18.7)	
	A-level	10 (7.6)	8 (5.9)	18 (6.7)	
	Vocational qualification	40 (30.3)	32 (23.7)	72 (27.0)	
	Undergraduate degree	25 (18.9)	32 (23.7)	57 (21.3)	
	Postgraduate degree	15 (11.4)	17 (12.6)	32 (12.0)	
	Other	9 (6.8)	9 (6.7)	18 (6.7)	
	Missing	2 (1.5)	3 (2.2)	5 (1.9)	
Age (years)	n (%)	132 (100.0)	135 (100.0)	267 (100.0)	
	Mean (SD)	41.5 (14.2)	39.9 (12.5)	40.7 (13.4)	
	Median (IQR)	40.7 (27.9–52.3)	41.0 (28.0–48.8)	40.8 (28.0–49.4)	
	Minimum to maximum	18.5–77.6	18.5–73.1	18.5–77.6	
Body weight (kg)	n (%)	132 (100.0)	135 (100.0)	267 (100.0)	
	Mean (SD)	82.4 (18.2)	80.0 (17.4)	81.2 (17.8)	
	Median (IQR)	81.2 (69.1–91.6)	78.1 (67.0–91.0)	79.6 (68.4–91.2)	
	Minimum to maximum	50.4–144.8	46.5–148.4	46.5–148.4	

TABLE 13 Demographics and characteristics of participants at baseline (*continued*)

Variable	Scoring	Treatment group		
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)
BMI (kg/m ²)	n (%)	132 (100.0)	135 (100.0)	267 (100.0)
	Mean (SD)	27.4 (5.0)	27.0 (5.0)	27.2 (5.0)
	Median (IQR)	27.1 (23.8–29.7)	26.6 (23.5–29.2)	26.9 (23.7–29.5)
	Minimum to maximum	17.4–47.9	17.2–45.9	17.2–47.9
HFS behaviour score	n (%)	130 (98.5)	132 (97.8)	262 (98.1)
	Mean (SD)	30.3 (5.8)	29.1 (5.5)	29.7 (5.7)
	Median (IQR)	29.0 (27.0–34.0)	29.5 (25.0–33.0)	29.0 (26.0–33.0)
	Minimum to maximum	17.0–50.0	16.0–42.0	16.0–50.0
HFS worry score	n (%)	131 (99.2)	132 (97.8)	263 (98.5)
	Mean (SD)	40.7 (14.6)	37.9 (13.3)	39.3 (14.0)
	Median (IQR)	37.0 (30.0–47.0)	36.0 (28.0–45.0)	37.0 (29.0–46.0)
	Minimum to maximum	17.0–82.0	17.0–85.0	17.0–85.0
IMD ^c	n (%)	78 (59.1)	79 (58.5)	157 (58.8)
	Mean (SD)	15.9 (13.7)	17.2 (11.3)	16.5 (12.5)
	Median (IQR)	11.0 (7.7–18.9)	13.3 (9.5–22.3)	13.0 (8.6–19.6)
	Minimum to maximum	2.3–73.2	3.1–54.0	2.3–73.2
SIMD ^d	n (%)	51 (38.6)	53 (39.3)	104 (39.0)
	Mean (SD)	22.0 (18.3)	22.5 (17.0)	22.2 (17.6)
	Median (IQR)	16.9 (8.0–26.4)	18.6 (10.5–29.9)	17.5 (8.8–28.5)
	Minimum to maximum	2.4–73.8	1.9–74.7	1.9–74.7

GCSE, General Certificate of Secondary Education; ONS, Office for National Statistics; SIMD, Scottish Index of Multiple Deprivation.

a White British = English/Welsh/Scottish/Northern Irish/British.

b Level 1: elementary trade, service and admin roles; level 2: construction, building trade and agricultural, caring, protective services, public service workers or equivalent; level 3: managerial positions, public service professionals, skilled construction, building trade and electrical trades, health and social welfare professionals, science and technology professionals or equivalent; level 4: corporate managers and directors, research and teaching professionals, business and public service higher level professionals or equivalent.¹⁴⁹

c English Index of Multiple Deprivation (2010) displayed for English centres only.¹⁵⁰

d Scottish Index of Multiple Deprivation (2012) displayed for Scottish centres only.¹⁵¹

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Table 15 shows the history of severe hypoglycaemic episodes by baseline HbA_{1c} category: 5 (20%) of the 25 participants with HbA_{1c} of < 7.5% had an episode in the 12 months prior to baseline; 26 (11%) of the 242 participants with baseline HbA_{1c} of ≥ 7.5% had an episode in the 12 months prior to baseline.

Table 16 shows laboratory results of participants at baseline. The mean HbA_{1c} was 9.3% or 77.9 mmol/mol in the pump group and 9.0% or 74.8 mmol/mol in the MDI group. Other than this difference in baseline HbA_{1c}, the data appear to be well balanced across treatment groups.

Table 17 summarises the proportion of participants with above and below 7.5% HbA_{1c} at baseline in each centre, stratified by treatment group.

TABLE 14 History of diabetes among study participants at baseline

Variable	Scoring	Treatment group		
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)
Duration of diabetes (years)	n (%)	132 (100.0)	135 (100.0)	267 (100.0)
	Mean (SD)	18.5 (12.9)	17.5 (12.1)	18.0 (12.5)
	Median (IQR)	16.5 (7.8–27.7)	14.9 (7.7–25.4)	15.8 (7.7–26.4)
	Minimum to maximum	1.1–56.9	1.1–51.9	1.1–56.9
Prior history of complications	No	63 (47.7)	56 (41.5)	119 (44.6)
	Yes	69 (52.3)	79 (58.5)	148 (55.4)
Retinopathy as a complication	Yes	51 (38.6)	65 (48.1)	116 (43.4)
	No	81 (61.4)	70 (51.9)	151 (56.6)
Neuropathy as a complication	Yes	13 (9.8)	6 (4.4)	19 (7.1)
	No	119 (90.2)	129 (95.6)	248 (92.9)
Number of all forms of complications	≥ 1 (%)	68 (51.5)	79 (58.5)	147 (55.1)
	n (%)	132 (100)	135 (100)	267 (100)
	Mean (SD)	1.0 (1.3)	1.1 (1.2)	1.1 (1.3)
	Median (IQR)	1.0 (0–2)	1.0 (0–2)	1.0 (0–2)
	Minimum to maximum	0–6	0–5	0–6
Number of confirmed moderate hypoglycaemic episodes ^a	≥ 1 (%)	89 (67.4)	90 (66.7)	179 (67.0)
	n (%)	132 (100)	135 (100)	267 (100)
	Mean (SD)	2.6 (3.9)	2.0 (2.7)	2.3 (3.4)
	Median (IQR)	1.0 (0–3)	1.0 (0–3)	1.0 (0–3)
	Minimum to maximum	0–27	0–16	0–27
Number of moderate nocturnal hypoglycaemic episodes ^a	≥ 1 (%)	41 (31.1)	46 (34.1)	87 (32.6)
	n (%)	132 (100)	135 (100)	267 (100)
	Mean (SD)	0.5 (1.0)	0.7 (1.3)	0.6 (1.2)
	Median (IQR)	0.0 (0–1)	0.0 (0–1)	0.0 (0–1)
	Minimum to maximum	0–5	0–10	0–10
Number of severe hypoglycaemia ^b	≥ 1 (%)	16 (12.1)	15 (11.1)	31 (11.6)
	n (%)	132 (100)	135 (100)	267 (100)
	Mean (SD)	0.17 (0.52)	0.16 (0.50)	0.16 (0.51)
	Median (IQR)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
	Minimum to maximum	0–3	0–3	0–3

a History in the previous 4 weeks prior to DAFNE course attendance.

b Twelve-month history prior to baseline.

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TABLE 15 History of severe hypoglycaemic episodes at baseline by baseline HbA_{1c} category

Scoring	Number of severe hypoglycaemic episodes ^a		
	HbA _{1c} < 7.5% (N = 25)	HbA _{1c} ≥ 7.5% (N = 242)	Total (N = 267)
≥ 1, n (%)	5 (20.0)	26 (10.7)	31 (11.6)
n (%)	25 (100)	242 (100)	267 (100)
Mean (SD)	0.36 (0.81)	0.14 (0.46)	0.16 (0.51)
Median (IQR)	0.0 (0–0)	0.0 (0–0)	0.0 (0–0)
Minimum to maximum	0–3	0–3	0–3

a 12-month history prior to baseline.

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TABLE 16 Laboratory test results of participants at baseline

Variable	Scoring	Treatment group		
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)
HbA _{1c} , n (%)	< 7.5	13 (9.8)	12 (8.9)	25 (9.4)
	≥ 7.5	119 (90.2)	123 (91.1)	242 (90.6)
Proteinuria (unconfirmed), n (%)	Normal	90 (68.2)	86 (63.7)	176 (65.9)
	Microalbuminuria	18 (13.6)	14 (10.4)	32 (12.0)
	Macroalbuminuria	3 (2.3)	9 (6.7)	12 (4.5)
	Missing	21 (15.9)	26 (19.3)	47 (17.6)
Classification of chronic kidney disease, n (%)	None	82 (62.1)	85 (63.0)	167 (62.5)
	Mild	19 (14.4)	15 (11.1)	34 (12.7)
	Moderate	5 (3.8)	2 (1.5)	7 (2.6)
	Severe	2 (1.5)	7 (5.2)	9 (3.4)
	Missing	24 (18.2)	26 (19.3)	50 (18.7)
HbA _{1c}	n (%)	132 (100.0)	135 (100.0)	267 (100.0)
	Mean (SD)	9.3 (1.9)	9.0 (1.4)	9.1 (1.7)
	Median (IQR)	8.9 (8.1–10.2)	8.6 (8.0–9.9)	8.7 (8.1–9.9)
	Minimum to maximum	5.7–16.7	6.1–14.1	5.7–16.7
HbA _{1c} (mmol/mol)	n (%)	132 (100.0)	135 (100.0)	267 (100.0)
	Mean (SD)	77.9 (21.0)	74.8 (15.6)	76.3 (18.5)
	Median (IQR)	74.0 (65.0–88.0)	71.0 (64.0–85.0)	72.0 (65.0–85.0)
	Minimum to maximum	39.0–159.0	43.0–131.0	39.0–159.0
Creatinine (µmol/l)	n (%)	129 (97.7)	134 (99.3)	263 (98.5)
	Mean (SD)	76.8 (17.4)	78.4 (20.5)	77.6 (19.0)
	Median (IQR)	73.0 (64.0–85.0)	73.0 (64.0–89.0)	73.0 (64.0–86.0)
	Minimum to maximum	49.0–163.0	42.0–158.0	42.0–163.0

continued

TABLE 16 Laboratory test results of participants at baseline (continued)

Variable	Scoring	Treatment group		
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)
ACR (mg/mol)	n (%)	130 (98.5)	129 (95.6)	259 (97.0)
	Unable to calculate	20 (15.4)	20 (15.5)	40 (15.4)
	< 3	90 (69.2)	86 (66.7)	176 (68.0)
	3–10	10 (7.7)	12 (9.3)	22 (8.5)
	10–30	8 (6.2)	2 (1.6)	10 (3.9)
	30+	2 (1.5)	9 (7.0)	11 (4.2)
eGFR (mmol/l)	n (%)	129 (97.7)	135 (100.0)	264 (98.9)
	30–44	3 (2.3)	2 (1.5)	5 (1.9)
	45–59	5 (3.9)	6 (4.4)	11 (4.2)
	≤ 60–90	90 (69.8)	89 (65.9)	179 (67.8)
	≥ 90	31 (24.0)	38 (28.1)	69 (26.1)
Cholesterol (mmol/l)	n (%)	132 (100.0)	134 (99.3)	266 (99.6)
	Mean (SD)	5.0 (1.0)	4.9 (0.9)	5.0 (0.9)
	Median (IQR)	5.0 (4.4–5.6)	4.8 (4.2–5.4)	4.9 (4.3–5.6)
	Minimum to maximum	2.8–8.6	2.7–8.0	2.7–8.6
Triglycerides (mmol/l)	n (%)	132 (100.0)	135 (100.0)	267 (100.0)
	Mean (SD)	1.4 (1.2)	1.4 (0.8)	1.4 (1.0)
	Median (IQR)	1.1 (0.8–1.6)	1.2 (0.8–1.7)	1.1 (0.8–1.6)
	Minimum to maximum	0.3–11.2	0.3–5.9	0.3–11.2
HDL cholesterol (mmol/l)	n (%)	125 (94.7)	133 (98.5)	258 (96.6)
	Mean (SD)	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)
	Median (IQR)	1.6 (1.3–1.9)	1.4 (1.2–1.7)	1.5 (1.2–1.8)
	Minimum to maximum	0.6–3.2	0.5–2.7	0.5–3.2
QAID, units/body weight (kg)	n (%)	128 (97.0)	133 (98.5)	261 (97.8)
	Mean (SD)	0.37 (0.17)	0.37 (0.16)	0.37 (0.16)
	Median (IQR)	0.33 (0.25–0.49)	0.35 (0.24–0.47)	0.33 (0.24–0.47)
	Minimum to maximum	0.10–0.99	0.12–1.17	0.10–1.17
BID, units/body weight (kg)	n (%)	128 (97.0)	134 (99.3)	262 (98.1)
	Mean (SD)	0.35 (0.17)	0.38 (0.21)	0.37 (0.19)
	Median (IQR)	0.32 (0.23–0.45)	0.34 (0.26–0.45)	0.33 (0.25–0.45)
	Minimum to maximum	0.08–1.04	0.10–1.48	0.08–1.48
PMID, units/body weight (kg)	n (%)	4 (3.0)	1 (0.7)	5 (1.9)
	Mean (SD)	0.78 (0.32)	1.43 ^a	0.91 (0.40)
	Median (IQR)	0.84 (0.53–1.03)	1.43 (1.43–1.43)	0.99 (0.69–1.07)
	Minimum to maximum	0.36–1.07	1.43–1.43	0.36–1.43

BID, background insulin dose; eGFR, estimated glomerular filtration rate; PMID, Pre-Mixed Insulin Dose; QAID, Quick-Acting Insulin Dose.

^a A SD cannot be provided here as this value is based on data for one person.

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TABLE 17 Baseline HbA_{1c} level by centre

Recruitment centre	HbA _{1c} (%)	Treatment group		
		Pump (N = 132), n (%)	MDI (N = 135), n (%)	Total (N = 267), n (%)
All	≥ 7.5	119 (90.2)	123 (91.1)	242 (90.6)
London (King's College Hospital)	< 7.5	1 (7.1)	5 (33.3)	6 (20.7)
	≥ 7.5	13 (92.9)	10 (66.7)	23 (79.3)
Sheffield	< 7.5	2 (11.1)	1 (5.0)	3 (7.9)
	≥ 7.5	16 (88.9)	19 (95.0)	35 (92.1)
Glasgow	< 7.5	0 (0.0)	1 (5.3)	1 (2.5)
	≥ 7.5	21 (100.0)	18 (94.7)	39 (97.5)
Dumfries	< 7.5	2 (12.5)	0 (0.0)	2 (6.7)
	≥ 7.5	14 (87.5)	14 (100.0)	28 (93.3)
Cambridge	< 7.5	3 (15.8)	1 (6.7)	4 (11.8)
	≥ 7.5	16 (84.2)	14 (93.3)	30 (88.2)
Harrogate	< 7.5	4 (16.0)	1 (3.8)	5 (9.8)
	≥ 7.5	21 (84.0)	25 (96.2)	46 (90.2)
Edinburgh	< 7.5	1 (6.7)	3 (15.0)	4 (11.4)
	≥ 7.5	14 (93.3)	17 (85.0)	31 (88.6)
Nottingham	< 7.5	0 (0.0)	0 (0.0)	0 (0.0)
	≥ 7.5	4 (100.0)	6 (100.0)	10 (100.0)

Protocol deviations

One participant was excluded from the per-protocol analysis set, as they did not adhere to the DAFNE course (this is not including the dropouts prior to the DAFNE course).

Twenty-five patients had a single treatment change form that recorded change across study treatments; 17 patients switched from pump to MDI and eight patients switched from MDI to pump. Two patients on the pump arm changed to MDI and back again (recorded on treatment change forms), and other participants recorded temporary treatment breaks at the follow-up appointments. After review, excluding any reasonable temporary treatment interruptions, 236 out of the 260 ITT participants were considered as compliant with the protocol. Of the 235 ITT participants with baseline HbA_{1c} of ≥ 7.5%, 18 were considered protocol deviations, leaving 217 in the per-protocol analysis set. Participants who deviated from the protocol started with higher baseline HbA_{1c} across both the treatment groups (Table 18); however, greater improvement was seen for the protocol deviants in the MDI group. The reasons for protocol deviation/treatment change are shown in Table 19.

Primary outcome

Table 20 shows the primary outcome, change in HbA_{1c} at 24 months in participants whose baseline HbA_{1c} was ≥ 7.5%. The mean change in the pump group was a decrease of 0.85% or 9.3 mmol/mol, whereas the mean decrease in the MDI group was 0.42% or 4.5 mmol/mol. After adjusting for centre, course and baseline HbA_{1c}, the MD in HbA_{1c} change from baseline was -0.24% (95% CI -0.53% to 0.05%) or -2.7 mmol/mol (95% CI -5.8 to 0.5 mmol/mol; *p* = 0.098).²³ Figure 4 shows the distribution of HbA_{1c} change at 2 years, by treatment group.

TABLE 18 Glycated haemoglobin (% and mmol/mol) by treatment group and protocol adherence

Timing	HbA _{1c} unit	Statistics	Protocol deviation		Per protocol	
			Pump (<i>n</i> = 11)	MDI (<i>n</i> = 7)	Pump (<i>n</i> = 108)	MDI (<i>n</i> = 109)
Baseline		<i>n</i>	11	7	108	109
	%	Mean (SD)	10.4 (2.4)	10.3 (1.4)	9.5 (1.7)	9.1 (1.3)
	mmol/mol	Mean (SD)	90.5 (26.1)	89.4 (15.3)	80.1 (18.7)	75.6 (14.0)
6 months		<i>n</i>	11	7	108	104
	%	Mean (SD)	9.9 (2.5)	10.0 (2.6)	8.7 (1.4)	8.6 (1.4)
	mmol/mol	Mean (SD)	84.2 (26.9)	85.7 (28.8)	71.5 (15.8)	71.0 (15.1)
12 months		<i>n</i>	7	7	106	101
	%	Mean (SD)	10.6 (2.3)	9.5 (2.0)	8.8 (1.5)	8.6 (1.4)
	mmol/mol	Mean (SD)	92.7 (25.4)	79.9 (21.4)	72.4 (16.6)	70.5 (15.0)
24 months		<i>n</i>	9	7	106	102
	%	Mean (SD)	9.7 (2.1)	8.3 (1.6)	8.6 (1.4)	8.7 (1.4)
	mmol/mol	Mean (SD)	82.4 (23.1)	67.1 (17.8)	70.5 (15.7)	71.5 (15.5)

TABLE 19 Details of treatment change

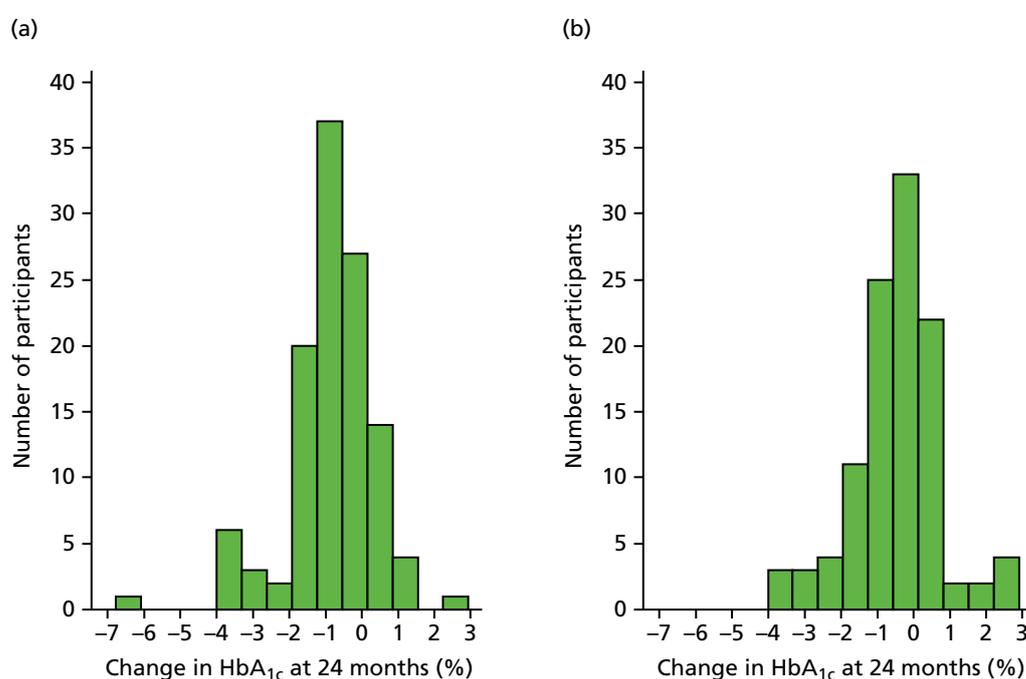
Treatment change	ID	Month of treatment change ^a	Reason for treatment change
Switched from pump to MDI	1	0	Participant withdrawal from the DAFNE course
	2	0	Participant did not tolerate trial treatment: risk of DKA as a result of not following safety protocols
	3	3	Participant did not tolerate trial treatment: problems with cannula sites
	4	4	Participant did not tolerate trial treatment: problems with cannulas
	5	7	Participant did not tolerate trial treatment: headaches, erratic blood glucose and stress
	6	12	Participant did not tolerate trial treatment: inconvenience of delivery method
	7	13	Participant did not tolerate trial treatment: found pump difficult to manage
	8	13	Other: did not like the practicalities of being on a pump
	9	14	Participant did not tolerate trial treatment: pump did not suit him
	10	23	Other: patient decision without input from team
	11	23	Participant did not tolerate trial treatment: painful cannula sites reported
Switched from MDI to pump	12	9	Other: fear of disabling hypoglycaemia
	13	14	Other: persistently elevated morning glycaemia
	14	15	Other: pump therapy clinically appropriate
	15	15	Other: clinical need for pump therapy
	16	18	Investigator decision: deterioration in HbA _{1c} ; meets criteria for trial of pump therapy
	17	19	Other: continuing problems with hypoglycaemia
	18	20	Other: dawn phenomenon

^a Calculated as months from the start of the DAFNE course.

TABLE 20 Effectiveness of the intervention: MD in change in HbA_{1c} (% or mmol/mol) at 24 months in participants whose baseline HbA_{1c} was $\geq 7.5\%$

Primary outcome	Treatment group				Difference in mean change ^a (95% CI)	p-value
	Pump		MDI			
	n	Mean (SD)	n	Mean (SD)		
Change in HbA _{1c} (%)	119	-0.85 (1.25)	116	-0.42 (1.21)	-0.24 (-0.53 to 0.05)	0.098
Change in HbA _{1c} (mmol/mol)	119	-9.3 (13.66)	116	-4.5 (13.19)	-2.7 (-5.8 to 0.5)	

a Adjusted for baseline HbA_{1c}, centre and DAFNE course using a mixed-effects regression model. Multiple imputation, using chained equations (regression), based on 50 imputed data sets with baseline, 6- and 12-month HbA_{1c} measurements, DAFNE course, centre, age, sex and HFS behaviour as covariates, was used to impute missing 24-month data, if a participant had some HbA_{1c} follow-up data. SDs reported for complete data.

**FIGURE 4** Changes in HbA_{1c} (%) at 24 months in participants whose baseline HbA_{1c} was $\geq 7.5\%$. (a) Pump; and (b) MDI.

The treatment difference was larger for the per-protocol analysis: MD -0.36% (95% CI -0.64% to -0.07%) or -3.9 mmol/mol (95% CI -7.0 to -0.8 mmol/mol) in favour of the pump; $p = 0.015$. However, the observed point estimate was still smaller than the minimum clinically important difference of 0.5% or 5.5 mmol/mol,²³ although the 95% CI includes this clinically important effect.

Table 21 shows sensitivity analysis on the primary outcome; the analysis was repeated for complete case, imputing data for all participants, excluding mistimed measurements and excluding pregnant women. The results from Tables 20 and 21 are presented graphically in Figure 5. All sensitivity analyses show similar results to the primary analysis shown in Table 20.

Notes: (1) Thirteen local laboratory HbA_{1c} values were used in the final analysis (two at 6 months, one at 12 months, 10 at 24 months), seven HbA_{1c} values were taken from patient notes (one at 6 months, four at 12 months, two at 24 months). (2) ICC from complete case model at 24 months is 0.005. If centre is excluded from the model (as a fixed effect), the ICC is 0.08.

TABLE 21 Sensitivity analysis on the primary outcome (change in HbA_{1c} at 24 months in participants whose baseline HbA_{1c} was ≥ 7.5%)

Sensitivity analysis set	HbA _{1c} unit of measurement	Treatment group		n	Mean change (SD)	n	Mean change (SD)	Difference ^a (95% CI)	p-value
		Pump	MDI						
Per protocol	%	108	-0.85 (1.28)	109	-0.31 (1.12)			-0.36 (-0.64 to -0.07)	0.015
	mmol/mol	108	-9.3 (13.96)	109	-3.4 (12.23)			-3.9 (-7.0 to -0.8)	
Multiple imputation ^b	%	119	-0.85 (1.25)	123	-0.44 (1.21)			-0.24 (-0.53 to 0.05)	0.104
	mmol/mol	119	-9.3 (13.66)	123	-4.8 (13.19)			-2.7 (-5.8 to 0.5)	
Mean value imputation	%	119	-0.83 (1.23)	123	-0.45 (1.14)			-0.22 (-0.49 to 0.05)	0.105
	mmol/mol	119	-9.1 (13.43)	123	-4.9 (12.44)			-2.4 (-5.3 to 0.5)	
Complete case	%	115	-0.84 (1.25)	109	-0.43 (1.21)			-0.22 (-0.50 to 0.06)	0.127
	mmol/mol	115	-9.2 (13.66)	109	-4.7 (13.19)			-2.4 (-5.4 to 0.7)	
Excluding mistimed measurements	%	114	-0.85 (1.25)	104	-0.44 (1.16)			-0.19 (-0.47 to 0.09)	0.186
	mmol/mol	114	-9.3 (13.69)	104	-4.8 (12.72)			-2.1 (-5.2 to 1.0)	
Excluding pregnant women	%	115	-0.84 (1.25)	107	-0.41 (1.21)			-0.23 (-0.52 to 0.05)	0.104
	mmol/mol	115	-9.2 (13.66)	107	-4.5 (13.22)			-2.6 (-5.7 to 0.5)	

a Adjusted for baseline HbA_{1c}, centre and course using a mixed-effects regression model.

b Multiple imputation using chained equations (regression) based on 50 imputed data sets with baseline, 6- and 12-month HbA_{1c} measurements, DAFNE course, centre, age, sex, and HFS behaviour as covariates: SDs reported for complete data.

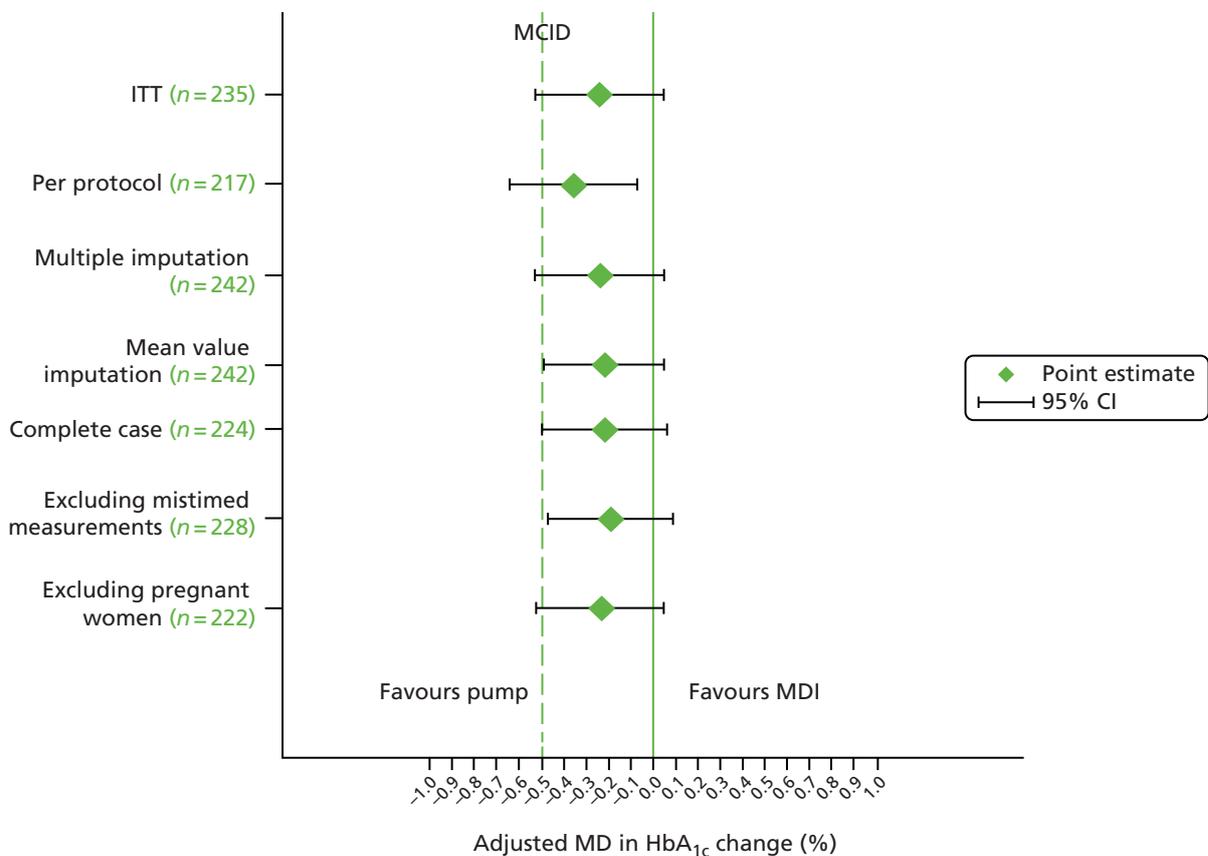


FIGURE 5 Forest plot of MD in change from baseline in HbA_{1c} (%) at 24 months between groups for the sensitivity analysis samples. MCID, minimum clinically important difference, adjusted for baseline HbA_{1c}, centre and DAFNE course.

The change in HbA_{1c} for participants with data at all four time points is displayed, by treatment group, in *Figure 6*. The majority of improvement in HbA_{1c} occurred in the first 6 months; HbA_{1c} stayed roughly constant between 6 and 24 months. The change in HbA_{1c} over time is also displayed in *Figure 7*, but here all of the participants with post-baseline data are included. Each coloured line represents a participant, and the thick black line is the mean for each treatment group.

Table 22 shows the mean change at 24 months for the treatment groups combined; the change in all participants with complete 24-month HbA_{1c} data was a decrease of 0.54% (95% CI 0.38% to 0.69%) or 5.9 mmol/mol (95% CI 4.2 to 7.6 mmol/mol). For participants with baseline HbA_{1c} ≥ 7.5%, the reduction was slightly bigger, of 0.64% (95% CI 0.48% to 0.80%) or 7 mmol/mol (95% CI 5.2 to 8.8 mmol/mol).²³

Sensitivity analysis: effect of centre and lead Dose Adjustment For Normal Eating course educator

We undertook a further analysis that used a nested model of patients within courses, which, in turn, are nested within course lead educators, to investigate differences in outcomes between lead educators. For this nested model, the ICC of the lower-level clustering variable, DAFNE course, is 0.5%; for the upper-level clusters, lead educator, ICC < 0.1%. We found no evidence of notable differences in outcomes between lead course educators. This analysis was performed for available data only.

We explored the centre effect through an interaction test between centre and treatment group. Results of estimated MD in HbA_{1c} change (% or mmol/mol) at 24 months are presented by centre with the aid of forest plots (*Figure 8*). The overall *p*-value for the interaction between treatment and centre was 0.565, suggesting that there is no centre effect. The centre with the largest difference between treatments was Nottingham, although the CI for this centre is large because of the small number of participants with outcome data at that centre.

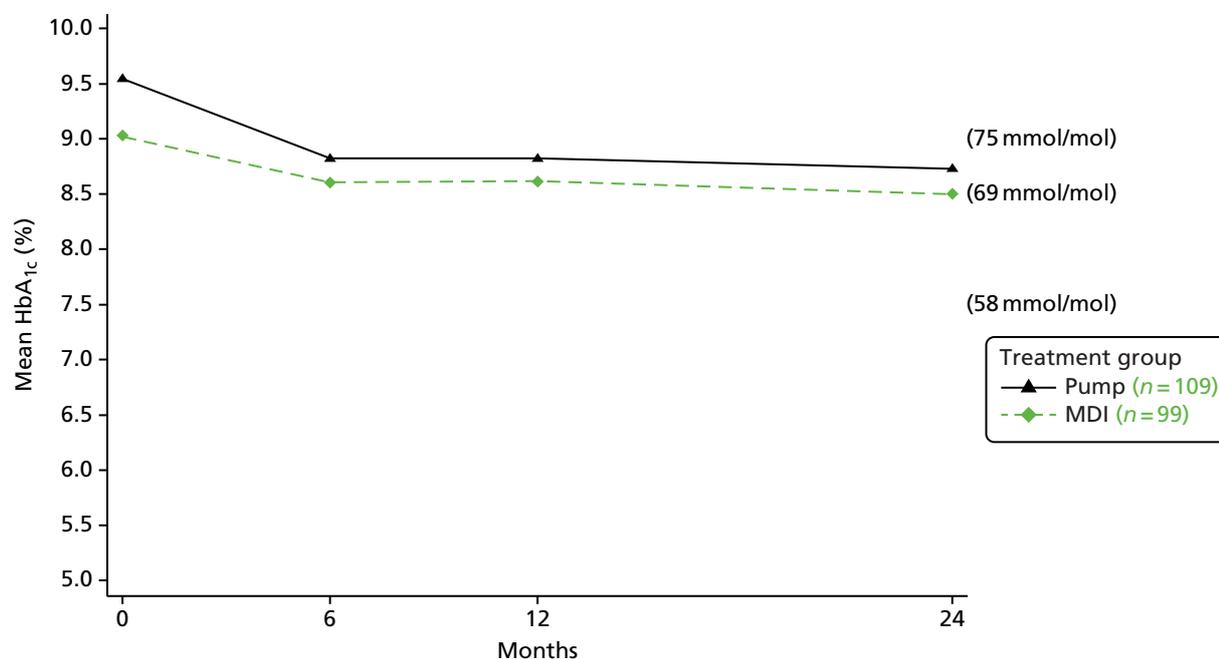


FIGURE 6 Mean HbA_{1c} (%) over time in participants whose baseline HbA_{1c} was ≥ 7.5% (58 mmol/mol) (including only participants with data at all four visits, *n* = 208). Numbers in parentheses are mmol/mol equivalent. Reproduced from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

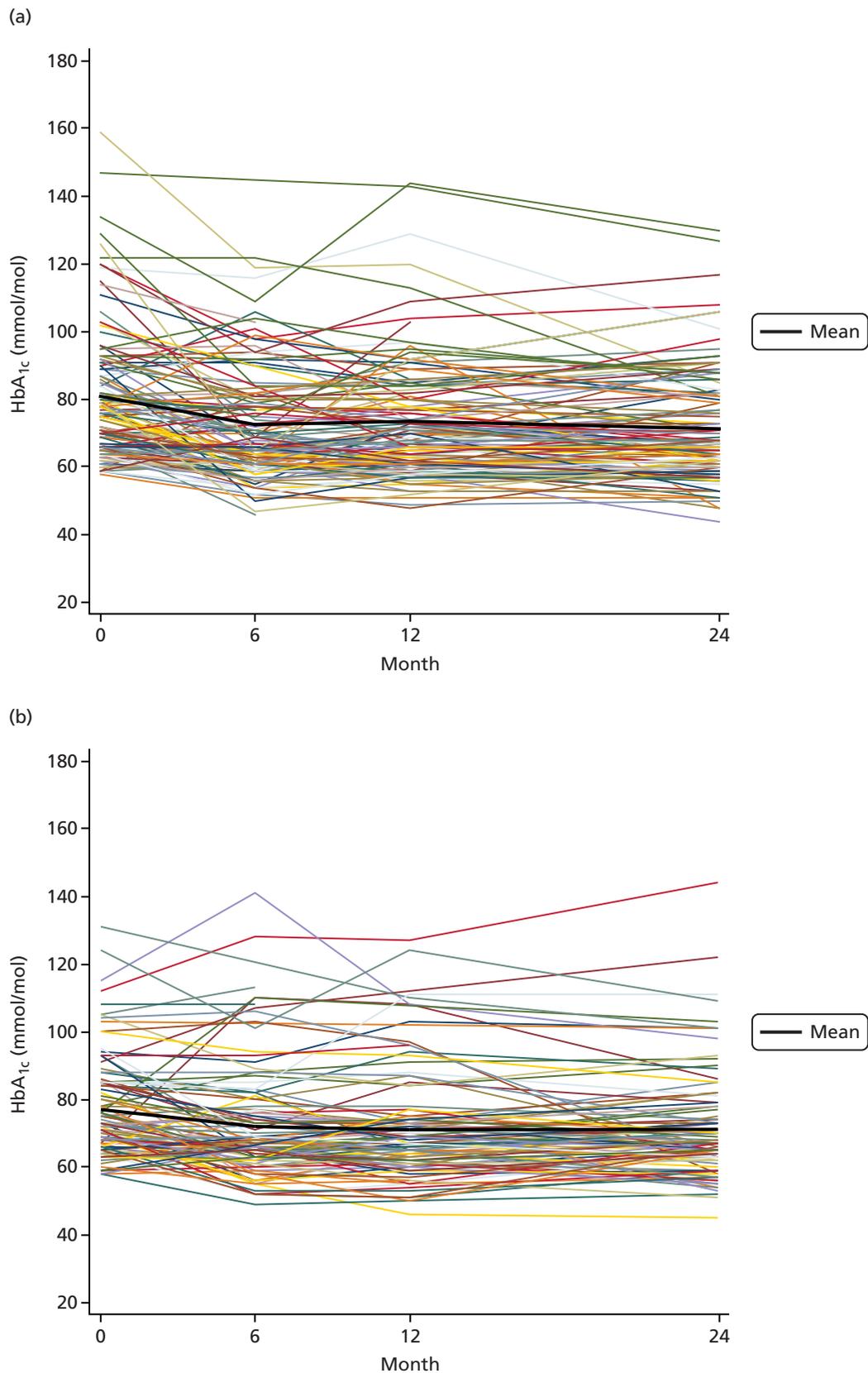
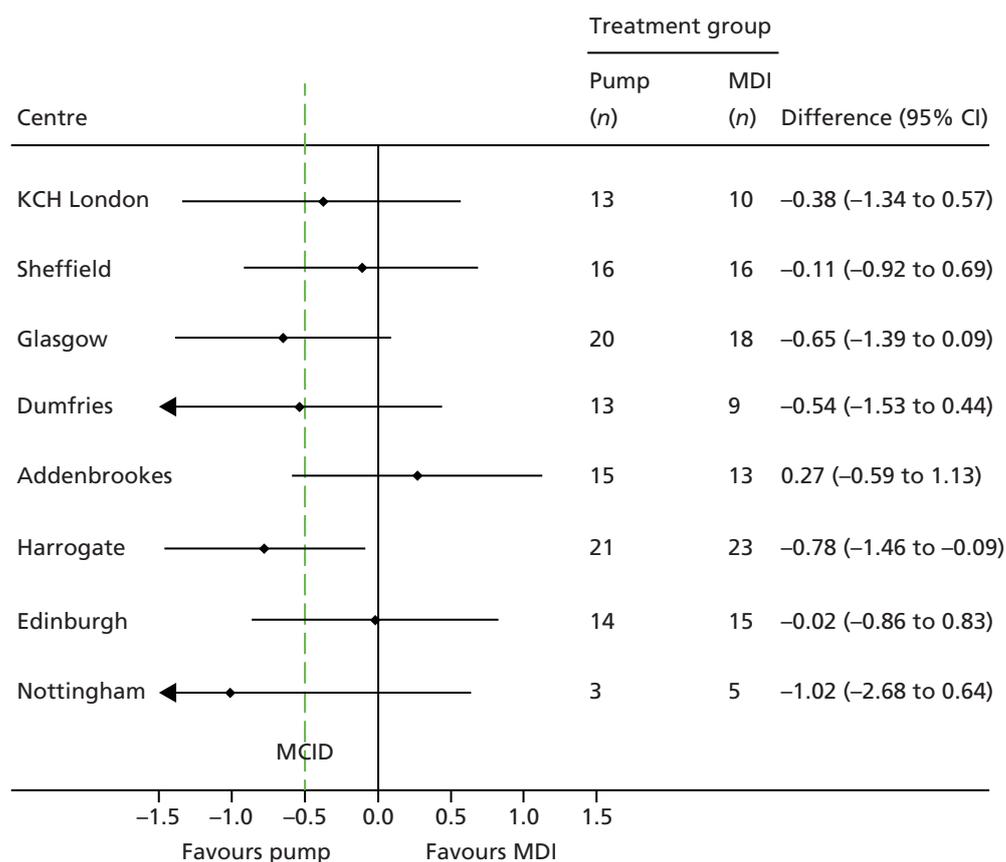


FIGURE 7 Glycated haemoglobin (mmol/mol) over time in participants whose baseline HbA_{1c} was $\geq 7.5\%$ (58 mmol/mol) (including participants with any post-baseline HbA_{1c} data, $n = 235$). (a) Pump; and (b) MDI.

TABLE 22 Change in HbA_{1c} (% or mmol/mol) from baseline to 24-month follow-up, treatment groups combined

HbA _{1c} (mmol/mol)	HbA _{1c} units	n	Mean change (95% CI)
All participants with complete 24-month data	%	248	-0.54 (-0.69 to -0.38)
	mmol/mol	248	-5.9 (-7.6 to -4.2)
Participants with baseline HbA _{1c} ≥ 7.5% and complete 24-month data	%	224	-0.64 (-0.80 to -0.48)
	mmol/mol	224	-7.0 (-8.8 to -5.2)

**FIGURE 8** Forest plot of MD in 24-month HbA_{1c} change (%) at 24 months between groups for participants with baseline HbA_{1c} ≥ 7.5% by centre (complete cases with HbA_{1c} ≥ 7.5% at baseline, n = 224). MDs are calculated from mixed-effects regression analysis adjusted for DAFNE course. KCH, King's College Hospital; MCID, minimum clinically important difference.

Secondary outcomes

Glycated haemoglobin

The proportion of participants reaching the NICE target of HbA_{1c} of ≤ 7.5% (58 mmol/mol) after 2 years is displayed in *Table 23* (including all participants regardless of baseline HbA_{1c} value). The proportion of patients with HbA_{1c} ≤ 7.5% was similar across the groups. The results are very similar at 6 and 12 months (*Table 24*).

Table 25 shows the distribution of HbA_{1c} categories at baseline and 24 months. Of the participants who ended with HbA_{1c} of ≤ 7.5% at 24 months, 12 began the study with baseline HbA_{1c} of ≥ 8.5%.

The primary analysis at 24 months displayed above (see *Primary outcome*) is repeated for 6- and 12-month follow-up visits among participants with complete data. The results for these interim follow-ups are

TABLE 23 Effectiveness of the intervention: proportion of participants with HbA_{1c} of ≤ 7.5% (58 mmol/mol) at 24 months (including all participants regardless of HbA_{1c} at baseline)

Outcome	Treatment group, n/N (%)		OR ^a (95% CI)	p-value
	Pump	MDI		
HbA _{1c} ≤ 7.5%	32/128 (25.0)	28/120 (23.3)	1.22 (0.62 to 2.39)	0.566

a Adjusted for baseline HbA_{1c}, centre and DAFNE course using a mixed-effects logistic regression model. Adapted from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

TABLE 24 Effectiveness of the intervention: proportion of participants with HbA_{1c} ≤ 7.5% (58 mmol/mol) at 6 and 12 months

Outcome	Follow-up (months)	Treatment group, n/N (%)		OR ^a (95% CI)	p-value
		Pump	MDI		
HbA _{1c} ≤ 7.5% (58 mmol/mol)	6	26/132 (20.5)	26/123 (21.1)	1.03 (0.51 to 2.10)	0.930
	12	29/126 (23.0)	27/120 (22.5)	1.32 (0.62 to 2.80)	0.478

a Adjusted for baseline HbA_{1c}, centre and DAFNE course using a logistic mixed-effects model. Adapted from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

TABLE 25 Distribution of HbA_{1c} categories at 24 months for all participants

Outcome	Category	Treatment group, n (%)		Total (N = 267), n (%)
		Pump (n = 132)	MDI (n = 135)	
HbA _{1c} (%) at baseline	< 7	10 (7.6)	7 (5.2)	17 (6.4)
	≥ 7 to < 7.5	3 (2.3)	5 (3.7)	8 (3.0)
	≥ 7.5 to < 8	18 (13.6)	15 (11.1)	33 (12.4)
	≥ 8 to < 8.5	21 (15.9)	31 (23.0)	52 (19.5)
	≥ 8.5 to < 9	15 (11.4)	21 (15.6)	36 (13.5)
	≥ 9 to < 10	28 (21.2)	29 (21.5)	57 (21.3)
	≥ 10	37 (28.0)	27 (20.0)	64 (24.0)
HbA _{1c} (%) at 24 months	< 7	15 (11.4)	12 (8.9)	27 (10.1)
	≥ 7 to < 7.5	14 (10.6)	13 (9.6)	27 (10.1)
	≥ 7.5 to < 8	26 (19.7)	18 (13.3)	44 (16.5)
	≥ 8 to < 8.5	25 (18.9)	29 (21.5)	54 (20.2)
	≥ 8.5 to < 9	9 (6.8)	20 (14.8)	29 (10.9)
	≥ 9 to < 10	17 (12.9)	12 (8.9)	29 (10.9)
	≥ 10	22 (16.7)	16 (11.9)	38 (14.2)
	No data	4 (3.0)	15 (11.1)	19 (7.1)

consistent with the primary outcome analysis and are displayed in *Table 26*. The largest MD in HbA_{1c} change from baseline was observed at 6 months, -0.25% (95% CI -0.52% to 0.02%) or -2.7 mmol/mol (95% CI -5.6 to 0.2 mmol/mol), but is not clinically relevant or statistically significant at the 5% nominal level.

Episodes of moderate and severe hypoglycaemia

Few severe hypoglycaemic episodes were observed post baseline; 49 episodes recorded from 25 participants²³ (*Table 27*). All severe hypoglycaemic episodes occurred while participants were on their allocated treatment. Across both treatment groups the number of severe hypoglycaemic episodes reduced: the average number

TABLE 26 Effectiveness of the intervention: MD in change in HbA_{1c} at 6 and 12 months in participants whose baseline HbA_{1c} was $\geq 7.5\%$

Follow-up (months)	HbA _{1c} units	Treatment group		MD in change ^a (95% CI)	p-value		
		Pump	MDI				
		n	Mean change (SD)	n	Mean change (SD)		
6	%	118	-0.76 (1.19)	111	-0.36 (1.06)	-0.25 (-0.52 to 0.02)	0.069
	mmol/mol	118	-8.3 (12.05)	111	-3.9 (11.56)	-2.7 (-5.6 to 0.2)	
12	%	111	-0.70 (1.10)	107	-0.40 (1.02)	-0.13 (-0.40 to 0.14)	0.349
	mmol/mol	111	-7.6 (12.04)	107	-4.4 (11.10)	-1.4 (-4.3 to 1.5)	

a Adjusted for baseline HbA_{1c}, centre and DAFNE course using a mixed-effects regression model. Adapted from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

TABLE 27 Severe hypoglycaemic episodes per patient-year in study ($n = 267$, all participants with baseline data and who attended a DAFNE course)

Time period	Number of events: event per patient-year, incidence rate		
	Pump ($n = 132$)	MDI ($n = 135$)	Total ($N = 267$)
Before baseline	24, 0.18	21, 0.16	45, 0.17
Between baseline and 6-month follow-up	13, 0.18	7, 0.10	20, 0.14
Between 6 and 12 months' follow-up	8, 0.13	5, 0.09	13, 0.11
Between 12 and 24 months' follow-up	4, 0.03	12, 0.11	16, 0.07
Overall (post baseline)	25, 0.10	24, 0.10	49, 0.10
(Excluding first 6 months)	12, 0.06	17, 0.10	29, 0.08

IRR (95% CI):^a 1.13 (0.51 to 2.51); $p = 0.766$

(Excluding first 6 months) IRR (95% CI):^b 1.05 (0.44 to 2.53); $p = 0.912$

Test of overall change over time: IRR^c (95% CI) (study follow-up compared with the year before baseline, treatment groups combined) 0.46 (0.24 to 0.89); $p = 0.021$

- a IRR calculated using mixed-effects negative binomial regression adjusted for centre, DAFNE course, baseline HbA_{1c} and presence of at least one severe hypoglycaemic episode before baseline. IRR was calculated on the ITT set only ($n = 260$).
 b IRR calculated as above, but not adjusted for centre, as a result of the model failing to converge. IRR was calculated on the ITT set that were followed up for > 6 months ($n = 255$).
 c IRR calculated using mixed-effects negative binomial regression, with participant as the random effect, adjusted for treatment group, treatment group \times time interaction, baseline HbA_{1c} and centre, based on the ITT set $n = 260$.

of episodes per patient-year in the study reduced from 0.17 before baseline to 0.10 during follow-up. The IRR for the number of severe hypoglycaemic episodes in the 24-month follow-up, compared with the year before baseline, is 0.46 (95% CI 0.24 to 0.89; $p = 0.021$).²³ Therefore, compared with the year before baseline, the number of severe hypoglycaemic episodes per year were roughly halved in the 2 years of follow-up post baseline. There was no statistically significant difference in the rate of severe hypoglycaemia during follow-up between the treatment groups having adjusted for centre, DAFNE course, baseline HbA_{1c} and presence of at least one severe hypoglycaemic episode in the 12 months before baseline (IRR 1.13; 95% CI 0.51 to 2.51; $p = 0.766$). The comparison of severe hypoglycaemic episodes between groups was repeated excluding the first 6 months of follow-up, which is the 'settling in' period on the pump. This time the estimated IRR was almost equivocal, but the large CI around this reflects the amount of uncertainty as a result of these analyses being based on so few episodes from few participants (IRR 1.05; 95% CI 0.44 to 2.53; $p = 0.912$).

Across both treatment arms, on average, three moderate hypoglycaemic episodes were recorded per patient over a 4-week history at 6 months (Table 28). By 24 months, the average number of recorded moderate hypoglycaemic episodes during a 4-week history was slightly lower (2.6 for pump, 2.3 for MDI). There was no statistically significant difference between the groups in the rate of moderate hypoglycaemic episodes at any time point.²³

Few participants reported one or more severe hypoglycaemic episode during study follow-up: 14 (10.6%) in the pump group and 11 (8.6%) in the MDI group (Table 29). There was no evidence that the number of patients reporting at least one severe hypoglycaemic episode was different in the two groups: OR 1.22 (95% CI 0.49 to 3.03). More than half of the participants reported at least one moderate hypoglycaemic episode in the 4 weeks prior to follow-up at each time point and across both treatment groups. Slightly more participants reported at least one episode at 6 months in the pump group than in the MDI group ($p = 0.088$). However, a smaller proportion of participants reported episodes in the pump group at 12 and 14 months, although not statistically significant.

TABLE 28 Moderate hypoglycaemic episodes: IRR between pump and MDI

Outcome	Follow-up (months)	Classification	Treatment group, n, IR ^a		IRR ^b (95% CI)	p-value
			Pump	MD		
Episodes of moderate hypoglycaemia in 4 weeks before follow-up visit	6	All recorded episodes	131, 2.95	125, 3.04	1.21 (0.87 to 1.66)	0.258
		Confirmed episodes	131, 2.29	125, 2.14	1.24 (0.91 to 1.68)	0.168
		Confirmed episodes (US definition)	131, 2.92	125, 2.66	1.17 (0.87 to 1.57)	0.299
	12	All recorded episodes	124, 2.73	119, 2.90	0.89 (0.66 to 1.19)	0.416
		Confirmed episodes	124, 2.03	119, 2.22	0.88 (0.65 to 1.20)	0.433
		Confirmed episodes (US definition)	124, 2.71	119, 2.82	0.88 (0.66 to 1.18)	0.402
	24	All recorded episodes	127, 2.56	119, 2.26	1.00 (0.71 to 1.41)	0.992
		Confirmed episodes	127, 1.81	119, 1.76	1.02 (0.72 to 1.46)	0.894
		Confirmed episodes (US definition)	127, 2.51	119, 2.16	1.04 (0.73 to 1.48)	0.832

IR, incidence rate.

a Incidence rate is number of moderate hypoglycaemic episodes per 4-week period.

b Incidence rate ratio is calculated using mixed-effects negative binomial regression adjusted for centre, DAFNE course, baseline HbA_{1c} and presence of at least one moderate hypoglycaemic episode before baseline. Episodes are classed as 'confirmed' if both confirmed by an educator and with a blood glucose level (if recorded) of < 3.5 mmol/l or, for the US definition, < 4 mmol/l.

TABLE 29 Effectiveness of the intervention: proportion of participants who experienced at least one moderate or severe episode of hypoglycaemia

Outcome	Follow-up	Treatment group, n/N (%)			OR ^a (95% CI)	p-value
		Pump	MDI			
Severe hypoglycaemic episode	Entire duration	14/132 (10.6)	11/128 (8.6)	1.22 (0.49 to 3.03)	0.666	
Moderate hypoglycaemic episode	6 months	89/131 (67.9)	72/125 (57.6)	1.64 (0.93 to 2.91)	0.088	
	12 months	68/124 (54.8)	76/119 (63.9)	0.66 (0.37 to 1.19)	0.171	
	24 months	70/127 (55.1)	67/119 (56.3)	0.95 (0.49 to 1.85)	0.890	

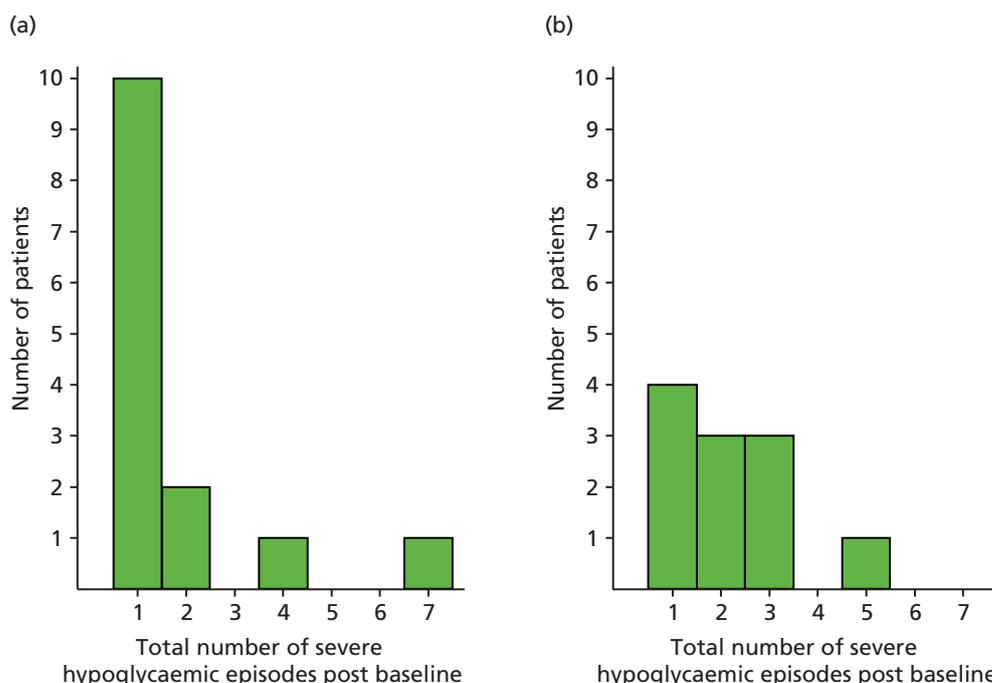
^a Adjusted for baseline HbA_{1c}, centre, DAFNE course and presence of at least one moderate hypoglycaemic episode before baseline using mixed-effects logistic regression.

Figure 9 shows the distribution of the number of severe hypoglycaemic episodes for those who had one or more episodes post baseline. The majority of participants had only one severe hypoglycaemic episode, 10 participants recorded more than one episode during the follow-up period and the maximum recorded by a participant was seven. The number of patients who had an episode makes up a small proportion of the study population (10%).

Figure 10 shows the timing of severe hypoglycaemic episodes. Each dot represents a severe hypoglycaemic episode. Dots connected by a line represent severe hypoglycaemic episodes experienced by the same person.

There is no statistically significant difference in the odds of proteinuria between the treatment groups (Table 30). At 6 months, the odds of being in a higher proteinuria category (where macroalbuminuria is the highest category) are estimated to be 21% lower in the pump group than the MDI group (OR 0.79), but 14% higher at 12 months, and almost identical at 24 months.

Table 31 shows exploratory descriptive analyses of self-reported physical activity for the two groups at each study visit; no formal statistical tests have been performed on these data. The amount of physical activity appears similar across the groups.

**FIGURE 9** Distribution of number of severe hypoglycaemic episodes in participants with at least one episode post baseline, by treatment group. (a) Pump, n = 14; and (b) MDI, n = 11.

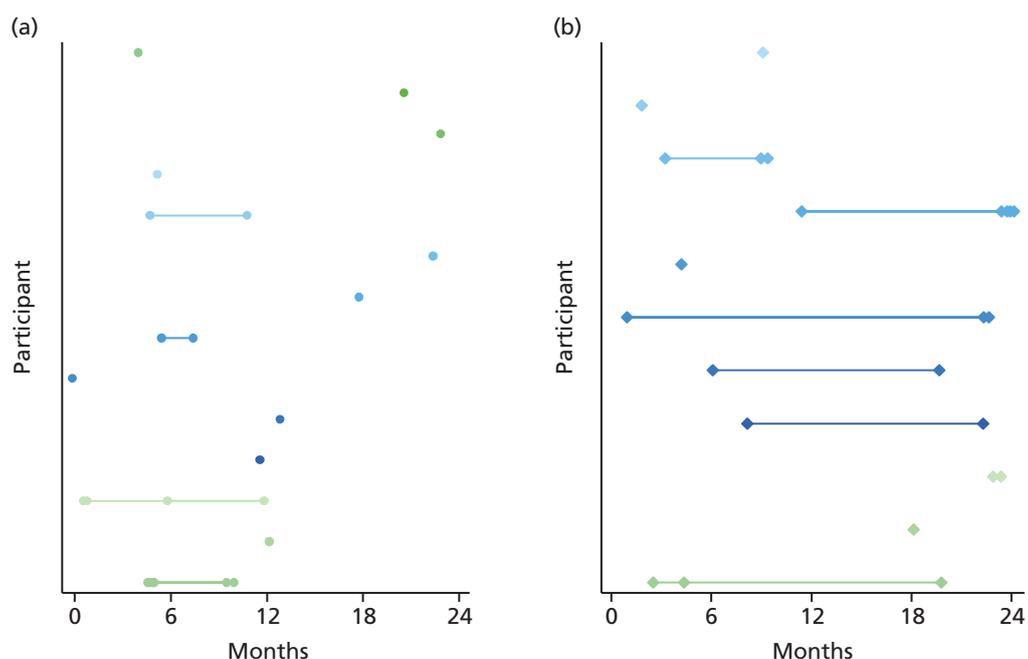


FIGURE 10 Severe hypoglycaemic episodes over time per participant with at least one episode post baseline, by treatment group. (a) Pump, *n* = 14; and (b) MDI, *n* = 11.

TABLE 30 Secondary outcomes: proteinuria – proportion of participants in each proteinuria category at 6, 12 and 24 months

Follow-up (months)	Secondary outcome	Treatment group, <i>n</i> (%)		OR ^a (95% CI)	<i>p</i> -value
		Pump	MDI		
6	Normal	76 (80.0)	81 (81.0)	0.79 (0.36 to 1.73)	0.558
	Microalbuminuria	17 (17.9)	14 (14.0)		
	Macroalbuminuria	2 (2.1)	5 (5.0)		
12	Normal	65 (75.6)	67 (80.7)	1.14 (0.53 to 2.48)	0.736
	Microalbuminuria	16 (18.6)	10 (12.0)		
	Macroalbuminuria	5 (5.8)	6 (7.2)		
24	Normal	77 (81.1)	70 (83.3)	1.04 (0.46 to 2.32)	0.932
	Microalbuminuria	16 (16.8)	9 (10.7)		
	Macroalbuminuria	2 (2.1)	5 (6.0)		

a Adjusted for centre, DAFNE course and baseline HbA_{1c} level. OR is odds of combined microalbuminuria and macroalbuminuria vs. normal, or macroalbuminuria vs. combined categories of microalbuminuria and normal for pump compared with MDI.

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Table 32 shows the results of comparing secondary continuous outcomes across treatment groups. Weight remained roughly constant throughout the study duration, and was not statistically significantly different between the treatment groups at any follow-up.²³ A slight increase in HDL cholesterol and a slight decrease in TC was observed across both treatment groups.²³ There was no evidence of a difference between treatment groups in cholesterol change from baseline, with *p*-values ranging from 0.219 to 0.856.

TABLE 31 Physical activity level by treatment group at baseline, 6, 12 and 24 months

Follow-up	Physical activity	Treatment group, <i>n</i> (%)		
		Pump	MDI	All, <i>N</i> (%)
Baseline	High	33 (25.0)	33 (24.4)	66 (24.7)
	Medium	63 (47.7)	70 (51.9)	133 (49.8)
	Low	36 (27.3)	32 (23.7)	68 (25.5)
6 months	High	36 (27.7)	36 (28.8)	72 (28.2)
	Medium	60 (46.2)	63 (50.4)	123 (48.2)
	Low	34 (26.2)	26 (20.8)	60 (23.5)
12 months	High	35 (28.5)	39 (32.8)	74 (30.6)
	Medium	60 (48.8)	51 (42.9)	111 (45.9)
	Low	28 (22.8)	29 (24.4)	57 (23.6)
24 months	High	41 (32.3)	37 (31.4)	78 (31.8)
	Medium	61 (48.0)	53 (44.9)	114 (46.5)
	Low	25 (19.7)	28 (23.7)	53 (21.6)

High physical activity = equivalent to > 8 hours' normal walking, 4 hours' fast walking or 2.5 hours' running per week; medium = equivalent to between 4 and 8 hours' normal walking, 2 and 4 hours' fast walking or 1.25 and 2.5 hours' running per week; low = equivalent to < 4 hours' normal walking, 2 hours' fast walking or 1.25 hours' running per week.

TABLE 32 Secondary continuous outcomes: MD in change from baseline at 6, 12 and 24 months

Outcome	Follow-up (months)	Treatment group				Adjusted difference ^a (95% CI)	<i>p</i> -value
		Pump		MDI			
		<i>n</i>	Mean change (SD)	<i>n</i>	Mean change (SD)		
Body weight (kg)	6	131	-0.05 (4.35)	124	-0.61 (4.32)	0.45 (-0.66 to 1.55)	0.430
	12	123	0.78 (4.95)	116	-0.05 (4.65)	0.67 (-0.64 to 1.98)	0.316
	24	127	0.71 (5.45)	117	0.20 (6.37)	0.42 (-1.17 to 2.01)	0.607
HDL cholesterol (mmol/l)	6	123	0.01 (0.28)	116	0.04 (0.36)	-0.05 (-0.13 to 0.03)	0.264
	12	109	0.04 (0.29)	113	0.04 (0.38)	-0.01 (-0.10 to 0.08)	0.801
	24	117	0.03 (0.30)	112	0.06 (0.39)	-0.04 (-0.12 to 0.05)	0.428
Cholesterol (mmol/l)	6	130	-0.17 (0.84)	122	-0.01 (0.84)	-0.14 (-0.35 to 0.08)	0.219
	12	121	-0.14 (1.02)	116	-0.08 (0.83)	-0.02 (-0.26 to 0.22)	0.856
	24	127	-0.21 (0.95)	116	-0.19 (1.03)	0.03 (-0.25 to 0.30)	0.848
Total insulin dose (IU/weight)	6	130	-0.07 (0.27)	124	-0.03 (0.21)	-0.04 (-0.10 to 0.02)	0.199
	12	123	-0.09 (0.26)	117	-0.02 (0.22)	-0.07 (-0.13 to -0.01)	0.017
	24	125	-0.06 (0.27)	116	-0.01 (0.23)	-0.05 (-0.11 to 0.02)	0.152

a Adjusted for centre, DAFNE course and baseline HbA_{1c} level.

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Insulin dose decreased across both pump and MDI arms. There was evidence of a difference in the mean change in insulin dose at 12 months between treatment groups; on average, participants in the pump group had a 0.07-IU/weight larger decrease (95% CI 0.01 to 0.013 IU/weight; $p = 0.017$) in insulin dose than those in the MDI group. However, the difference between treatments in insulin dose was slightly smaller at 6 and 24 months, but not statistically significant.

Table 33 summarises blood glucose testing per day averaged over a 2-week recorded period, stratified by the baseline HbA_{1c} category. A post hoc analysis indicated that there was no difference in the mean blood glucose testing frequency between treatment groups at 24 months, having adjusted for baseline number of blood glucose tests, centre and DAFNE course.²³ The adjusted MD in blood glucose tests (95% CI) was 0.22 (−0.24 to 0.68) per day or 3.1 (−3.4 to 9.6) over 2 weeks; $p = 0.352$. Overall, the number of blood glucose tests increased from 3.6 at baseline to 4.1 per day at 24 months (95% CI 0.33 to 0.82; $p < 0.001$).²³

Subgroup analysis

The potential moderating effects of subgroups were explored using mixed-effects linear regression, with an interaction between treatment and subgroup. Results of the subgroup analyses are presented in Tables 34–37, and the results are summarised graphically using forest plots in Figures 11 and 12.

We found no reliable statistical evidence of any subgroup effects or interactions between the pump and MDI groups. However, there was some indication that participants with qualifications up to A-level/equivalent did better in the pump arm than in the MDI arm – MD in HbA_{1c} change (95% CI) at 24 months of −0.67% (−1.21% to −0.14%) vs. −0.07% (−0.47% to 0.33%) or −7.4 mmol (−13.2 to −1.5 mmol) vs. −0.8 (−5.1 to 3.6 mmol) – although the interaction test was not statistically significant ($p = 0.07$).²³

TABLE 33 Blood glucose testing frequency over a 2-week period at baseline and 24 months, comparison by treatment group and baseline HbA_{1c} (%) category

Outcome	Baseline HbA _{1c} category (%)	Treatment group				Adjusted MD ^a (95% CI)	p-value
		Pump		MDI			
		n	Mean (SD)	n	Mean (SD)		
Baseline number of blood glucose tests performed per day (averaged over 2 weeks)	< 7.5	13	3.8 (1.7)	11	4.9 (2.1)		
	≥ 7.5% and < 8.5	38	3.9 (1.8)	43	3.8 (1.9)		
	≥ 8.5	76	3.3 (1.7)	65	3.2 (1.8)		
	All	127	3.6 (1.8)	119	3.6 (1.9)		
24 months: number of blood glucose tests performed per day (averaged over 2 weeks)	< 7.5	13	4.8 (1.0)	11	4.3 (1.9)		
	≥ 7.5 and < 8.5	38	5.2 (2.4)	43	3.8 (1.9)		
	≥ 8.5	76	3.7 (2.1)	64	4.1 (1.7)		
	All	127	4.3 (2.2)	118	4.0 (1.8)	0.22 (−0.24 to 0.68)	0.352

a Adjusted for centre, DAFNE course and baseline number of blood tests.

TABLE 34 Subgroup evaluation (demographics): change in HbA_{1c} (%) at 24 months within subgroup and subgroup treatment interaction tests

Variable	Subgroup	Treatment group				MD in change (95% CI) ^a	p-value ^b
		Pump		MDI			
		n	Mean (SD)	n	Mean (SD)		
Sex	Male	75	-5.97 (11.61)	73	-3.55 (11.72)	-0.19 (-0.59 to 0.21)	0.441
	Female	53	-9.85 (16.73)	47	-4.98 (14.57)	-0.43 (-0.91 to 0.05)	
Level of education	Up to A level/ equivalent	43	-10.58 (16.46)	40	-2.92 (15.75)	-0.67 (-1.21 to -0.14)	0.07
	Vocational/ beyond A level	82	-5.61 (12.46)	75	-4.76 (11.57)	-0.07 (-0.47 to 0.33)	
IMD	IMD below median	22	-2.64 (14.69)	23	0.57 (13.40)	-0.25 (-0.95 to 0.46)	0.929
	IMD above median	54	-6.20 (13.62)	49	-3.94 (12.34)	-0.21 (-0.68 to 0.26)	
SIMD	SIMD below median	24	-13.21 (14.27)	24	-5.38 (14.48)	-0.54 (-1.29 to 0.21)	0.351
	SIMD above median	25	-8.36 (13.10)	22	-8.05 (11.43)	-0.07 (-0.80 to 0.66)	
Age (years)	< 35	43	-0.89 (1.59)	42	-0.36 (1.35)	-0.53 (-1.05 to -0.01)	0.538
	35-49	49	-0.60 (1.19)	55	-0.43 (1.16)	-0.15 (-0.62 to 0.32)	
	≥ 50	36	-0.59 (0.98)	23	-0.28 (0.89)	-0.22 (-0.85 to 0.41)	
BMI (kg/m ²)	Normal < 25	45	-0.65 (1.43)	47	-0.52 (1.22)	-0.10 (-0.60 to 0.40)	0.626
	Overweight 25-29.9	53	-0.69 (1.16)	48	-0.27 (0.94)	-0.42 (-0.90 to 0.05)	
	Obese ≥ 30	30	-0.77 (1.31)	25	-0.32 (1.49)	-0.35 (-0.99 to 0.29)	
ONS occupational status	Level 1	31	-7.03 (13.45)	22	-1.91 (18.35)	-0.38 (-1.05 to 0.30)	0.915
	Level 2	35	-6.40 (12.83)	36	-5.86 (11.60)	-0.17 (-0.74 to 0.40)	
	Level 3	38	-8.24 (17.13)	41	-3.32 (13.27)	-0.36 (-0.90 to 0.17)	
	Level 4	12	-4.67 (7.64)	13	-4.54 (5.98)	-0.06 (-1.02 to 0.89)	

ONS, Office for National Statistics; SIMD, Scottish Index of Multiple Deprivation.

a Adjusted for centre and DAFNE course.

b The p-value from the interaction test.

Notes

English Index of Multiple Deprivation (2010) displayed for English centres only.

Scottish Index of Multiple Deprivation (2012) displayed for Scottish centres only.

Level 1: elementary trade, service and administration roles; level 2: construction, building trade and agricultural, caring, protective services, public service workers or equivalent; level 3: managerial positions, public service professionals, skilled construction, building trade and electrical trades, health and social welfare professionals, science and technology professionals or equivalent; level 4: corporate managers and directors, research and teaching professionals, business and public service higher level professionals or equivalent.

Ancillary analyses

Adverse events

Table 38 shows the AEs recorded throughout study follow-up. More participants in the pump arm (66%) reported AEs than in the MDI arm (37%). However, part of this difference can be attributed to the 23 cases of suspicion of pump malfunction, which, by definition, could occur only for participants using pump therapy. Table 39 shows the AEs that were recorded over different time periods during study follow-up.

TABLE 35 Subgroup evaluation (demographics): change in HbA_{1c} (mmol/mol) at 24 months within subgroup and subgroup treatment interaction tests

Variable	Subgroup	Treatment group				MD in change ^a (95% CI)	p-value ^b
		Pump		MDI			
		n	Mean (SD)	n	Mean (SD)		
Sex	Male	75	-6.0 (11.6)	73	-3.5 (11.7)	-2.1 (-6.4 to 2.3)	0.441
	Female	53	-9.8 (16.7)	47	-5.0 (14.6)	-4.7 (-9.9 to 0.6)	
Level of education	Up to A level/ equivalent	43	-10.6 (16.5)	40	-2.9 (15.8)	-7.4 (-13.2 to -1.5)	0.07
	Vocational/ beyond A level	82	-5.6 (12.5)	75	-4.8 (11.6)	-0.8 (-5.1 to 3.6)	
English IMD ^c	Below median	22	-2.6 (14.7)	23	0.6 (13.4)	-2.7 (-10.4 to 5.0)	0.929
	Above median	54	-6.2 (13.6)	49	-3.9 (12.3)	-2.3 (-7.4 to 2.8)	
SIMD ^d	Below median	24	-13.2 (14.3)	24	-5.4 (14.5)	-5.9 (-14.1 to 2.3)	0.351
	Above median	25	-8.4 (13.1)	22	-8.0 (11.4)	-0.7 (-8.7 to 7.2)	
Age (years)	< 35	43	-9.7 (17.4)	42	-3.9 (14.8)	-5.8 (-11.5 to -0.1)	0.538
	35 to 49	49	-6.5 (13.0)	55	-4.7 (12.6)	-1.6 (-6.8 to 3.5)	
	≥ 50	36	-6.5 (10.7)	23	-3.0 (9.7)	-2.4 (-9.3 to 4.5)	
BMI (kg/m ²)	Normal < 25	45	-7.1 (15.6)	47	-5.6 (13.4)	-1.1 (-6.6 to 4.4)	0.626
	Overweight/ 25–29.9	53	-7.5 (12.7)	48	-2.9 (10.2)	-4.6 (-9.8 to 0.6)	
	Obese ≥ 30	30	-8.4 (14.3)	25	-3.5 (16.3)	-3.8 (-10.9 to 3.2)	
ONS occupational status ^e	Level 1	31	-7.0 (13.5)	22	-1.9 (18.3)	-4.1 (-11.5 to 3.2)	0.915
	Level 2	35	-6.4 (12.8)	36	-5.9 (11.6)	-1.9 (-8.1 to 4.3)	
	Level 3	38	-8.2 (17.1)	41	-3.3 (13.3)	-4.0 (-9.9 to 1.9)	
	Level 4	12	-4.7 (7.6)	13	-4.5 (6.0)	-0.7 (-11.1 to 9.7)	

IMD, Index of Multiple Deprivation; ONS, Office for National Statistics; SIMD, Scottish Index of Multiple Deprivation.

a Adjusted for centre and DAFNE course.

b The p-value from the interaction test.

c English IMD (2010) displayed for English centres only.

d The SIMD (2012) displayed for Scottish centres only.

e Level 1: elementary trade, service and administration roles; level 2: construction, building trade and agricultural, caring, protective services, public service workers or equivalent; level 3: managerial positions, public service professionals, skilled construction, building trade and electrical trades, health and social welfare professionals, science and technology professionals or equivalent; level 4: corporate managers and directors, research and teaching professionals, business and public service higher-level professionals or equivalent.

During each time period, more participants in the pump arm experienced AEs than in the MDI arm. A total of 142 AEs were recorded for the pump group during the first 6 months of follow-up in comparison with 84 in the following 6 months, and 94 in the final 12 months of follow-up, suggesting that more AEs occurred during the early 'settling in' period on pump therapy.

Table 40 shows the AEs that were classified as being SAEs. The distribution of SAEs was similar across the treatment groups, with the exception that more participants experienced DKA in the pump group. Table 41 shows SAEs by study time period. Again, for the pump group, more SAEs were recorded in the first 6 months ($n = 17$) than in the following 6 months ($n = 11$) or when compared with the last 12 months ($n = 17$).

TABLE 36 Subgroup evaluation (diabetes characteristics): change in HbA_{1c} (%) at 24 months within subgroup and subgroup treatment interaction tests

Variable	Subgroup	Treatment Group				MD in change (95% CI) ^a	p-value ^b
		Pump		MDI			
		n	Mean (SD)	n	Mean (SD)		
Diabetes duration (years)	< 15	59	-7.25 (16.51)	59	-2.69 (12.66)	-0.43 (-0.87 to 0.02)	0.364
	≥ 15	69	-7.86 (11.62)	61	-5.48 (13.03)	-0.15 (-0.58 to 0.27)	
Experience of lead DAFNE course educator ^c	Less experienced	-	-	10	0.90 (13.37)	-	-
	More experienced	128	-7.58 (14.03)	110	-4.56 (12.79)	-0.26 (-0.59 to 0.06)	
Insulin dose (IU/weight)	< 0.7	68	-5.56 (10.48)	57	-3.32 (9.03)	-0.22 (-0.65 to 0.20)	0.607
	≥ 0.7	60	-9.87 (17.00)	63	-4.83 (15.60)	-0.38 (-0.81 to 0.05)	
HbA _{1c} (%)	< 7.5	13	0.59 (0.78)	11	0.14 (0.66)	0.42 (-0.47 to 1.31)	0.183
	≥ 7.5 to < 8.5	34	-0.10 (0.82)	39	0.05 (0.65)	-0.12 (-0.63 to 0.38)	
	≥ 8.5	81	-1.15 (1.27)	70	-0.70 (1.36)	-0.42 (-0.77 to -0.07)	
Symptoms of hypoglycaemia usually occur at blood glucose level (mmol/l)	≥ 3	92	-7.37 (13.94)	85	-3.41 (13.31)	-0.33 (-0.70 to 0.04)	0.660
	< 3 or do not feel symptoms	36	-8.11 (14.46)	35	-5.80 (11.75)	-0.18 (-0.75 to 0.38)	
Use of bolus advisor	Never or rarely	18	-0.44 (0.84)	55	-0.32 (1.23)	-0.18 (-0.81 to 0.46)	0.736
	Sometimes	10	-0.39 (1.49)	5	0.27 (1.94)	-0.72 (-2.00 to 0.55)	
	Often or always	100	-0.77 (1.33)	60	-0.48 (1.05)	-0.21 (-0.60 to 0.18)	
Moderate hypoglycaemic episodes ^d	0	41	-9.73 (15.92)	36	-4.14 (13.57)	-0.45 (-0.98 to 0.09)	0.795
	1	29	-7.17 (11.44)	33	-4.09 (12.80)	-0.26 (-0.85 to 0.33)	
	2 or 3	30	-9.07 (15.01)	25	-3.52 (9.67)	-0.35 (-0.98 to 0.29)	
	4-9	16	-8.13 (11.59)	19	-5.79 (15.62)	-0.41 (-1.20 to 0.37)	
	≥ 10	12	3.25 (9.42)	7	-1.57 (14.58)	0.32 (-0.77 to 1.42)	

a Adjusted for centre and DAFNE course.

b The p-value from the interaction test.

c 'Less experienced', leading six courses or fewer within previous 3 years, or completed DEP within the previous year; 'more experienced', seven or more courses within the previous 3 years or having continuous educator status for > 6 years.

d Number of moderate hypoglycaemic episodes recorded in the 4 weeks prior to baseline.

Note: All of the DKAs that occurred were reported as SAEs and resulted in hospitalisation. All of the SAEs have a corresponding AE; however, in some cases, a DKA SAE had a corresponding AE that was not labelled as DKA, which is why there are more DKA SAEs recorded than DKA AEs.

Characteristics of participants by missing data status

Tables 42 and 43 show baseline characteristics of patients with missing data.

TABLE 37 Subgroup evaluation (diabetes characteristics): change in HbA_{1c} (mmol/mol) at 24 months within subgroup and subgroup treatment interaction tests

Variable	Subgroup	Treatment group				MD in change ^a (95% CI)	p-value ^b
		Pump		MDI			
		n	Mean (SD)	n	Mean (SD)		
Diabetes duration (years)	< 15	59	-7.3 (16.5)	59	-2.7 (12.7)	-4.7 (-9.5 to 0.2)	0.364
	≥ 15	69	-7.9 (11.6)	61	-5.5 (13.0)	-1.7 (-6.3 to 3.0)	
Experience of lead DAFNE course educator	Less experienced	–	–	10	0.9 (13.4)	–	–
	More experienced	128	-7.6 (14.0)	110	-4.6 (12.8)	-2.9 (-6.4 to 0.7)	
Insulin dose (IU/weight)	< 0.7	68	-5.6 (10.5)	57	-3.3 (9.0)	-2.4 (-7.1 to 2.2)	0.607
	≥ 0.7	60	-9.9 (17.0)	63	-4.8 (15.6)	-4.1 (-8.8 to 0.6)	
HbA _{1c} (%)	< 7.5	13	6.5 (8.6)	11	1.5 (7.2)	4.6 (-5.2 to 14.4)	0.183
	≥ 7.5 to < 8.5	34	-1.1 (8.9)	39	0.6 (7.1)	-1.4 (-6.9 to 4.2)	
	≥ 8.5	81	-12.5 (13.9)	70	-7.6 (14.9)	-4.6 (-8.5 to -0.8)	
Symptoms of hypoglycaemia usually occur at blood glucose level	≥ 3 mmol/l	92	-7.4 (13.9)	85	-3.4 (13.3)	-3.6 (-7.7 to 0.4)	0.660
	< 3 mmol/l or do not feel symptoms	36	-8.1 (14.5)	35	-5.8 (11.8)	-2 (-8.2 to 4.2)	
Use of bolus advisor	Never or rarely	18	-4.8 (9.2)	55	-3.5 (13.4)	-1.9 (-8.9 to 5.0)	0.736
	Sometimes	10	-4.3 (16.3)	5	3.0 (21.2)	-7.9 (-21.8 to 6.0)	
	Often or always	100	-8.4 (14.5)	60	-5.3 (11.5)	-2.3 (-6.6 to 2.0)	
Moderate hypoglycaemic episodes ^c	0	41	-9.7 (15.9)	36	-4.1 (13.6)	-4.9 (-10.7 to 1.0)	0.795
	1	29	-7.2 (11.4)	33	-4.1 (12.8)	-2.9 (-9.3 to 3.6)	
	2 or 3	30	-9.1 (15.0)	25	-3.5 (9.7)	-3.8 (-10.7 to 3.1)	
	4–9	16	-8.1 (11.6)	19	-5.8 (15.6)	-4.5 (-13.1 to 4.1)	
	≥ 10	12	3.3 (9.4)	7	-1.6 (14.6)	3.5 (-8.5 to 15.6)	

a Adjusted for centre and DAFNE course.
b The p-value from interaction test.
c Number of moderate hypoglycaemic episodes recorded in the 4 weeks prior to baseline.

Findings of the fidelity assessment

Course characteristics

All eight REPOSE centres were fidelity tested. Four centres were fidelity tested on their second pump course and two centres were fidelity tested on their first pump course. One centre was fidelity tested on their third and final course as a result of personal circumstances of the FA precluding the assessment being undertaken on the second pump course. Nottingham ran one pair of courses and, thus, FT took place on its only pump course.

The number of REPOSE participants on the fidelity-tested pump courses ranged from 3 to 7 (for course sizes, see *Table 44*). The range of participants on the remaining pump courses was 3–8, with a mean of 5.7.

One pump course (Cambridge) included a non-REPOSE participant who had been on a pump for 10 years and was very keen to do DAFNE.

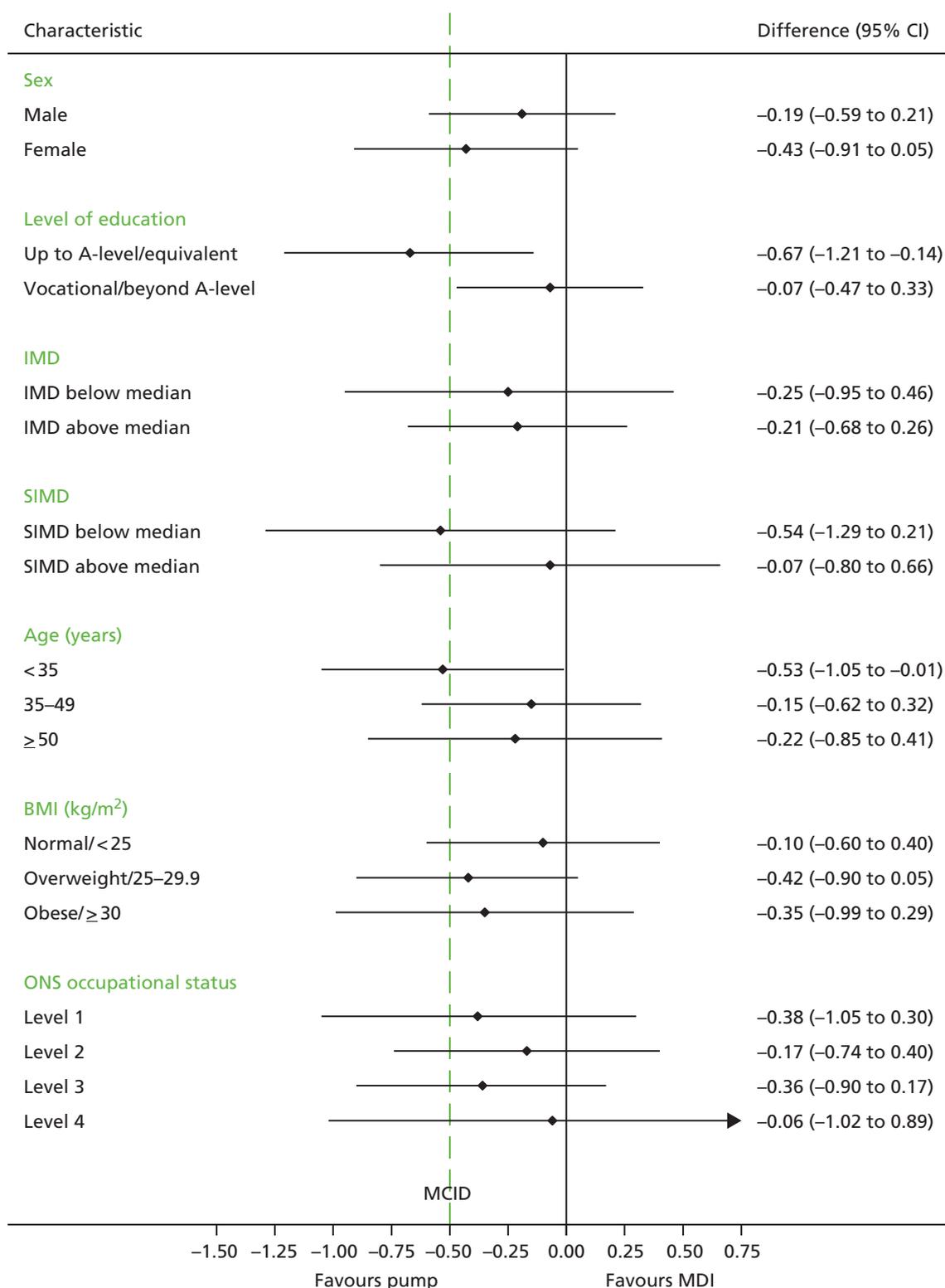


FIGURE 11 Subgroup evaluation (demographic characteristics) MD in HbA_{1c} change (%) at 24 months by demographic subgroup. MCID, minimum clinically important difference; ONS, Office for National Statistics; SIMD, Scottish Index of Multiple Deprivation. Reproduced from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

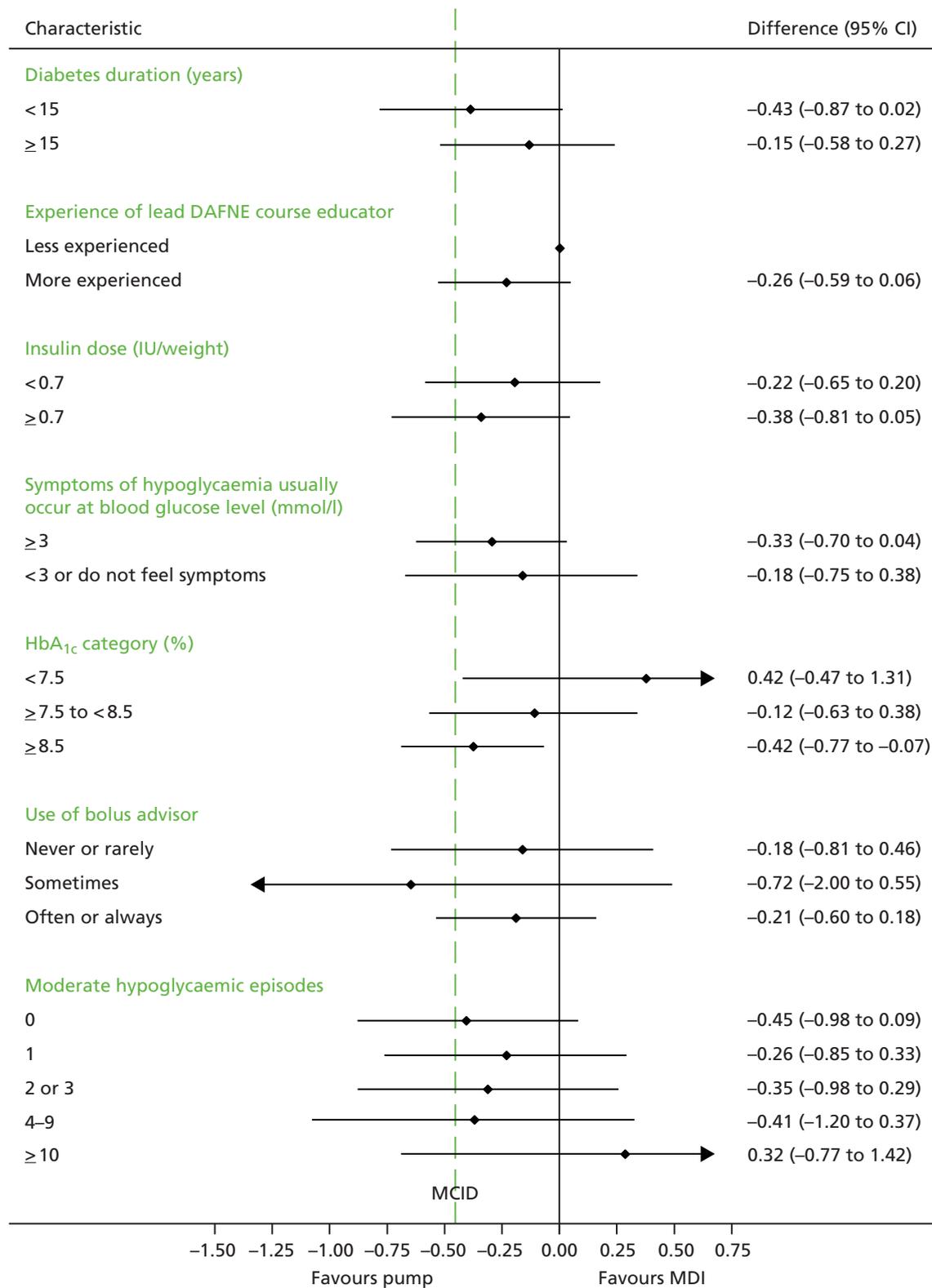


FIGURE 12 Subgroup evaluation (diabetes characteristics): MD in HbA_{1c} change (%) at 24 months by subgroup. MCID, minimum clinically important difference. Reproduced from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

TABLE 38 Safety analysis: AEs

Outcome	Classification	Treatment group		
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)
Participants with ≥ 1 AE, n (%)	Any AE	87 (65.9)	50 (37.0)	137 (51.3)
	Increase in hypoglycaemic episode frequency	11 (8.3)	8 (5.9)	19 (7.1)
	Blood glucose reading > 30 mmol/l	55 (41.7)	16 (11.9)	71 (26.6)
	Raised blood glucose ^a	16 (12.1)	6 (4.4)	22 (8.2)
	Suspicion of pump malfunction	23 (17.4)	–	23 (8.6)
	Pregnancy	6 (4.5)	4 (3.0)	10 (3.7)
	Infection at pump cannula site	2 (1.5)	–	2 (0.7)
	DKA	7 (5.3)	2 (1.5)	9 (3.4)
	Other	28 (21.2)	28 (20.7)	56 (21.0)
Participants with ≥ 1 AE related to study drug, n (%)	Any AE	40 (30.3)	14 (10.4)	54 (20.2)
	Increase in hypoglycaemic episode frequency	4 (3.0)	5 (3.7)	9 (3.4)
	Blood glucose reading > 30 mmol/l	27 (20.5)	5 (3.7)	32 (12.0)
	Raised blood glucose ^b	5 (3.8)	1 (0.7)	6 (2.2)
	Suspicion of pump malfunction	13 (9.8)	–	13 (4.9)
	Pregnancy	–	–	–
	Infection at pump cannula site	1 (0.8)	–	1 (0.4)
	DKA	1 (0.8)	–	1 (0.4)
Other	3 (2.3)	3 (2.2)	6 (2.2)	
Number of AEs ^b		321	102	423

a Unexplained constantly raised blood glucose readings.

b Four events in the pump group occurred while the participant was on MDI; 10 events in the MDI group occurred while the participant was on pump.

TABLE 39 Safety analysis: AEs by post-course time window

Participants with ≥ 1 AE	Follow-up period (months)	Treatment group		
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)
Any AE, n (%)	0–6	57 (28.9)	22 (15.0)	79 (23.0)
	6–12	48 (24.4)	16 (10.9)	64 (18.6)
	12–24	46 (23.4)	23 (15.6)	69 (20.1)
Number of AEs ^a	0–6	142	37	179
	6–12	84	22	106
	12–24	94	42	136

a Six months – three events in the pump group occurred while the participant was on MDI, one event in the MDI group occurred while the participant was on pump; 12 months – one event in the pump group occurred while the participant was on MDI, one event in the MDI group occurred while the participant was on pump; 24 months – no events in the pump group occurred while the participant was on MDI, eight events in the MDI group occurred while the participant was on pump. Two AEs had missing dates and so were excluded from this table.

TABLE 40 Safety analysis: SAE

Outcome	Classification	Treatment group		
		Pump (N = 132)	MDI (N = 135)	Total (N = 267)
Participants with ≥ 1 SAE, <i>n</i> (%)	Any SAE	31 (23.5)	26 (19.3)	57 (21.3)
	DKA	17 (12.9)	5 (3.7)	22 (8.2)
	MI	2 (1.5)	–	2 (0.7)
	Severe hypoglycaemia	–	1 (0.7)	1 (0.4)
	Foot ulcer	1 (0.8)	–	1 (0.4)
	Renal disease	1 (0.8)	–	1 (0.4)
	Abdominal pain	1 (0.8)	2 (1.5)	3 (1.1)
	Pregnancy ^a	4 (3.0)	3 (2.2)	7 (2.6)
	Hyperglycaemia	3 (2.3)	4 (3.0)	7 (2.6)
	Migraine	–	1 (0.7)	1 (0.4)
	Overdose/suicide attempt	1 (0.8)	1 (0.7)	2 (0.7)
	Chest pain	2 (1.5)	1 (0.7)	3 (1.1)
	Infection	2 (1.5)	2 (1.5)	4 (1.5)
	Other	5 (3.8)	12 (8.9)	17 (6.4)
	Participants with ≥ 1 SAE related to a treatment, <i>n</i> (%)	All	5 (3.8)	2 (1.5)
Participants with ≥ 1 SAE by intensity, <i>n</i> (%)	Mild	6 (4.5)	6 (4.4)	12 (4.5)
	Moderate	20 (15.2)	18 (13.3)	38 (14.2)
	Severe	9 (6.8)	5 (3.7)	14 (5.2)
Participants with ≥ 1 treatment-related SAE by intensity, <i>n</i> (%)	Mild	–	–	–
	Moderate	4 (3.0)	2 (1.5)	6 (2.2)
	Severe	1 (0.8)	–	1 (0.4)
Number of SAEs	All	45 ^b	44 ^b	89 ^b
Number of SAEs related to treatment	Definite	4	1	5
	Probable	1	1	2
	Possible	5	2	7
	Unlikely	14	13	27
	Unrelated	21	27	48
Number of SAEs by intensity	Mild	6	8	14
	Moderate	29	26	55
	Severe	10	10	20

a Pregnancy is included when there was a hospital admission.

b Two events in the pump group occurred while the participant was on MDI; seven events in the MDI group occurred while the participant was on the pump.

TABLE 41 Safety analysis: SAEs by post-course time window

Outcome	Classification	Follow-up period (months)	Treatment group		
			Pump (N = 132)	MDI (N = 135)	Total (N = 267)
Participants with ≥ 1 SAE, n (%)	Any SAE	0–6	14 (10.1)	7 (5.1)	21 (7.6)
		6–12	10 (7.2)	5 (3.6)	15 (5.4)
		12–24	13 (9.4)	17 (12.3)	30 (10.9)
	DKA	0–6	8 (5.8)	1 (0.7)	9 (3.3)
		6–12	7 (5.1)	–	7 (2.5)
		12–24	4 (2.9)	4 (2.9)	8 (2.9)
Number of SAEs ^a		0–6	17	10	27
		6–12	11	5	16
		12–24	17	29	46

a Six months – one event in the pump group occurred while the participant was on MDI, one event in the MDI group occurred while the participant was on pump; 12 months – one event in the pump group occurred while the participant was on MDI, one event in the MDI group occurred while the participant was on the pump; 24 months – no events in the pump group occurred while the participant was on MDI, five events in the MDI group occurred while the participant was on the pump.

TABLE 42 Continuous baseline characteristics by treatment group and 24-month missing data status

Variable	Statistic	Non-completers, n (%)			Completers, n (%)		
		Pump (N = 4)	MDI (N = 15)	All (N = 19)	Pump (N = 128)	MDI (N = 120)	All (N = 248)
Age (years)	Mean (SD)	33.4 (15.4)	32.6 (10.9)	32.8 (11.5)	41.7 (14.2)	40.8 (12.4)	41.3 (13.3)
	Median (IQR)	27.7 (22.9–44.0)	29.9 (23.6–39.8)	29.9 (23.0–39.8)	40.9 (29.0–52.3)	42.8 (30.9–49.1)	41.9 (30.2–49.5)
Diabetes duration (years)	Mean (SD)	21.6 (18.2)	13.8 (9.6)	15.4 (11.7)	18.5 (12.8)	18.0 (12.3)	18.2 (12.5)
	Median (IQR)	17.3 (9.7–33.5)	12.4 (5.4–20.2)	14.2 (5.4–20.2)	16.5 (7.8–27.7)	15.4 (8.2–25.9)	15.9 (7.9–26.7)
HbA _{1c} (mmol/mol)	Mean (SD)	94.0 (24.3)	83.4 (17.5)	85.6 (18.9)	77.4 (20.8)	73.7 (15.1)	75.6 (18.3)
	Median (IQR)	97 (73.5–114.5)	85 (68.0–97.0)	85 (68.0–103.0)	73 (65.0–87.0)	71 (64.0–82.0)	71.5 (64.0–85.0)
HbA _{1c} (%)	Mean (SD)	10.8 (2.2)	9.8 (1.6)	10.0 (1.7)	9.2 (1.9)	8.9 (1.4)	9.1 (1.7)
	Median (IQR)	11.0 (8.9–12.6)	9.9 (8.4–11.0)	9.9 (8.4–11.6)	8.8 (8.1–10.1)	8.6 (8.0–9.7)	8.7 (8.0–9.9)
BMI (kg/m ²)	Mean (SD)	29.8 (12.4)	27.0 (5.1)	27.6 (6.9)	27.3 (4.7)	27.0 (5.0)	27.1 (4.8)
	Median (IQR)	25.8 (22.5–37.2)	26.9 (22.3–29.8)	26.4 (22.3–29.8)	27.2 (23.8–29.7)	26.5 (23.7–29.2)	27 (23.8–29.5)

TABLE 43 Categorical baseline characteristics by treatment group and 24-month missing data status

Variable	Scoring	Non-completers, <i>n</i> (%)			Completers, <i>n</i> (%)		
		Pump (<i>N</i> = 4)	MDI (<i>N</i> = 15)	All (<i>N</i> = 19)	Pump (<i>N</i> = 128)	MDI (<i>N</i> = 120)	All (<i>N</i> = 248)
Sex	Male	3 (75.0)	9 (60.0)	12 (63.2)	75 (58.6)	73 (60.8)	148 (59.7)
	Female	1 (25.0)	6 (40.0)	7 (36.8)	53 (41.4)	47 (39.2)	100 (40.3)
Smoking status	Smoker	2 (50.0)	5 (33.3)	7 (36.8)	21 (16.4)	25 (20.8)	46 (18.5)
	Ex-smoker	1 (25.0)	6 (40.0)	7 (36.8)	41 (32.0)	21 (17.5)	62 (25.0)
	Never smoker	1 (25.0)	4 (26.7)	5 (26.3)	66 (51.6)	74 (61.7)	140 (56.5)
Ethnicity	White British	4 (100.0)	14 (93.3)	18 (94.7)	121 (94.5)	105 (87.5)	226 (91.1)
	Other	–	1 (6.7)	1 (5.3)	3 (2.3)	11 (9.2)	14 (5.6)
	Prefer not to say	–	–	–	1 (0.8)	3 (2.5)	4 (1.6)

TABLE 44 Size of fidelity-tested pump courses

Centre	Number of participants on fidelity-tested course
Cambridge	7
Dumfries	7
Edinburgh	4
Glasgow	7
Harrogate	6
London (King's College Hospital)	3
Nottingham	4
Sheffield	7

Pump pre-course session

All participants attended the pump pre-course session to learn the mechanics of pump therapy and to programme and load the pump with saline to enable practice and familiarisation prior to undertaking the course. This session was scheduled to run for 2 hours and 30 minutes (\pm 15 minutes). Seven out of the eight centres ran sessions within this duration window. The centre that did not (Nottingham) ran a pump pre-course session of 2 hours and so was 15 minutes short of the specified duration window.

The majority of centres delivered the pump pre-course session solely by REPOSE educators (diabetes specialist nurses and dietitians). Two centres (Glasgow and Edinburgh) had a Medtronic representative present to provide technical support and help with elements of pump set-up. One centre (Glasgow) also had the PI present.

All pump pre-course session lesson plans were evaluated by the FA as relating to the objectives set for this session.

Insulin switchover

Participants were asked to switch over their pump from saline to insulin the evening before their pump DAFNE course if they felt happy to do so.

All course participants switched the evening before their course at three centres (Nottingham, Edinburgh and Harrogate). At Glasgow, all participants switched to insulin on the morning of course. This was a decision taken by the personnel at that centre who, after already having run one pump course, felt that this approach worked best, and course participants had not expressed any preference for the Sunday evening. At the remaining centres, the majority of participants switched to insulin the night before their course. Those who did not cited the following reasons:

- unsure of how to fit reservoir
- started in previous week but stopped, as wanted support from health professionals
- anxiety regarding change
- timing issues and technical problems with pump
- pump failure/motor alarming problem
- ran out of consumables and had cannula problems.

Pump courses

The pump course timetable was reviewed by the FA. All centres provided timetables that were evaluated as incorporating all elements of the pump DAFNE curriculum in a logical order. Based on the times allocated for sessions on the pump course timetable, all centres planned to deliver the curriculum in the specified duration window of ≥ 1870 minutes but ≤ 2280 minutes. The mean course duration was 2006 minutes, that is 33 hours and 26 minutes.

All sessions planned to be observed were reviewed during the fidelity visit and their lesson plans were reviewed.

The sick day rules lesson plan was reviewed for each centre. Seven of the eight centres were evaluated as having no issues with this session lesson plan, with only minor problems noted, for example no aims or objectives listed, timings not written on. One centre (Glasgow) was evaluated as having an issue with the sick day rule lesson plan. The lesson plan was lifted directly from the pump DAFNE curriculum without personalisation. The Glasgow educator explained that there was no time to personalise the lesson plan but agreed to remedy for future courses.

Essential learning outcomes

The FA recorded (with evidence) if all essential learning outcomes were met in the sessions observed. Sessions were recorded as having met all learning outcomes: 'yes' or 'no' or partially achieving essential learning outcomes. *Table 45* provides a summary.

For three sessions ('Insulin dose adjustment theory and basal rate testing', 'Setting up the bolus wizard' and 'Alcohol') all of the centres met all of the essential learning outcomes. For the 'Exercise' session, seven centres met the essential learning outcomes and the remaining centre (Sheffield) met 95% of learning outcomes.

For the dose escalation and reduction sessions, all of the centres either met or partly met all of the essential learning outcomes. For the centres that partly met the learning outcomes for these sessions, 80–98% of learning outcomes were met.

The essential learning outcomes for the session 'Daily goals, blood glucose results and insulin doses' were partly met at seven of the eight centres and fully met at one centre (100%). It is important to note for this session, which is delivered at the beginning and end of each day, it is expected that some essential learning outcomes will not be covered in one session, as it is guided by situations that the patients have recorded in their diaries. During the DAFNE course, as new situations are observed, further essential learning outcomes are generally covered.

TABLE 45 Summary of essential outcomes achieved^a

Centre	Daily goals, blood glucose results and insulin doses ^b	Insulin dose adjustment theory, basal rate testing	DA escalation	DA reduction	Setting up bolus wizard	Exercise	Alcohol	Lunchtime CP	Corrections
Sheffield	Y	Y	Y	P (95%)	Y	P (95%)	Y	Y	Not observed
Cambridge	P (70%)	Y	Y	Y	Y	Y	Y	Not observed	Y
London (King's College Hospital)	P (60%)	Y	Y	P (80%)	Y	Y	Y	Y	P (95%)
Harrogate	P (90%)	Y	P (95%)	P (95%)	Y	Y	Y	P (98%)	Not observed
Nottingham	P (80%)	Y	P (90%)	P (90%)	Y	Not observed ^c	Not observed ^d	P (70%)	Not observed
Glasgow	P (85%)	Y	P (98%)	P (95%)	Y	Y	Y	Y	Y
Edinburgh	P (85%)	Y	Y	Y	Y	Y	Y	P (60%)	Not observed
Dumfries	P (55%)	Y	Y	Y	Y	Y	Y	Not observed	Y

DA, dose adjustment; CP, carbohydrate portion; P, partial; Y, yes.

^a Percentages reported are approximate and based on FA's estimation of the proportion of learning outcomes covered.

^b It is not expected that all essential learning outcomes will be covered in this session because of the session content being determined by patients' diaries.

^c The educator delivering these sessions was a Sheffield educator who had been observed on the Sheffield pump course previously.

Although not essential for the FT, the FA observed the 'Lunchtime CP (carbohydrate portion)' and the 'Corrections' sessions at some centres.

Overall fidelity assessment concerns and action plans

The FA was asked to make an overall assessment of whether or not there were any major concerns about the delivery of the pump course and, if there were, any recommended actions to be taken. These are summarised by centre in *Table 46*.

TABLE 46 Concerns and actions required per centre

Centre	Concerns	Action
Sheffield	Main issue was timing. Bolus wizard set-up also took longer than timetabled	Team to discuss and consider allocating more time for these
London (King's College Hospital)	Pump set-up lesson plan not seen, as not available on the day. Some learning outcomes not observed on the day but not a cause for concern	Pump set-up plan to be e-mailed
Cambridge	No concerns. Discussion regarding CP estimation and corrections that were not observed, as covered in detail on other days at beginning of the week. No deviation from curriculum	None
Harrogate	Discussed timings around pump set-up session. Some learning outcomes were covered earlier in the week or will be covered in other sessions, especially around dose adjustment	Educators to reflect on the week and consider group evaluation and timings, etc.
Nottingham	Some lesson plans were not very detailed, for example dose escalation and reduction, and so some essential learning outcomes were left out. Educator agreed and noted that no internal QA had been done for a while because of the inconsistency of staffing levels	This is a priority to rewrite lesson plans and to think about QA once their new DAFNE educator has run some courses and had the training
Glasgow	Term 'rebound hyperglycaemia' used, that is, when blood glucose level is normal at bedtime but high in the morning. Educator said it is due to hypoglycaemic episodes in the night and the liver releasing glucose. DAFNE does not say this and educator referred to p. 134 of curriculum escalation. Educator said that they did not know that this was the case and will make it clear to educators that the explanation will be overtreatment of a hypoglycaemia/dawn phenomenon/basal rate not correct Lesson plan for sick day rules not personalised Some DA practice escalation and reduction essential learning outcomes not covered	Personalisation of sick days rules lesson plan Educator to ensure that all of the team knows not to use 'rebound hyperglycaemia' term
Edinburgh	No major concerns regarding delivery. Lots of questions from participants on one session, so it went over time. Rebound hyperglycaemia (after night-time hypoglycaemia and increased blood glucose in the morning) was used	Explained that the term 'rebound hyperglycaemia' was not used in the DAFNE curriculum. The group understood, however, that they should not correct a raise of blood glucose following an episode of hypoglycaemia
Dumfries	Rebound hyperglycaemia term being used (i.e. raised blood glucose in the morning after a normal bedtime reading owing to rebound after night-time hypoglycaemia); discussed that not used in DAFNE and educator confirmed that they had not wished it to come over like this but patients obviously interpreting as such	Discussed the need to word things differently and educators agreed to make sure that the group understood this over the rest of the course

DA, dose adjustment; QA, quality assessment.

Conclusion

Overall, the pump courses appear to have been delivered according to the pump course curriculum. The pump courses observed seem representative of pump courses on REPOSE in terms of course characteristics. The pre-course session was delivered consistently and met the objectives set. All pump courses were planned to run in a logical order within the time frame specified. There were problems with the term 'rebound hyperglycaemia' being used (three centres) and non-personalisation of lesson plan (one centre).

Generally, essential learning outcomes were consistently delivered during the sessions. The session 'Daily goals, blood glucose results and insulin doses' had the lowest percentage of essential outcomes met. This is not unusual for this session, when learning outcomes are met during the week of the course. In standard care, learning outcomes may also be omitted in other sessions during the week of the DAFNE course, but are subsequently covered in other sessions. This can be for various reasons, for example more pressing issues and questions raised by the participants. With appropriate timetabling and timings allocated to sessions, there should be sufficient time for experienced educators to deliver all of the essential learning outcomes for all sessions. The key thing is that educators have awareness of any learning outcomes that have been missed and can produce a strategy for how they will incorporate the missed content at another relevant stage of the week, or indeed at the 6-week follow-up session if necessary.

The quality assurance programme for MDI DAFNE courses in standard care audits the entire DAFNE course week, whereas the REPOSE FT was restricted to 1 day of the course. Therefore, although the quality assurance programme of MDI courses can examine if missed learning outcomes are covered in later sessions, this was not possible for the REPOSE FT of the pump courses, and is a limitation. Nevertheless, the number of missed learning outcomes was still low.

Chapter 6 Results of the economic evaluation

Cost of insulin pumps and consumables

The weighted average cost of an insulin pump from the pump costing survey was £2571. The cost of insulin pumps was converted into a yearly cost using annuitisation. The lifetime of the insulin pumps was taken to be 4.5 years and the discount rate was that used by NICE (3.5%).²² This gave a weighted average yearly cost of insulin pumps to be £627. The weighted average yearly cost of insulin pump consumables was £1433.

Within-trial cost-effectiveness analysis

Base-case analysis

The results of the within-trial cost-effectiveness analysis are presented using a confidence ellipse in *Figure 13*. In the base case, pump + DAFNE was dominated by MDI + DAFNE, as pump + DAFNE produced fewer mean QALYs at a higher mean cost. The confidence ellipse shows that pump + DAFNE was associated with statistically significantly higher costs than MDI + DAFNE at the 5% significance level, as the confidence ellipse does not cross the x-axis at £0. The confidence ellipse also shows that pump + DAFNE was not associated with statistically significantly lower QALYs than MDI + DAFNE at the 5% significance level. This is because the confidence ellipse crosses the y-axis of the graph at 0. Another point to note is that the confidence ellipses do not cross a threshold ICER of £20,000 per QALY gained; therefore, the ICER of pump + DAFNE compared with MDI + DAFNE is greater than £20,000 per QALY gained at the 95% confidence level.

The cost-effectiveness acceptability curve is presented in *Figure 14*. It shows that pump + DAFNE has a 0.0% chance of being considered cost-effective at threshold ICERs of £20,000 per QALY gained and £30,000 per QALY gained. This is important as, based on the data in the REPOSE Trial, pump + DAFNE has a 0% probability of being cost-effective at the thresholds used by NICE in the UK for decision-making.²²

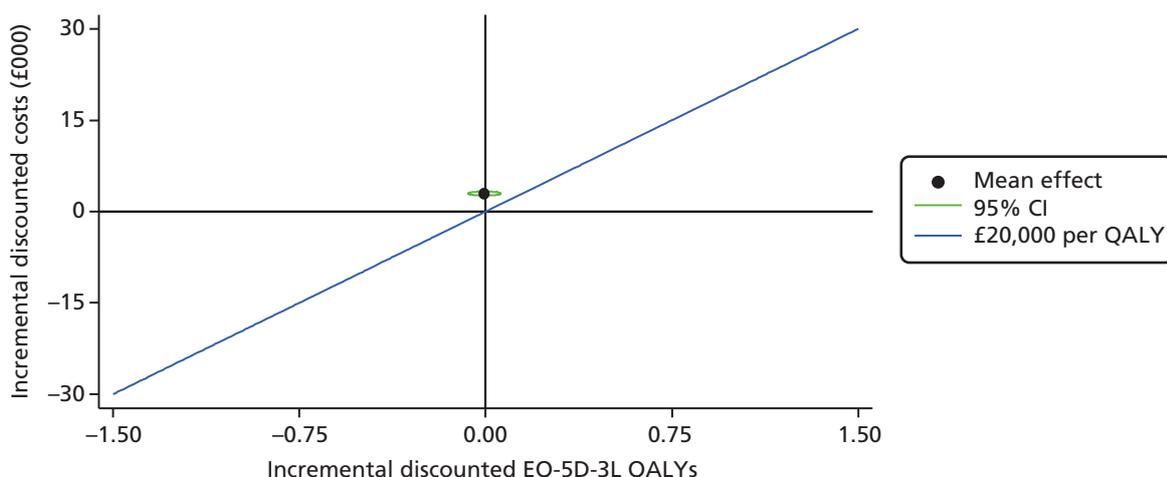


FIGURE 13 Confidence ellipse for the base-case within-trial analysis: controlling for baseline utility.

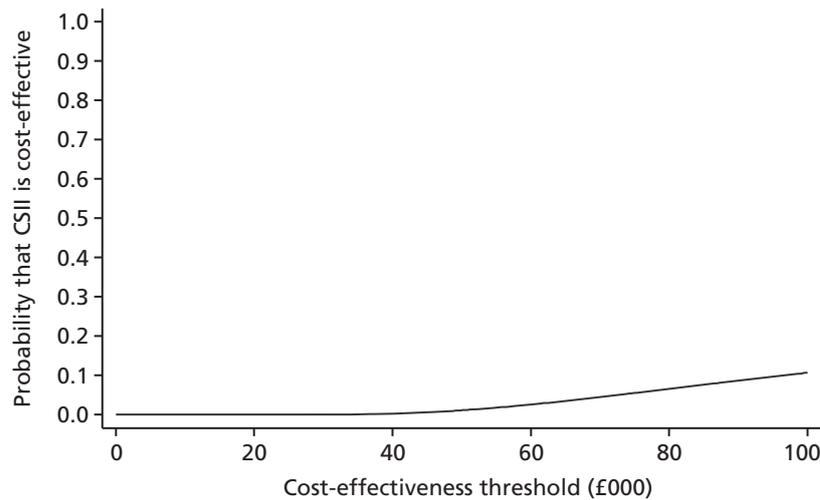


FIGURE 14 Cost-effectiveness acceptability curve for the base-case within-trial analysis: controlling for baseline utility.

Table 47 presents the incremental cost and QALY outcomes of pump + DAFNE compared with MDI + DAFNE in each year of the trial and for both years combined. In the base case, the incremental cost in year 2 is lower than the cost in year 1. This is probably due to (1) treatment switching and (2) the rate of DKAs and severe hypoglycaemic events being noticeably lower in the pump + DAFNE arm in the second year than in the first year. The incremental QALYs are negative in the first year and positive in the second year. However, in neither year is this result statistically significant and, in both years, the central estimates are less than one-hundredth of a QALY. This is not unusual in diabetes trials, in which the crucial QALY gains due to an intervention come much later in the patient experience because of a reduced risk of long-term complications.

Summary of the scenario analyses

The following scenario analyses were undertaken to explore structural uncertainty in the base-case analysis:

1. per-protocol population
2. missing cost and QALY data were imputed
3. QALYs measured by the SF-6D were used instead of QALYs measured using the EQ-5D
4. imputed data and QALYs measured by SF-6D QALYs
5. pump costs measured by Riemsma *et al.*⁸ were used
6. Riemsma *et al.*⁸ pump costs were used and missing data were imputed
7. the cost of pumps and consumables are 25% lower
8. the cost of pumps and consumables are 25% lower in a per-protocol population
9. the cost of pumps and consumables are 50% lower
10. the cost of pumps and consumables are 50% lower in a per-protocol population.

In the first scenario, EECT was conducted in the per-protocol population as this was a pre-specified subgroup analysis (see Chapter 2, *Population and subgroups for analysis*). In the second scenario, missing cost and QALY data were imputed to explore the uncertainty that may result from having incomplete data, as in the base-case analysis only 78.85% of people had complete cost and QALY data. Details of the imputation procedure used are provided in Chapter 3 (see *Estimating the within-trial cost effects* and *Estimating within-trial quality-adjusted life-year effects using the EuroQol-5 Dimensions and the Short Form questionnaire-12 items*). A further sensitivity analysis was conducted, for which the SF-6D measure, instead of the EQ-5D, was used to calculate QALYs. This scenario analysis was conducted to explore if changing the preference-based measure of health changed the estimated QALY values significantly enough to

TABLE 47 Within-trial cost-effectiveness analysis results of pump vs. MDI, both with DAFNE structured education

	n	Incremental costs (£), mean (95% CI)			Incremental QALYs, mean (95% CI)			ICER, £/QALY gained
		Year 1	Year 2	Total	Year 1	Year 2	Total	
		Base case			Scenario analyses			
ITT population with complete costs and QALYs	205	1732 (1511 to 1952)	1228 (1063 to 1392)	2959 (2692 to 3227)	-0.007 (-0.036 to 0.022)	0.003 (-0.029 to 0.035)	-0.004 (-0.057 to 0.048)	Dominated
Per-protocol population	188	1780 (1520 to 2041)	1434 (1328 to 1539)	3214 (2916 to 3513)	-0.003 (-0.034 to 0.027)	0.006 (-0.026 to 0.037)	0.002 (-0.051 to 0.056)	1,369,287
Imputed data	260	1697 (1492 to 1901)	1175 (1006 to 1345)	2872 (2602 to 3142)	-0.013 (-0.039 to 0.014)	0.004 (-0.029 to 0.037)	-0.009 (-0.058 to 0.04)	Dominated
SF-6D QALYs	196	1746 (1514 to 1978)	1254 (1096 to 1412)	3000 (2729 to 3271)	-0.001 (-0.021 to 0.019)	-0.002 (-0.027 to 0.023)	-0.003 (-0.045 to 0.039)	Dominated
Imputed data and SF-6D QALYs	256	1701 (1494 to 1908)	1186 (1016 to 1357)	2888 (2616 to 3159)	-0.003 (-0.021 to 0.015)	-0.001 (-0.024 to 0.022)	-0.004 (-0.041 to 0.034)	Dominated
Riemsma <i>et al.</i> ⁸ , pump costs	205	1679 (1450 to 1908)	1184 (1024 to 1343)	2863 (2586 to 3140)	-0.007 (-0.036 to 0.022)	0.003 (-0.029 to 0.035)	-0.004 (-0.057 to 0.048)	Dominated
Imputed data Riemsma <i>et al.</i> ⁸ , pump costs	260	1648 (1434 to 1861)	1125 (964 to 1286)	2772 (2498 to 3047)	-0.013 (-0.039 to 0.014)	0.004 (-0.029 to 0.037)	-0.009 (-0.058 to 0.04)	Dominated
The cost of pumps and consumables are 25% lower	205	1285 (1022 to 1547)	955 (850 to 1059)	2239 (1786 to 2314)	-0.007 (-0.036 to 0.022)	0.003 (-0.104 to 0.11)	-0.004 (-0.057 to 0.048)	Dominated
The cost of pumps and consumables are 25% lower in a per-protocol analysis	188	1223 (1010 to 1436)	768 (634 to 902)	1991 (1939 to 2540)	-0.003 (-0.034 to 0.027)	0.006 (-0.026 to 0.037)	0.002 (-0.051 to 0.056)	966,218
The cost of pumps and consumables are 50% lower	205	767 (532 to 1001)	375 (255 to 494)	1141 (873 to 1409)	-0.007 (-0.036 to 0.022)	0.003 (-0.029 to 0.035)	-0.004 (-0.057 to 0.048)	Dominated
The cost of pumps and consumables are 50% lower in a per-protocol analysis	188	789 (524 to 1053)	475 (372 to 579)	1264 (961 to 1567)	-0.004 (-0.034 to 0.027)	0.006 (-0.026 to 0.037)	0.002 (-0.051 to 0.056)	552,866

potentially change the conclusions on cost-effectiveness (see *Chapter 3, Estimating within-trial quality-adjusted life-year effects using the EuroQol-5 Dimensions and the Short Form questionnaire-12 items*). Uncertainty in insulin pump costs was also explored, to see if significant discounts from the prices observed at the REPOSE Trial sites would lead to pump + DAFNE being considered to be cost-effective compared with MDI + DAFNE. Several of these uncertainties were also combined in other scenarios to determine if the joint effect of the uncertainties had any meaningful effect on the conclusions.

Results of the scenario analyses

The results of the scenario analyses are also presented in *Table 47*. It is clear that pump + DAFNE compared with MDI + DAFNE generated fewer QALYS at a higher cost in all analyses, apart from those scenarios conducted in the per-protocol population. The lowest ICER is observed in the scenario for which the per-protocol population is used, and there is a cost reduction in insulin pumps and consumables of 50%. The ICER in this scenario is £552,866, which is above the £20,000–30,000 per QALY gained threshold considered by NICE.²² Therefore, based on the data observed directly in the REPOSE Trial, pump + DAFNE would be unlikely to be considered cost-effective if it were to be assessed by NICE.

Clinical evidence used to inform the cost-effectiveness of pump + Dose Adjustment For Normal Eating compared with multiple daily injection + Dose Adjustment For Normal Eating

This section details the results of the statistical models fitted to estimate the incidence of treatment switching, HbA_{1c}, the risk of severe hypoglycaemia, the risk of DKA, the cost of insulin, the cost of diabetes-related contacts and the cost of insulin pumps. The parameters presented in these statistical models were directly included in the long-term health economic model, except for the risk of severe hypoglycaemia and the risk of DKA, for which simulations of the expected number of events were inputted into the long-term health economic model. In the PSA, the uncertainty in the parameters of these statistical models was assumed to follow a multivariate normal distribution. Variance–covariance matrices are available from the authors on request.

Treatment switching

The results of the exponential and Weibull parametric survival models for individuals randomised to MDI + DAFNE and pump + DAFNE are given in *Table 48*. The results for the Gompertz, log-logistic and log-normal parametric models are given in *Appendix 14*. It was not possible to estimate a survival curve using a generalised gamma distribution, as the model did not converge in either trial arm.

In the pump + DAFNE arm, it was predicted that an individual was more likely to switch treatment if they had a severe hypoglycaemic event or if they had a higher HbA_{1c}. It was also observed that an individual was less likely to switch from CSII to MDI if they had experienced a DKA event in the previous year. All of these results are statistically significant at the 5% level in the Weibull and exponential models, except for the effect of HbA_{1c} on the probability of switching in the exponential model.

In the MDI + DAFNE arm, the relationships between HbA_{1c}, number of severe hypoglycaemic episodes in the year prior to switching and the number of DKAs in the year prior to switching worked in a similar way to the pump + DAFNE arm. It should be noted that the effect sizes are different in the two arms for different covariates. In the MDI + DAFNE arm, all of the coefficients were statistically significant at the 5% level.

Table 49 shows the AIC and BIC for the different survival models fitted to pump + DAFNE individuals and MDI + DAFNE individuals. In the pump + DAFNE arm, the curve with lowest AIC and BIC was the exponential model. For the MDI + DAFNE individuals, the curve with the lowest AIC was the Weibull model and the curve with the lowest BIC was the exponential model.

TABLE 48 Results of the exponential and Weibull parametric survival models fitted to individuals in both arms of the REPOSE Trial

Parameter	Coefficient	Robust SE	95% CI
Pump + DAFNE			
<i>Exponential model</i>			
HbA _{1c}	0.222	0.241	-0.251 to 0.695
Number of DKAs	-0.972	0.474	-1.901 to -0.042
Number of severe hypoglycaemic events	0.427	0.087	0.257 to 0.598
Constant	-4.616	2.125	-8.781 to -0.451
<i>Weibull model</i>			
HbA _{1c}	0.221	0.234	0.016 to 0.694
Number of DKAs	-0.981	0.471	-7.113 to -4.910
Number of severe hypoglycaemic events	0.404	0.085	0.337 to 0.684
Constant	-4.460	2.100	-10.607 to -4.696
In-scale parameter	-0.258	0.220	0.111 to 1.377
MDI + DAFNE			
<i>Exponential model</i>			
HbA _{1c}	0.336	0.164	0.014 to 0.657
Number of DKAs	-5.555	0.561	-6.655 to -4.455
Number of severe hypoglycaemic events	0.460	0.074	0.315 to 0.605
Constant	-6.725	1.450	-9.567 to -3.884
<i>Weibull model</i>			
HbA _{1c}	0.355	0.173	0.016 to 0.694
Number of DKAs	-6.012	0.562	-7.113 to -4.910
Number of severe hypoglycaemic events	0.510	0.089	0.337 to 0.684
Constant	-7.652	1.508	-10.607 to -4.696
In-scale parameter	0.744	0.323	0.111 to 1.377
ln, natural logarithm.			

TABLE 49 Summary of the AIC and the BIC for the fitted survival curves used in the long-term modelling

Distribution	AIC	BIC
Pump + DAFNE		
Exponential	145.77	157.24
Weibull	146.46	160.80
Gompertz	147.25	161.59
Log-logistic	147.49	161.83
Log-normal	148.48	162.82
MDI + DAFNE		
Exponential	64.36	75.77
Weibull	62.55	76.81
Gompertz	63.76	78.02
Log-logistic	63.78	78.04
Log-normal	64.97	79.23

The visual plot of the survival curves for remaining on the initially allocated treatment for the pump + DAFNE and MDI + DAFNE individuals are presented in *Figures 15* and *16*, respectively. The curves fitted to the treatment switching data show a reasonable fit to the Kaplan–Meier curves for individuals who were randomised to pump + DAFNE and MDI + DAFNE. A visual inspection of curves showed that the exponential curve for pump + DAFNE showed the best fit to the Kaplan–Meier curve at the 1- and 2-year time points, although a visual check does not indicate that it has the best fit for all of the time points. A visual inspection of the curves in the MDI + DAFNE arm shows that all curves had a reasonable fit to the Kaplan–Meier curve, except the exponential curve, which had a poor fit to the Kaplan–Meier curve, especially in the first year.

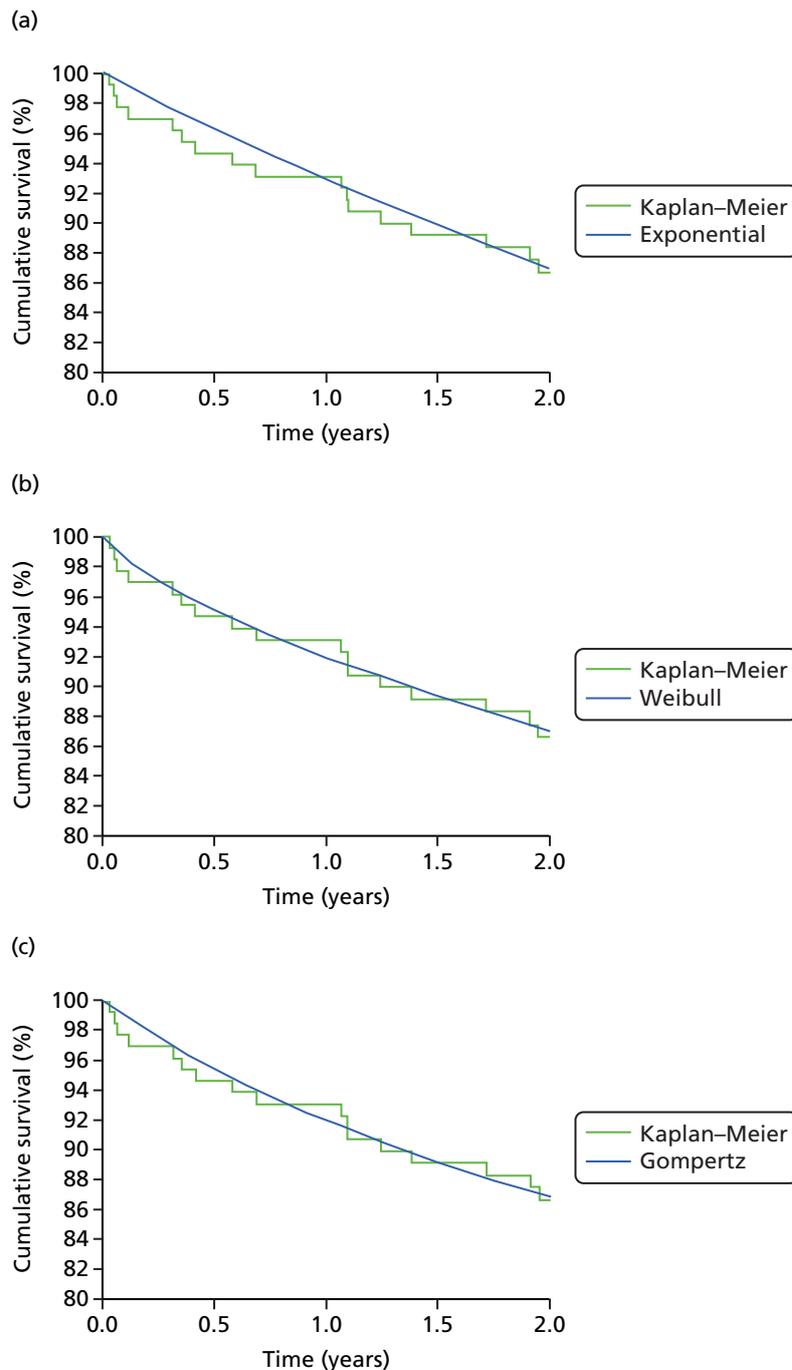


FIGURE 15 A visual plot of the Kaplan–Meier and parametric survival curves for those individuals who were randomised to pump with DAFNE. (a) Exponential curve; (b) Weibull curve; (c) Gompertz curve; (d) log-logistic curve; and (e) log-normal curve. (*continued*)

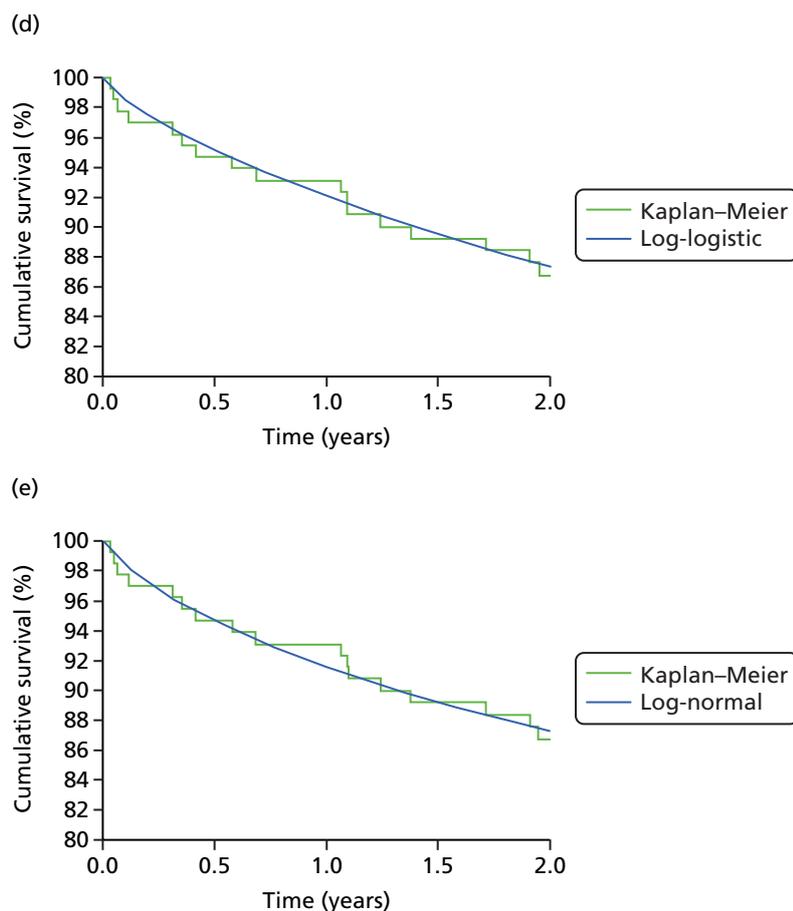


FIGURE 15 A visual plot of the Kaplan–Meier and parametric survival curves for those individuals who were randomised to pump with DAFNE. (a) Exponential curve; (b) Weibull curve; (c) Gompertz curve; (d) log-logistic curve; and (e) log-normal curve.

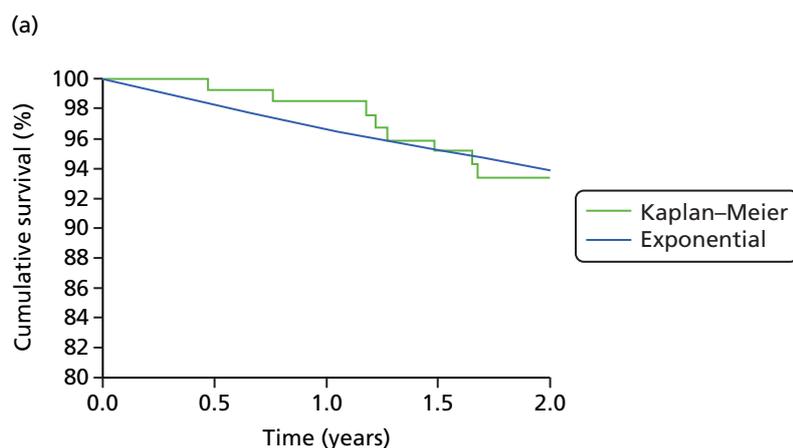


FIGURE 16 A visual plot of the Kaplan–Meier and parametric survival curves for those individuals who were randomised to MDI with DAFNE. (a) Exponential curve; (b) Weibull curve; (c) Gompertz curve; (d) log-logistic curve; and (e) log-normal curve. (*continued*)

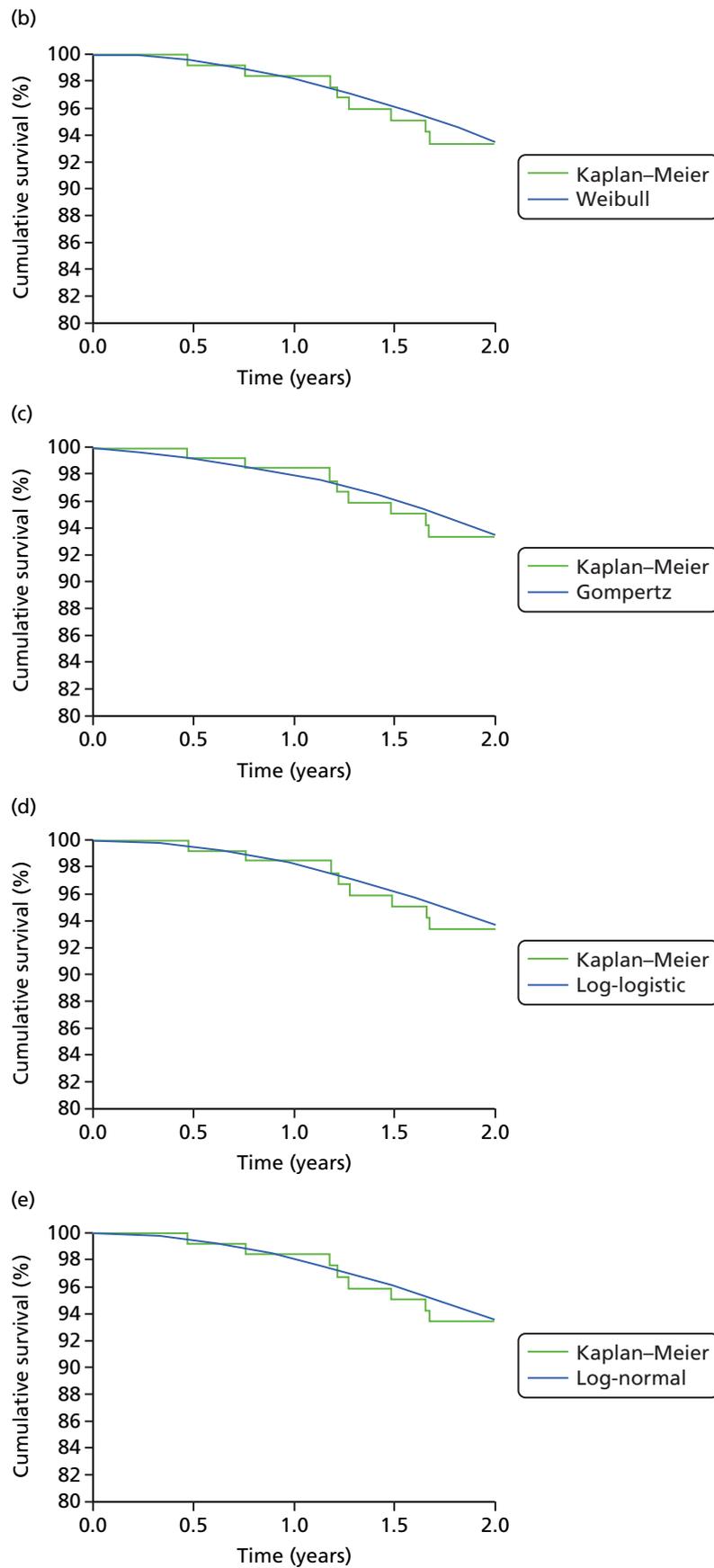


FIGURE 16 A visual plot of the Kaplan–Meier and parametric survival curves for those individuals who were randomised to MDI with DAFNE. (a) Exponential curve; (b) Weibull curve; (c) Gompertz curve; (d) log-logistic curve; and (e) log-normal curve.

In the base case, the exponential model will be used to model the treatment switching of individuals in the pump + DAFNE arm, and the Weibull model will be used to model the treatment switching of individuals in the MDI + DAFNE arm. Uncertainties in the coefficients of these models were included in the PSA using a multivariate normal distribution. Scenario analyses were conducted when the risk of switching treatment was estimated directly from the Kaplan–Meier curves at years 1 and 2. The risk of switching treatment for a pump individual, given that he/she was receiving pump therapy at the start of the year, was 6.94% at year 1 and 6.89% at year 2. The risk of switching for a MDI individual, given that they were receiving MDI at the start of the year, was 1.58% in year 1 and 5.13% in year 2.

Glycated haemoglobin

The results of the beta regressions used to model the effectiveness of pump + DAFNE versus MDI + DAFNE in the ITT population is given in *Table 50*. Pump + DAFNE has a coefficient on HbA_{1c} reduction of -0.056 at year 1 and -0.018 at year 2; neither result was statistically significant at the 5% significance level. These coefficients are not easily interpretable, as changes in HbA_{1c}, as the mean effects are estimated using a logit link function.

In the per-protocol population as in this group, the statistical analysis showed a significant improvement in HbA_{1c} for pump + DAFNE. The results of the beta regression fitted to the per-protocol population is given in *Table 51*. Pump + DAFNE was associated with a coefficient of -0.056 in year 1 and -0.047 in year 2. Neither of these coefficients was statistically significant at the 5% level. The uncertainty in the coefficients in these statistical models was included in the PSA of the Sheffield Type 1 Diabetes Model by sampling the coefficients from a multivariate normal distribution using the known variance covariance matrices.

Severe hypoglycaemia and diabetic ketoacidosis

The results of the negative binomial regressions for the incidence of severe hypoglycaemia are given in *Table 52*. The regression predicts that the number of severe hypoglycaemic events increases as a patient's HbA_{1c} decreases; however, this result is not statistically significant at the 5% level in the second year. Pump + DAFNE compared with MDI + DAFNE was associated with a higher incidence of severe hypoglycaemia in year 1 and a lower incidence of severe hypoglycaemia in year 2. Neither result was statistically significant at the 5% level.

The results of the negative binomial regressions for the incidence of DKA are given in *Table 53*. The predicted number of DKAs increase with a patient's HbA_{1c}. This result is statistically significant in the first year, but not in the second year. Pump + DAFNE when compared with MDI + DAFNE was associated with a higher incidence of DKA in year 1 and a lower incidence of DKA in year 2. Neither result was statistically significant at the 5% level.

Cost of insulin, diabetes-related contacts and insulin pumps

The results of the analyses on the cost of insulin used in the long-term modelling are given in *Table 54*. Pump treatment was associated with a reduction in insulin costs of around £500 per annum in years 1 and 2 compared with MDI treatment. This result was statistically significant in both years. Switching from pump to MDI treatment was associated with an increase in insulin costs of around £550 in year 1 and £150 in year 2. No coefficient could be estimated on whether or not a MDI individual switched to pump, as this parameter was collinear with model parameters. Switching from MDI to pump was associated with a decrease in insulin costs of around £350 in year 2. All of these results were statistically significant at the 5% level.

TABLE 50 Effect of pump compared with MDI for all individuals in the ITT population

HbA _{1c}	Coefficient	SE	t	p > t	95% CI
At 1 year (beta scale)					
<i>Mean effect (Mu)</i>					
Treatment allocation (1 = pump + DAFNE, 0 = MDI + DAFNE)	-0.056	0.038	-1.49	0.137	-0.131 to 0.018
Baseline HbA _{1c} (beta scale)	3.978	0.248	16.01	0	3.491 to 4.465
Constant	-2.223	0.088	-25.28	0	-2.395 to -2.050
Centre effects (Cambridge is the reference centre):					
Dumfries and Galloway	-0.025	0.074	-0.33	0.738	-0.171 to 0.121
Edinburgh	-0.019	0.065	-0.3	0.768	-0.147 to 0.108
Glasgow	-0.154	0.099	-1.55	0.12	-0.348 to 0.040
Harrogate	0.022	0.041	0.52	0.602	-0.060 to 0.103
London (King's College Hospital)	0.013	0.065	0.21	0.837	-0.114 to 0.140
Nottingham	0.214	0.060	3.58	0	0.097 to 0.331
Sheffield	0.066	0.057	1.17	0.241	-0.045 to 0.178
<i>Natural logarithm of the dispersion parameter [ln(phi)]</i>					
Baseline HbA _{1c} (beta scale)	-2.996862	0.9980645	-3	0.003	-4.954 to -1.040
Constant	4.912	0.332	14.79	0	4.261 to 5.563
At 2 years (beta scale)					
<i>Mean effect (Mu)</i>					
Treatment allocation (1 = pump + DAFNE, 0 = MDI + DAFNE)	-0.018	0.035	-0.52	0.603	-0.086 to 0.050
1-year HbA _{1c} (beta scale)	0.797	0.318	2.51	0.012	0.175 to 1.419
Baseline HbA _{1c} (beta scale)	3.599	0.342	10.51	0	2.927 to 4.271
Constant	-2.380	0.091	-26.14	0	-2.558 to -2.201
Centre effects (Cambridge is the reference centre):					
Dumfries and Galloway	0.047	0.093	0.5	0.617	-0.137 to 0.230
Edinburgh	0.067	0.085	0.8	0.426	-0.098 to 0.233
Glasgow	0.137	0.097	1.42	0.155	-0.052 to 0.327
Harrogate	0.123	0.087	1.41	0.158	-0.048 to 0.294
London (King's College Hospital)	0.079	0.087	0.9	0.366	-0.092 to 0.249
Nottingham	0.120	0.110	1.09	0.279	-0.098 to 0.337
Sheffield	0.156	0.080	1.96	0.05	0.000 to 0.312
<i>Natural logarithm of the dispersion parameter [ln(phi)]</i>					
1-year HbA _{1c} (beta scale)	-4.667	1.129	-4.13	0	-6.881 to -2.453
Constant	5.422	0.277	19.56	0	4.879 to 5.966

TABLE 51 Effect of pump compared with MDI for all individuals in the per-protocol population

HbA _{1c}	Coefficient	SE	t	p > t	95% CI
At 1 year (beta scale)					
<i>Mean effect (Mu)</i>					
Treatment allocation (1 = pump + DAFNE, 0 = MDI + DAFNE)	-0.056	0.044	-1.37	0.171	-0.148 to 0.026
Baseline HbA _{1c} (beta scale)	3.938	0.255	13.62	0	2.978 to 3.980
Constant	-2.219	0.093	-23.94	0	-2.401 to -2.038
Centre effects (Cambridge is the reference centre):					
Dumfries and Galloway	-0.019	0.078	-0.25	0.805	-0.172 to 0.134
Edinburgh	0.020	0.056	0.37	0.714	-0.089 to 0.130
Glasgow	-0.129	0.095	-1.36	0.175	-0.315 to 0.057
Harrogate	0.025	0.040	0.62	0.534	-0.054 to 0.104
London (King's College Hospital)	0.018	0.064	0.28	0.779	-0.107 to 0.143
Nottingham	0.172	0.039	4.46	0	0.096 to 0.247
Sheffield	0.084	0.064	1.31	0.191	-0.042 to 0.209
<i>Natural logarithm of the dispersion parameter [ln(phi)]</i>					
Baseline HbA _{1c} (beta scale)	-3.504	1.050	-3.34	0.001	-5.563 to -1.446
Constant	5.062	0.351	14.41	0	4.373 to 5.751
At 2 years (beta scale)					
<i>Mean effect (Mu)</i>					
Treatment allocation (1 = pump + DAFNE, 0 = MDI + DAFNE)	-0.047	0.035	-1.35	0.177	-0.116 to 0.021
1-year HbA _{1c} (beta scale)	3.475	0.340	10.23	0	2.809 to 4.141
Baseline HbA _{1c} (beta scale)	1.053	0.351	3	0.003	0.365 to 1.740
Constant	-2.382	0.092	-26.01	0	-2.562 to -2.203
Centre effects (Cambridge is the reference centre):					
Dumfries and Galloway	0.022	0.088	0.26	0.799	-0.150 to 0.194
Edinburgh	0.076	0.085	0.89	0.374	-0.091 to 0.243
Glasgow	0.105	0.096	1.1	0.271	-0.082 to 0.293
Harrogate	0.092	0.085	1.08	0.28	-0.075 to 0.258
London (King's College Hospital)	0.053	0.085	0.62	0.538	-0.115 to 0.220
Nottingham	0.109	0.100	1.1	0.276	-0.089 to 0.308
Sheffield	0.157	0.078	2.02	0.043	0.005 to 0.310
<i>Natural logarithm of the dispersion parameter [ln(phi)]</i>					
1-year HbA _{1c} (beta scale)	-4.809	1.231	-3.9	0	-7.223 to -2.394
Constant	5.474	0.302	18.13	0	4.882 to 6.066

TABLE 52 Negative binomial model fitted to the incidence of severe hypoglycaemia at baseline, 1 and 2 years

Severe hypoglycaemia	Coefficient	SE	z-value	p > z
Year 1				
Treatment allocation (1 = pump + DAFNE, 0 = MDI + DAFNE)	0.2861	0.5149	0.556	0.578
1-year HbA _{1c} (DCCT% scale)	-0.5010	0.2323	2.157	0.03
Number of severe hypoglycaemic events experienced in the year prior to baseline	2.0708	0.5638	3.673	> 0.000
Constant	1.2689	1.8676	0.679	0.49687
Year 2				
Treatment allocation (1 = pump + DAFNE, 0 = MDI + DAFNE)	-1.1141	0.7202	-1.547	0.122
2-year HbA _{1c} (DCCT% scale)	-0.2019	0.2668	-0.757	0.449
Constant	-0.6367	2.2625	-0.281	0.778

TABLE 53 Negative binomial model fitted to the incidence of DKA at baseline, 1 and 2 years

DKA	Coefficient	SE	z-value	p > z
Year 1				
Treatment allocation (1 = pump + DAFNE, 0 = MDI + DAFNE)	0.3369	0.4786	0.704	0.481
1-year HbA _{1c} (DCCT% scale)	0.4089	0.1246	3.283	0.001
Constant	-5.9443	1.1879	-5.004	> 0.00
Year 2				
Treatment allocation (1 = pump + DAFNE, 0 = MDI + DAFNE)	-0.07564	0.70426	-0.107	0.914
2-year HbA _{1c} (DCCT% scale)	0.32667	0.19447	1.680	0.093
Number of DKAs in year 1	0.86618	0.51682	1.676	0.094
Constant	-5.98206	1.82156	-3.284	0.01

The model uses the parameters in the regression model presented in *Table 53* to estimate their cost of insulin. For example, the formula used to estimate the cost of insulin beyond the second year in a deterministic analysis is as follows:

$$\begin{aligned}
 \text{Cost of insulin} = & \text{£}324.53 + \text{£}1.04 \text{ (patient's baseline cost of insulin)} \\
 & + \text{£}12.81 \text{ [patient's baseline HbA}_{1c} \text{ (DCCT\% scale)]} \\
 & + \text{£}527.64 \text{ (1 = was receiving a pump at the start of the year, 0 = otherwise)} \\
 & + \text{£}153.35 \text{ (1 = switched from pump to MDI this year, 0 = otherwise)} \\
 & + \text{£}353.27 \text{ (1 = switched from MDI to pump this year, 0 = otherwise).}
 \end{aligned} \tag{7}$$

The results of the analyses on the cost of diabetes-related contacts are given in *Table 55*. Pump + DAFNE was associated with an increase in the cost of diabetes-related contacts of £130 per annum in year 1 and £90 per annum in year 2 compared with MDI. These results were not statistically significant in year 1 or 2. Switching from insulin pump therapy to MDI was associated with an increase in diabetes-related contact costs of £280 per annum in year 1 and a decrease of £50 per annum in year 2. Switching from MDI to insulin pump therapy was associated with an increase in diabetes-related contact costs of £730 per annum in year 1 and £300 per annum in year 2. None of the treatment switching coefficients was statistically significant at the 5% significance level.

TABLE 54 Result of seemingly unrelated regression on insulin costs (£) in years 1 and 2

Parameter	Coefficient	Robust SE	95% CI
Year 1			
Baseline insulin cost	0.97	0.14	0.69 to 1.25
Baseline HbA _{1c} (DCCT% scale)	5.08	6.65	-7.95 to 18.10
Randomised treatment group (1 = pump + DAFNE, 0 = MDI + DAFNE)	-517.91	25.57	-568.02 to -467.80
Did the individual switch from pump to MDI in year 1? (1 = switched, 0 = did not switch)	554.47	114.26	330.53 to 778.41
Constant	381.77	70.20	244.19 to 519.36
Year 2			
Baseline insulin cost	1.04	0.11	0.82 to 1.26
Baseline HbA _{1c} (DCCT% scale)	12.81	8.72	-4.27 to 29.90
Patient's treatment at 1 year follow-up (1 = pump, 0 = MDI)	-527.64	30.22	-586.87 to -468.42
Did the individual switch from pump to MDI in year 2? (1 = switched, 0 = did not switch)	153.35	55.96	43.67 to 263.02
Did the individual switch from MDI to pump in year 2? (1 = switched, 0 = did not switch)	-353.27	80.06	-510.18 to -196.36
Constant	324.53	79.15	169.40 to 479.66

TABLE 55 Result of seemingly unrelated regression on diabetes-related contact costs (£) in years 1 and 2

Parameter	Coefficient	Robust SE	95% CI
Year 1			
Baseline diabetes-related contacts cost	0.11	0.04	0.04 0.18
Baseline HbA _{1c} (DCCT% scale)	-21.66	20.72	-62.27 18.94
Randomised treatment group (1 = pump + DAFNE, 0 = MDI + DAFNE)	129.08	68.35	-4.88 263.05
Did the individual switch from pump to MDI in year 1? (1 = switched, 0 = did not switch)	280.16	368.38	-441.86 1002.17
Did the individual switch from MDI to pump in year 1? (1 = switched, 0 = did not switch)	733.95	633.94	-508.55 1976.45
Constant	415.46	132.54	155.69 675.24
Year 2			
Baseline diabetes-related contacts cost	0.03	0.02	-0.02 0.07
Baseline HbA _{1c} (DCCT% scale)	12.15	25.18	-37.20 61.50
Patient's treatment at 1 year follow-up (1 = pump, 0 = MDI)	88.99	69.17	-46.58 224.56
Did the individual switch from pump to MDI in year 2? (1 = switched, 0 = did not switch)	-47.10	66.92	-178.25 84.05
Did the individual switch from MDI to pump in year 2? (1 = switched, 0 = did not switch)	299.80	153.43	-0.92 600.52
Constant	201.93	171.22	-133.64 537.51

The cost of DRCs for each individual was predicted using the values in *Table 55*. For example, in a deterministic model run, a patient's cost of DRCs in the first year was given by the following formula:

$$\begin{aligned}
 \text{Cost of DRCs} = & \text{£}415.46 + \text{£}0.11 \text{ (patient's baseline cost of DRC)} \\
 & + \text{£} -21.66 \text{ [patient's baseline HbA}_{1c} \text{ (DCCT\% scale)}] \\
 & + \text{£}129.08 \text{ (1 = randomised to pump + DAFNE, 0 = otherwise)} \\
 & + \text{£}280.16 \text{ (1 = switched from pump to MDI in year 1, 0 = otherwise)} \\
 & + \text{£}733.95 \text{ (1 = switched from MDI to pump in year 1, 0 = otherwise)}.
 \end{aligned} \tag{8}$$

The results of the analyses on the cost in insulin pump therapy (includes the yearly cost of the pump and the associated consumables) is given in *Table 56*. Insulin pump therapy was associated with a cost per annum of £2056 in year 1 and £2051 in year 2. Switching from insulin pump therapy to MDI was associated with a decrease in insulin pump therapy costs of £1140 in year 1 and a reduction of £910 in year 2. Switching from MDI to insulin pump therapy was associated with an increase in costs of £840 in year 1 and £130 in year 2. All of these results were statistically significant at 5% level.

The coefficients in these statistical models were included in the model to predict the cost of insulin, diabetes-related contact and insulin pump therapy. The uncertainty in these parameters was included in the PSA by using a multivariate normal distribution for each regression equation.

TABLE 56 Result of seemingly unrelated regression on insulin pump therapy costs (£) in years 1 and 2

Parameter	Coefficient	Robust SE	95% CI
Year 1			
Randomised treatment group (1 = pump + DAFNE, 0 = MDI + DAFNE)	2056.11	15.54	2025.65 to 2086.56
Did the individual switch from pump to MDI in year 1? (1 = switched, 0 = did not switch)	-1143.68	287.44	-1707.04 to -580.31
Did the individual switch from MDI to pump in year 1? (1 = switched, 0 = did not switch)	804.57	208.95	395.03 to 1214.11
Constant	0.00	0.00	0.00 to 0.00
Year 2			
Patient's treatment at 1 year follow-up (1 = pump, 0 = MDI)	2050.99	13.79	2023.97 to 2078.01
Did the individual switch from pump to MDI in year 2? (1 = switched, 0 = did not switch)	-905.03	226.55	-1349.07 to -461.00
Did the individual switch from MDI to pump in year 2? (1 = switched, 0 = did not switch)	1134.27	152.67	835.04 to 1433.49
Constant	0.00	0.00	0.00 to 0.00

Long-term cost-effectiveness

Base-case analysis

The results of the long-term cost-effectiveness analysis base case results using the PSA is shown in *Table 57*. For the pump arm, the mean costs of the intervention are £42,143 discounted over the lifetime horizon, which compares with £20,398 for the MDI arm. The difference between the intervention costs for the two arms is £21,745. AE costs are slightly lower in the pump arm, £1040 versus £1509, a mean lifetime saving of £470 per person. Complication costs are also lower £57,435 versus £59,877, a mean lifetime saving of £2443 per person, which is mostly due to reductions in the occurrence of end-stage renal failure in the nephropathy complications. The net incremental lifetime cost of pump versus MDI is therefore estimated as £18,832 (95% CI £535 to £34,978) per person.

TABLE 57 Base-case PSA results from the Sheffield Type 1 Diabetes Policy Model

	MDI + DAFNE	Pump + DAFNE	Incremental (95% CI)
Mean lifetime discounted costs per person (£)			
<i>Intervention costs</i>			
Insulin	12,542	5634	-6908 (-8329 to -5344)
Diabetes-related contacts	5166	6451	1285 (-426 to 3108)
Insulin pumps and consumables	2327	29,667	27,339 (22,771 to 31,368)
DAFNE course	363	392	29 (29 to 29)
Subtotal intervention costs	20,398	42,143	21,745 (17,321 to 25,569)
<i>AE costs</i>			
Severe hypoglycaemia	136	42	-94 (-221 to -54)
DKA	1373	998	-375 (-1811 to 285)
Subtotal cost of AEs	1509	1040	-470 (-1880 to 160)
<i>Long-term complication costs</i>			
Nephropathy	51,515	49,139	-2376 (-19,397 to 11,957)
Neuropathy	1975	1915	-60 (-419 to 255)
Retinopathy + macular oedema	2212	2203	-8 (-85 to 58)
MI	1996	1994	-2 (-258 to 206)
HF	663	666	2 (-76 to 89)
Stroke	278	278	0 (-43 to 41)
Angina	1238	1239	1 (-143 to 123)
Total cost of long-term complications	59,877	57,435	-2443 (-20,177 to 12,381)
Total costs	81,785	100,617	18,832 (535 to 34,978)
Mean discounted QALYs per person			
QALYs lived (excluding decrements due to complications)	14.2894	14.3898	0.1005 (-0.6522 to 0.8383)
<i>QALYs lost because of AEs</i>			
Severe hypoglycaemia	-0.0014	-0.0004	0.0010 (0 to 0.0042)
DKA	-0.0088	-0.0064	0.0024 (-0.0018 to 0.0171)
Subtotal QALYs due to AEs	-0.0102	-0.0068	0.0034 (-0.0009 to 0.0174)

continued

TABLE 57 Base-case PSA results from the Sheffield Type 1 Diabetes Policy Model (*continued*)

	MDI + DAFNE	Pump + DAFNE	Incremental (95% CI)
<i>QALYs lost because of complications</i>			
Nephropathy	-0.2179	-0.2105	0.0074 (-0.0527 to 0.0714)
Neuropathy	-0.3301	-0.3210	0.0091 (-0.0387 to 0.0629)
Retinopathy and macular oedema	-0.5202	-0.5139	0.0064 (-0.0292 to 0.0488)
MI	-0.0647	-0.0649	-0.0002 (-0.0072 to 0.0067)
HF	-0.0420	-0.0422	-0.0002 (-0.0062 to 0.0055)
Stroke	-0.0376	-0.0378	-0.0002 (-0.0065 to 0.0061)
Angina	-0.0821	-0.0822	-0.0001 (-0.0081 to 0.0084)
Subtotal QALYs lost because of complications	-1.2947	-1.2725	0.0222 (-0.112 to 0.1773)
Total QALYs	12.9845	13.1105	0.1260 (-0.7533 to 0.9705)
Summary			
Total mean discounted costs per person (£)	81,785	100,617	18,832
Total mean discounted QALYs per person	12.9845	13.1105	0.1260
ICER (£/QALY gained)	-	-	149,483
Probability (%) that pump + DAFNE is cost-effective at a threshold of £20,000 per QALY gained	-	-	15.4

The 'QALYs lived without diabetic complications' captures all of the QALYs gains from the increased life expectancy of patients who receive pump + DAFNE prior to adjusting their utility downwards for the incidence of diabetic complications. The 'QALYs lived without complications' in the pump + DAFNE arm is 14.3898 QALYs compared with 14.2894 QALYs in the MDI + DAFNE arm, a mean increase of 0.1005 QALYs. The QALYs lost because of AEs are slightly lower in the pump + DAFNE arm than in the MDI + DAFNE arm, -0.0068 versus -0.0102 QALYs, leading to a mean increase of 0.0034 QALYs in favour of pump + DAFNE. The overall QALYs lost because of the incidence of diabetic complications was again slightly lower in the pump + DAFNE arm than in the MDI + DAFNE arm, -1.2725 versus -1.2947 QALYs, a mean increase in lifetime QALYs of 0.0222. However, pump + DAFNE is not associated with a mean increase in QALYs for each of the individual long-term diabetic complications. This is because although the incidence of the complications is expected to be lower in the pump + DAFNE arm, as they have a lower HbA_{1c}, people are also expected to live longer in the pump + DAFNE arm, so they may be at a greater overall risk of suffering a diabetic complication within their lifetime. The net incremental QALY gain per person is 0.1260 QALYs (95% CI -0.7381 to 0.9705 QALYs) per person.

Pump + DAFNE generated more QALYs - 0.1260 QALYs (95% CI -0.7381 to 0.9705 QALYs) - at a higher incremental cost of £18,832 (95% CI £535 to £34,978) than MDI + DAFNE. The ICER associated with pump + DAFNE was £149,483 per QALY gained. This is outside the range of £20,000-30,000 per QALY gained at which NICE would usually consider to be cost-effective. *Figure 17* shows the base-case cost-effectiveness plane for the PSA. It is clear that, when using the £20,000 per QALY gained threshold, most PSA runs lie in the region where pump + DAFNE would not be considered to be cost-effective, as they are above the £20,000 per QALY gained line. The cost-effectiveness acceptability curve presented in *Figure 18* shows the probability that pump + DAFNE and MDI + DAFNE are cost-effective across a range of cost-effectiveness thresholds.¹⁵² It is clear that MDI + DAFNE has a higher probability of being cost-effective than pump + DAFNE at all cost-effectiveness thresholds in the range of £0-50,000 per QALY gained.

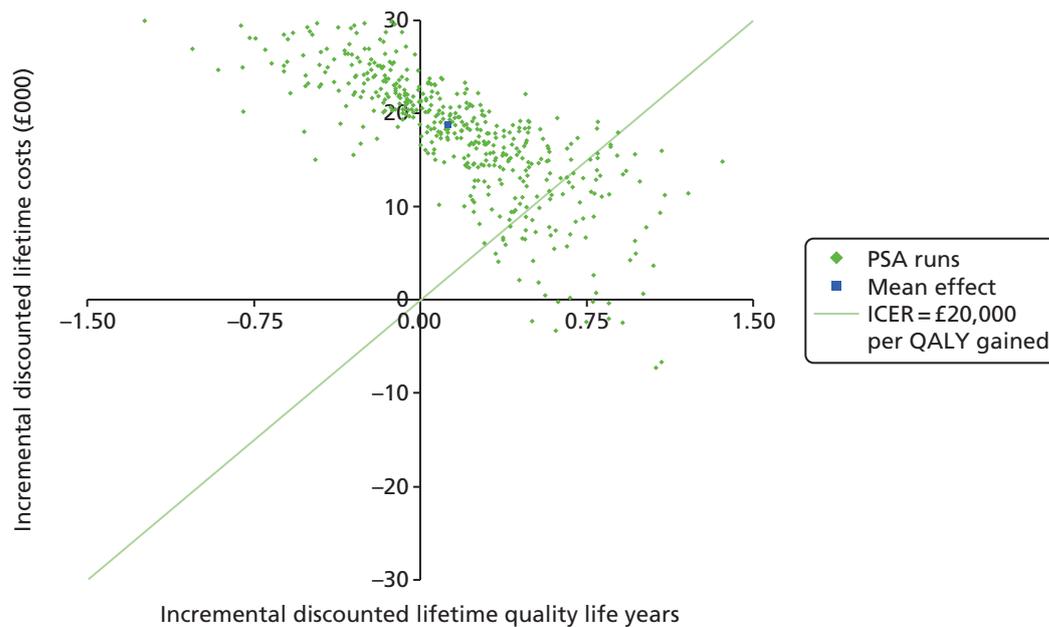


FIGURE 17 Cost-effectiveness plane of the base-case analysis using the Sheffield Type 1 Diabetes Policy Model.

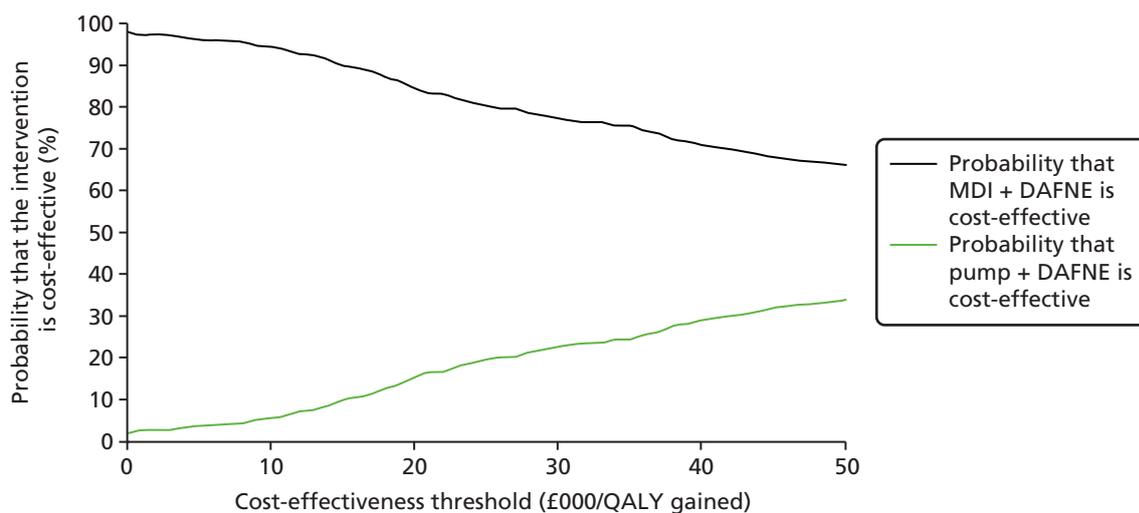


FIGURE 18 Cost-effectiveness acceptability curve of the base-case analysis using the Sheffield Type 1 Diabetes Policy Model.

The modelled lifetime incidence of diabetic complications in the PSA is given in *Table 58*. Pump + DAFNE was associated with fewer diabetic complications than MDI + DAFNE. However, this is to be expected, as the treatment effect coefficient was negative in the beta regression that was used to estimate HbA_{1c} in the model (see *Tables 50* and *51*). It should also be noted that the incidence of proliferative retinopathy, macular oedema and blindness were higher in the pump + DAFNE arm than the MDI + DAFNE arm. This seems to be counterintuitive; however, there are two effects. The first is that, in a given year, patients in the pump + DAFNE arm are at a lower risk of these complications. The second effect is that as the HbA_{1c} of patients in the pump + DAFNE arm is, on average, lower than the MDI + DAFNE arm then they are expected to live longer, increasing their absolute risk of experiencing a complication. For the proliferative retinopathy, macular oedema and blindness complications, the increased risk as a result of living longer outweighs the decreased annual risk of a complication as a result of these patients having a lower HbA_{1c} value.

TABLE 58 Lifetime incidence of diabetic complications per 100 years for an adult with T1DM in the base-case economic model

Diabetic complication	MDI + DAFNE	Pump + DAFNE	Incremental
Microalbuminuria	2.1610	2.0818	-0.0792
Macroalbuminuria	1.9461	1.8419	-0.1042
ESRD	1.7084	1.6162	-0.0922
Death due to ESRD	1.0070	0.9474	-0.0597
Clinical neuropathy	1.6179	1.5292	-0.0888
PAD with amputation	0.4526	0.4320	-0.0205
Background retinopathy	1.1388	1.0645	-0.0743
Proliferative retinopathy	0.0441	0.0457	0.0015
Macular oedema	0.0385	0.0398	0.0013
Blindness	0.0252	0.0254	0.0002
First cardiovascular disease	1.9191	1.9106	-0.0085
Cardiovascular disease	4.7381	4.7198	-0.0183
MI	2.4818	2.4709	-0.0110
First MI	1.6111	1.6048	-0.0062
Fatal MI	1.2331	1.2306	-0.0025
Stroke	0.3251	0.3241	-0.0010
First stroke	0.2924	0.2915	-0.0008
Fatal stroke	0.0713	0.0713	0.0000
HF	0.5720	0.5695	-0.0025
First HF	0.4601	0.4581	-0.0020
Fatal HF	0.0334	0.0330	-0.0004
Angina	1.3592	1.3553	-0.0039
Severe hypoglycaemia	4.3911	1.2783	-3.1128
DKA	7.0059	4.6286	-2.3773
Life expectancy (years)	29.7615	30.0851	0.3236

Summary of the scenario analyses in the long-term model

The following scenario analyses were conducted in the long-term modelling:

1. pump costs estimated using data in Riemsma *et al.*⁸ on the yearly cost of insulin pump therapy
2. a 25% price reduction in insulin pumps and consumables
3. a 50% price reduction in insulin pumps and consumables
4. the ITT estimate of treatment effect was used
5. the ITT estimate of treatment effect was used and there was no change in HbA_{1c} if an individual switches treatment
6. post-trial HbA_{1c} progression in both arms is estimated from the DCCT at +0.045% per annum
7. individuals return to their baseline HbA_{1c} after 3 years and experience no progression in their HbA_{1c} thereafter
8. HbA_{1c} effects occur one model cycle earlier
9. individuals return to baseline risk of hypoglycaemic episodes and DKA at 3 years
10. treatment switching probabilities were estimated directly from the Kaplan–Meier curves
11. subgroup – individuals with a baseline HbA_{1c} of < 8.5% (69 mmol/mol)
12. subgroup – individuals with a baseline HbA_{1c} of ≥ 8.5% (69 mmol/mol)

13. subgroup – individuals with a baseline HbA_{1c} of $\geq 7.5\%$ (58 mmol/mol)
14. subgroup – individuals with a baseline HbA_{1c} of $\geq 7.5\%$ (58 mmol/mol) and $< 8.5\%$ (69 mmol/mol)
15. subgroup – individuals with a baseline HbA_{1c} of $\geq 8.5\%$ (69 mmol/mol) and $< 9.5\%$ (80 mmol/mol)
16. subgroup – individuals with a baseline HbA_{1c} of $\geq 9.5\%$ (80 mmol/mol)
17. subgroup – individuals in the per-protocol population
18. subgroup – individuals in the per-protocol population and no treatment switching is included in the model.

Structural uncertainty and potential subgroup effects were explored in the scenario analyses with the long-term model.

Much like the EEACT, uncertainty due to potential decreases in price of insulin pumps was explored in these scenario analyses.

Four further scenario analyses were conducted around the different methods that could be used to estimate each patient's HbA_{1c} in the model. A scenario analysis was conducted in which HbA_{1c} was estimated using beta regression in the ITT population rather than the per-protocol population. As the ITT population includes switchers in their originally assigned treatment groups, a further scenario analysis was conducted using the regression estimated in the ITT population where the individuals in the model did not experience a change in HbA_{1c} when they switched treatment, as these effects were already included in the estimate of the relative treatment effect of pump + DAFNE versus MDI + DAFNE. Uncertainty in the long-term changes in HbA_{1c} was explored by using data observed in the DDCT trial for both of the model arms. As there was no information in the DDCT trial on different HbA_{1c} trajectories for pump or MDI users, the same trajectory was used in both model arms, which effectively assumes that the treatment effect for pump users in the REPOSE Trial is maintained for a lifetime. Uncertainty in the HbA_{1c} of individuals after the REPOSE Trial was also explored by assuming that all individuals returned to their baseline HbA_{1c} after the third model year. This is a very conservative assumption, but gives some idea of the least favourable scenario to pump + DAFNE. The effect of assuming that changes in HbA_{1c} occurred one model cycle (1 year) earlier than the base case on the model outcomes was explored. Full details on the reason for and rationale behind scenario analyses 4–8 are given earlier (see *Chapter 3, Estimation of each individual's glycated haemoglobin and Duration of treatment effectiveness beyond the trial period*).

The effect of assuming that the second-year risk functions for severe hypoglycaemia and DKA were applied for the rest of an individual's lifetime was tested by instead assuming that individuals in both arms returned to their risk of severe hypoglycaemia and DKA at baseline. Full details on this scenario analysis is given earlier (see *Chapter 3, Estimating severe hypoglycaemic events and diabetic ketoacidosis events*).

Finally, the validity of the treatment switching models was testing by assuming directly using the risks of switching observed in the Kaplan–Meier curves. In this scenario, treatment switching was a random event that did not depend on HbA_{1c}, number of severe hypoglycaemic episodes in the last year and number of DKAs last year, as was used in the base case. Full details on this scenario analysis are given earlier (see *Chapter 3, Incorporating treatment switching*).

Further to the one-way scenario analyses, a threshold analysis was conducted to determine the HbA_{1c} fall that future pumps would need to have to be considered cost-effective. Full details on this threshold analysis are given earlier (see *Chapter 3, Threshold analysis*).

Results of the one-way scenario analyses

The one-way scenario analyses are presented in *Table 59*. The ICER did not fall below £30,000 per QALY gained in any of the scenario analyses. Furthermore, the subgroup analyses did not indicate that the ICER for pump + DAFNE compared with MDI + DAFNE will fall below £30,000 per QALY gained for any identified pre-specified subgroup in the REPOSE Trial patient population. The most favourable ICER to pump + DAFNE was observed when a 50% reduction in the price of insulin and insulin pump consumables was modelled; however, the ICER in this scenario was £46,578, which is above the maximum acceptable

TABLE 59 One-way sensitivity analyses and subgroup analyses conducted using the Sheffield Type 1 Diabetes Policy Model

Analysis	MDI + DAFNE		Pump + DAFNE		Incremental		
	Total discounted costs (£)	Total discounted QALYs	Total discounted costs (£)	Total discounted QALYs	Total discounted costs (£)	Total discounted QALYs	ICER (£ per QALY gained)
Base case							
PSA	81,785	12.9845	100,617	13.1105	18,832	0.1260	149,483
Deterministic	70,132	12.6719	90,581	12.8166	20,448	0.1447	141,312
Scenario							
Pump prices were estimated from Riemsma <i>et al.</i> ⁸	70,083	12.6719	89,759	12.8166	19,677	0.1447	135,977
25% price reduction in insulin pumps and consumables	69,690	12.6719	83,285	12.8166	13,594	0.1447	93,945
50% price reduction in insulin pumps and consumables	69,248	12.6719	75,989	12.8166	6740	0.1447	46,578
ITT estimate of treatment effect	71,238	12.7130	91,307	12.7935	20,069	0.0805	249,338
ITT estimate of treatment effect and no change in HbA _{1c} if an individual switches treatment	70,994	12.8239	70,994	12.6475	19,390	0.1764	109,897
Post-trial HbA _{1c} progression in both arms is estimated from the DCCT	69,382	12.7211	89,523	12.8412	20,141	0.1202	167,613
Individuals return to their baseline HbA _{1c} after 3 years and no progression thereafter	67,471	12.9472	88,462	12.9162	20,991	-0.0310	Dominated
HbA _{1c} effects occur one model cycle earlier	71,220	12.6514	90,589	12.7528	19,369	0.1014	190,974
Individuals return to their baseline risk of hypoglycaemic episodes and DKA at 3 years	70,102	12.6725	90,719	12.8565	20,616	0.1841	111,998
Switching probabilities were estimated directly from the Kaplan–Meier curves	69,318	12.6740	90,904	12.7735	21,586	0.0995	216,871
Subgroup							
Individuals with a baseline HbA _{1c} < 8.5%	54,473	13.2733	76,758	13.3434	22,284	0.0701	317,893
Individuals with a baseline HbA _{1c} ≥ 8.5%	82,769	12.1320	100,508	12.2979	17,739	0.1659	106,909

TABLE 59 One-way sensitivity analyses and subgroup analyses conducted using the Sheffield Type 1 Diabetes Policy Model (*continued*)

Analysis	MDI + DAFNE		Pump + DAFNE		Incremental		
	Total discounted costs (£)	Total discounted QALYs	Total discounted costs (£)	Total discounted QALYs	Total discounted costs (£)	Total discounted QALYs	ICER (£ per QALY gained)
Individuals with a baseline HbA _{1c} ≥ 7.5%	73,944	12.4866	92,481	12.6614	18,536	0.1747	106,090
Individuals with a baseline HbA _{1c} ≥ 7.5% and < 8.5%	58,654	12.9513	79,560	13.0973	20,906	0.1460	143,214
Individuals with a baseline HbA _{1c} ≥ 8.5% and < 9.5%	62,515	13.3038	83,006	13.4234	20,491	0.1195	171,447
Individuals with a baseline HbA _{1c} ≥ 9.5%	97,111	11.5164	111,862	11.6564	14,751	0.1400	105,351
Individuals in the per-protocol population	69,739	12.5982	89,363	12.7142	19,623	0.1160	169,143
Individuals in the per-protocol population and no treatment switching	69,874	12.6018	92,601	12.7380	22,727	0.1362	166,831

ICER range of £20,000–30,000 that is usually used by UK decision-makers when deciding whether or not a health technology is cost-effective. Although the ICERs are more favourable to pump + DAFNE in the long-term modelling than in the EEACT, the long-term modelling does not indicate that pump + DAFNE is likely to be considered a cost-effective treatment pathway if it were to be appraised by NICE.

An important scenario to note is the one in which the HbA_{1c} effects occur one model cycle earlier.

Results of the threshold analysis

The results of the two-way price and effectiveness threshold analysis for a certain reduction in HbA_{1c} are given in *Table 60*. When the annual pump cost is assumed to be £2060 then the analysis shows that the reduction in HbA_{1c} (for CSII compared with MDI) would need to be ≥ 11 mmol/mol (1.0%) for pumps to be considered cost-effective (ICER £22,757). When the annual cost is 25% lower (£1545) then a HbA_{1c} reduction of > 7.7 mmol/mol (0.7%) would be needed to have an ICER of < £20,000 per QALY gained. When the annual cost is halved (£1030) then a HbA_{1c} reduction of 4.4 mmol/mol (0.4%) would be sufficient to have an ICER of < £20,000 per QALY gained.

The results of the two-way price and effectiveness threshold analysis for when the uncertainty in the treatment effect is estimated using the dispersion parameter formula used in the REPOSE Trial is given in *Table 61*. When the annual cost is assumed to be £2060 then the analysis shows that the reduction in HbA_{1c} (for pumps vs. MDI) would need to be > 9.8 mmol/mol (0.9%) for pumps to have an ICER of < £30,000 per QALY gained. When the annual cost of insulin pumps and consumables is 25% lower (£1545), then a HbA_{1c} reduction of 7 mmol/mol (0.6%) would be needed to have an ICER of < £30,000 per QALY gained. When the annual cost is halved (£1030) then a HbA_{1c} reduction of 4.4 mmol/mol (0.4%) would be sufficient to have an ICER of < £20,000 per QALY gained.

TABLE 60 Incremental cost-effectiveness ratio associated with CSII for different HbA_{1c} reductions (for all adults with T1DM) and annualised prices (£) of insulin pumps and insulin pump consumables when no uncertainty in the HbA_{1c} reduction is assumed

	HbA _{1c} reduction associated with an insulin pump, mmol/mol (%)										
	3.3 (0.3)	4.4 (0.4)	5.5 (0.5)	6.6 (0.6)	7.7 (0.7)	8.7 (0.8)	9.8 (0.9)	10.9 (1.0)	12.0 (1.1)	13.1 (1.2)	
The annual cost (£) of insulin pumps and insulin pump consumables											
£2060	£102,654	£63,887	£51,752	£48,912	£41,272	£32,840	£30,560	£22,757	£20,852	£18,409	
£1957	£95,154	£59,254	£47,299	£44,867	£37,634	£29,712	£27,863	£20,365	£18,727	£16,252	
£1854	£87,653	£54,621	£42,846	£40,822	£33,997	£26,584	£25,167	£17,973	£16,602	£14,094	
£1751	£80,153	£49,988	£38,392	£36,777	£30,359	£23,456	£22,471	£15,582	£14,477	£11,937	
£1648	£72,652	£45,354	£33,939	£32,732	£26,722	£20,328	£19,775	£13,190	£12,352	£9780	
£1545	£65,151	£40,721	£29,486	£28,687	£23,084	£17,200	£17,079	£10,799	£10,227	£7623	
£1442	£57,651	£36,088	£25,032	£24,642	£19,446	£14,072	£14,382	£8407	£8102	£5465	
£1339	£50,150	£31,455	£20,579	£20,597	£15,809	£10,944	£11,686	£6015	£5977	£3308	
£1236	£42,650	£26,822	£16,126	£16,552	£12,171	£7816	£8990	£3624	£3852	£1151	
£1133	£35,149	£22,189	£11,672	£12,506	£8534	£4688	£6294	£1232	£1727	Dominates	
£1030	£27,648	£17,555	£7219	£8461	£4896	£1560	£3598	Dominates	Dominates	Dominates	

Green = unaffordable, ICER ≥ £30,000; blue = ICER < £30,000 but > £20,000; light green = definitely affordable.

TABLE 61 Incremental cost-effectiveness ratio associated with CSII for different HbA_{1c} reductions (for all adults with T1DM) and annualised prices (£) of insulin pumps and insulin pump consumables when the HbA_{1c} reduction associated with insulin pumps is uncertain

	HbA _{1c} reduction associated with an insulin pump, mmol/mol (%)										
	The annual cost (£) of insulin pumps and insulin pump consumables	3.3 (0.3)	4.4 (0.4)	5.5 (0.5)	6.6 (0.6)	7.7 (0.7)	8.7 (0.8)	9.8 (0.9)	10.9 (1.0)	12.0 (1.1)	13.1 (1.2)
£2060		£90,343	£80,074	£53,002	£47,577	£37,626	£33,373	£26,946	£23,903	£18,344	£20,968
£1957		£83,668	£74,071	£48,550	£43,798	£34,341	£30,216	£24,424	£21,325	£16,340	£18,670
£1854		£76,994	£68,069	£44,099	£40,018	£31,056	£27,058	£21,901	£18,746	£14,336	£16,371
£1751		£70,319	£62,066	£39,647	£36,239	£27,771	£23,901	£19,379	£16,167	£12,332	£14,073
£1648		£63,644	£56,064	£35,195	£32,459	£24,486	£20,744	£16,857	£13,588	£10,328	£11,775
£1545		£56,970	£50,061	£30,743	£28,680	£21,201	£17,587	£14,334	£11,010	£8324	£9477
£1442		£50,295	£44,059	£26,292	£24,900	£17,916	£14,430	£11,812	£8431	£6320	£7178
£1339		£43,621	£38,056	£21,840	£21,120	£14,631	£11,272	£9290	£5852	£4316	£4880
£1236		£36,946	£32,054	£17,388	£17,341	£11,346	£8115	£6767	£3273	£2312	£2582
£1133		£30,271	£26,052	£12,936	£13,561	£8061	£4958	£4245	£695	£308	£284
£1030		£23,597	£20,049	£8485	£9782	£4776	£1801	£1723	Dominates	Dominates	Dominates

Green = unaffordable, ICER ≥ £30,000; blue = ICER < £30,000 but > £20,000; light green = definitely affordable.

The threshold analysis indicates if a future study of pumps + DAFNE versus MDI + DAFNE were to be conducted then the cost of insulin pumps and their associated consumables should be taken into account when determining the appropriate effect size to power the study on. At current prices, per-protocol effect sizes of > 5.5 mmol/mol would be required in the whole population who would be eligible for pump therapy for insulin pumps to have an ICER in the £20,000–30,000 per QALY gained range at which NICE is likely to consider them to be a cost-effective use of NHS resources.

Summary of the economic analysis results

None of the analyses conducted in the EEACT or the long-term modelling had an ICER of < £30,000 per QALY gained. Furthermore, no subgroup was identified for which the ICER was < £30,000 per QALY gained. This indicates that pump + DAFNE is unlikely to be considered to be a cost-effective use of NHS resources by NICE in the UK compared with the current practice of MDI + DAFNE, as the ICERs are all above the ICER range of £20,000–30,000 per QALY gained, which is usually used by NICE to determine the cost-effectiveness of health technologies. The findings of this analysis are consistent with the current recommended care pathway for adults with T1DM in the UK, who should be offered structured education with MDI, ideally around 12 months after diagnosis (but failing that at any later stage).

Chapter 7 Results of the psychosocial evaluation

Completion rates and final sample

Quantitative data

Questionnaires were administered to all of the participants at all of the time points. *Table 62* shows completion rates at each time point. High levels of questionnaire completeness were observed across all questionnaires and follow-up (around 90% completed at each follow-up). A total of 264 participants of

TABLE 62 Questionnaire completeness stratified by treatment group and follow-up

Questionnaire	Follow-up	Treatment group, n (%)		Total (N = 267), n (%)
		Pump (N = 132)	MDI (N = 135)	
SF-12	Baseline	131 (99.2)	132 (97.8)	264 (98.9)
	6 months	128 (97.0)	120 (88.9)	248 (92.9)
	12 months	121 (91.7)	119 (88.1)	240 (89.9)
	24 months	124 (93.9)	117 (86.7)	241 (90.3)
DSQOL	Baseline	131 (99.2)	132 (97.8)	264 (98.9)
	6 months	129 (97.7)	120 (88.9)	249 (93.3)
	12 months	121 (91.7)	119 (88.1)	240 (89.9)
	24 months	124 (93.9)	116 (85.9)	240 (89.9)
WHOQOL-BREF	Baseline	131 (99.2)	132 (97.8)	264 (98.9)
	6 months	129 (97.7)	120 (88.9)	249 (93.3)
	12 months	121 (91.7)	119 (88.1)	240 (89.9)
	24 months	124 (93.9)	117 (86.7)	241 (90.3)
HFS	Baseline	131 (99.2)	132 (97.8)	264 (98.9)
	6 months	129 (97.7)	120 (88.9)	249 (93.3)
	12 months	121 (91.7)	119 (88.1)	240 (89.9)
	24 months	124 (93.9)	117 (86.7)	241 (90.3)
HADS	Baseline	131 (99.2)	132 (97.8)	264 (98.9)
	6 months	129 (97.7)	120 (88.9)	249 (93.3)
	12 months	121 (91.7)	119 (88.1)	240 (89.9)
	24 months	124 (93.9)	117 (86.7)	241 (90.3)
EQ-5D	Baseline	131 (99.2)	132 (97.8)	264 (98.9)
	6 months	128 (97.0)	120 (88.9)	248 (92.9)
	12 months	120 (90.9)	116 (85.9)	236 (88.4)
	24 months	124 (93.9)	116 (85.9)	240 (89.9)
DTSQ	Baseline	131 (99.2)	132 (97.8)	264 (98.9)
	6 months	128 (97.0)	119 (88.1)	247 (92.5)
	12 months	121 (91.7)	118 (87.4)	239 (89.5)
	24 months	124 (93.9)	116 (85.9)	240 (89.9)

the 267 participants attending the DAFNE course completed at least one of the psychosocial questionnaires ($n = 128$ pump, $n = 117$ MDI), with a minimum of 236 participants completing questionnaires at all time points. The lowest completion rate on any individual measure was 86% of participants. The completion rate was slightly higher for participants who were allocated to pump than participants allocated to MDI, which reflects the slightly higher dropout rate in the MDI group.

Qualitative interviews

A total of 45 patients were recruited, of whom 25 were randomised to the pump and 20 to the MDI arm of the trial. Full details of the sample are provided in *Table 63*. Three participants (two 'pump', one 'MDI') could not be contacted for round 2 interviews.

The final educator sample comprised 12 nurses and six dietitians; owing to staff leave it was not possible to interview the dietitian in one of the centres. See *Table 64* for full details of the educator sample. As can be seen from this table, there was diversity among the educators in terms of diabetes, DAFNE and pump experience. All of the educators were women.

Findings

The findings of the mixed-methods study are structured and reported under the six original study aims, with qualitative and/or quantitative data drawn on, as appropriate, to answer and address particular questions.

TABLE 63 Demographic and clinical characteristics of patient sample at baseline (qualitative substudy)

Variable	Scoring	Total ($N = 45$)	
Age (years)	Mean (SD)	40 (12.8)	
	Range	19–66	
Sex (%)	Female	48.9	
Diabetes duration (years)	Mean (SD)	17.4 (12.4)	
	Range	1 to 41	
Occupation, n (%)	Professional	14 (31)	
	Semiskilled	16 (35.5)	
	Student	4 (9)	
	Unemployed	4 (9)	
	Unskilled	7 (15.5)	
HbA _{1c}	mmol/mol	Mean (SD)	71 (14)
		Range	46–109
	%	Mean (SD)	8.6 (1.3)
		Range	6.4–11.7

TABLE 64 Educator sample (qualitative substudy)

Variable	Scoring	Total (N = 18)
Occupation, n (%)	Nurse	12 (67)
	Dietitian	6 (33)
Experience of working in T1DM (years)	Mean (SD)	14 (7.7)
	Range	5–29
Experience of DAFNE (years)	Mean (SD)	7.9 (4.3)
	Range	1–15
Experience of pump therapy (years)	Mean (SD)	4 (4.3)
	Range	0–15

Study aims 1 and 2

1. To establish whether or not, and why, there are differences in QoL and other psychological outcomes between patients using pump and MDI regimens.
2. To examine whether or not, and why, QoL and other outcomes change over time.

Overview

Material that is relevant to addressing aims 1 and 2 has been combined in this final report because of the strong overlaps in the content. In this section we begin by presenting quantitative data on ≥ 236 participants before going on to draw on patients' interview accounts to aid interpretation of quantitative findings.

Quantitative data

Tables 65–67 show QoL outcomes at 6, 12 and 24 months, respectively. Table 68 shows DTSQ data at the same time points.

Improvement was seen across most psychosocial outcomes and time points for both treatment groups. There were no statistically significant differences at 6 months between the pump and MDI cohorts on any psychosocial measure. Participants in the pump group had better improvement in treatment satisfaction at all time points using DTSQ, but not using DSQOL; however, the difference was statistically significant only at 12 and 24 months ($p = 0.067$ at 6 months; $p < 0.001$ at both 12 and 24 months). Furthermore, participants in the pump group reported statistically improved diabetes-specific QoL at 24 months compared with the MDI group ($p = 0.006$); however, this was not the case at 6 or 12 months and could be due to chance rather than the treatment effect. We note that, if 6-month treatment satisfaction is reanalysed using a mixed-effects linear regression adjusted for baseline score, HbA_{1c}, centre and course, as was done for the other QoL measures (rather than a non-parametric test), the treatment difference is similar and is statistically significant ($p = 0.004$), in part due to the increased precision from covariate adjustment.

There were some statistically significant differences on some subdomains, using $p < 5\%$ as the level for statistical significance. A caveat is required concerning the number of variables examined and tests performed, as multiple testing was not adjusted for. A statistically significant difference was observed on the social relations domain of the WHOQoL-BREF generic QoL measure in favour of the pump participants ($p = 0.026$), but this was seen only at 6 months, was one of 12 tests of significance and is likely to be a chance finding.

TABLE 65 Quality-of-life secondary outcomes: MD in change from baseline at 6 months

QoL outcome	Domain	Treatment group				Adjusted difference ^a (95% CI)	p-value	
		Pump		MDI				
		n	Mean (SD)	n	Mean (SD)			
SF-12	PCS	127	1.2 (6.1)	116	0.5 (8.6)	0.3 (-1.4 to 2.0)	0.721	
	MCS	127	0.2 (8.8)	117	0.9 (9.9)	-0.8 (-2.9 to 1.3)	0.452	
DSQOL	Total score	128	-5.2 (12.2)	117	-4.4 (11.2)	-0.1 (-2.8 to 2.6)	0.935	
	Social relations	128	-2.2 (11.8)	117	-3.0 (13.2)	1.5 (-1.2 to 4.2)	0.276	
	Leisure time restrictions and flexibility	128	-5.1 (16.6)	117	-4.4 (18.5)	-0.1 (-3.8 to 3.7)	0.968	
	Physical complaints	128	-6.0 (17.0)	117	-4.8 (13.8)	-0.1 (-3.5 to 3.3)	0.953	
	Worries about the future	128	-7.9 (20.4)	117	-7.5 (19.4)	-0.7 (-5.5 to 4.1)	0.779	
	Daily hassle of functions	128	-6.3 (18.9)	117	-5.0 (18.7)	-0.8 (-5.0 to 3.4)	0.700	
	Diet restrictions	128	-11.3 (18.3)	117	-6.4 (16.0)	-3.3 (-6.9 to 0.2)	0.061	
	Treatment satisfaction (PWTSS)	118	2.1 (4.4)	109	2.1 (4.8)	0.1 (-0.7 to 1.0)	0.791	
	WHOQOL-BREF	Physical health	127	0.4 (2.3)	117	0.2 (2.3)	0.1 (-0.4 to 0.6)	0.740
		Psychological	128	0.1 (1.9)	117	0.4 (2.2)	-0.3 (-0.7 to 0.2)	0.225
Social relationships		127	-0.3 (2.7)	117	0.3 (3.0)	-0.7 (-1.3 to -0.1)	0.026	
Environment		128	0.1 (1.7)	117	0.4 (1.6)	-0.3 (-0.7 to 0.1)	0.170	
HFS	Behaviour score	127	-1.7 (4.9)	117	-0.2 (4.8)	-0.9 (-2.0 to 0.1)	0.074	
	Worry score	128	-4.0 (10.9)	117	-2.8 (9.5)	-0.1 (-2.4 to 2.1)	0.906	
HADS	Anxiety score	128	-0.2 (3.0)	117	-0.6 (3.3)	0.4 (-0.3 to 1.1)	0.260	
	Depression score	128	-0.3 (2.9)	117	-0.2 (2.5)	0.1 (-0.5 to 0.7)	0.735	
EQ-5D	Utility index	127	-0.02 (0.17)	117	-0.01 (0.18)	-0.02 (-0.06 to 0.02)	0.382	

MCS, Mental Component Summary; PCS, Physical Component Summary; PWTSS, Preference-Weighted Treatment Satisfaction Score.

a Calculated using mixed-effects regression adjusted for baseline QoL score, centre, DAFNE course and baseline HbA_{1c}.

The SF-12 summaries are scored on a scale from 0 (poor) to 100 (good). The DSQOL domains and total score are scored on a 0 (good) to 100 (poor) scale and DSQOL treatment satisfaction is scored on a scale from 0 (poor) to 100 (good).

WHOQOL-BREF domains are scored from 0 (poor) to 100 (good). The HFS behaviour score is scaled from 10 to 50 and the HFS worry score is scaled from 17 to 85; in both cases, higher scores represent more fear. HADS domains are scored from 0 (good) to 21 (poor) scale. The EQ-5D score is measured on a scale from -0.56 to 1.00 (good health).

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The DSQOL results (see *Table 69*) at 24 months showed statistically significant improvements (reductions) in both the pump (mean reduction of 8.2, 95% CI 5.84 to 10.50; $p < 0.00001$) and MDI (mean reduction 4.2, 95% CI 1.71 to 6.61; $p = 0.001$) groups, but with greater improvements in the pump group in the overall score (difference 3.8; $p = 0.006$) and some subdomains. The improvement in DSQOL diet restrictions was larger for the pump group than the MDI group at both 12 and 24 months (12-month adjusted MD in change from baseline -4.1, 95% CI -7.2 to -1.0; $p = 0.010$; 24-month adjusted MD in change from baseline -5.1, 95% CI -8.6 to -1.6; $p = 0.004$: lower scores represent better outcomes). A slightly smaller difference was observed at 6 months, which was not statistically significant (adjusted MD -3.3, 95% CI -6.9 to 0.2; $p = 0.061$). The pump group also had better improvement in DSQOL daily hassle

TABLE 66 Quality-of-life secondary outcomes: MD in change from baseline at 12 months

QoL outcome	Domain	Treatment group				Adjusted difference ^a (95% CI)	p-value	
		Pump		MDI				
		n	Mean (SD)	n	Mean (SD)			
SF-12	PCS	119	0.7 (7.7)	115	1.1 (6.9)	-0.4 (-2.1 to 1.3)	0.669	
	MCS	121	-1.1 (10.8)	116	-1.0 (10.9)	-0.1 (-2.6 to 2.3)	0.912	
DSQOL	Total score	121	-5.8 (11.4)	116	-3.6 (10.1)	-1.5 (-4.0 to 1.1)	0.254	
	Social relations	121	-2.9 (12.4)	116	-1.5 (11.2)	-0.7 (-3.6 to 2.1)	0.620	
	Leisure time restrictions and flexibility	121	-5.2 (17.7)	115	-4.5 (15.9)	0.0 (-3.8 to 3.7)	0.981	
	Physical complaints	121	-5.6 (15.2)	115	-4.4 (13.0)	-0.4 (-3.5 to 2.8)	0.824	
	Worries about the future	121	-8.1 (21.7)	116	-6.4 (20.9)	-2.0 (-7.0 to 2.9)	0.421	
	Daily hassle or functions	121	-9.1 (19.4)	116	-3.5 (18.7)	-5.0 (-9.2 to -0.8)	0.019	
	Diet restrictions	121	-12.8 (17.1)	115	-7.0 (16.7)	-4.1 (-7.2 to -1.0)	0.010	
	Treatment satisfaction (PWTSS)	109	1.5 (4.6)	112	1.4 (4.4)	0.1 (-0.8 to 1.0)	0.839	
	WHOQOL-BREF	Physical health	121	0.0 (2.0)	116	0.1 (2.2)	-0.1 (-0.6 to 0.4)	0.596
		Psychological	121	-0.1 (1.9)	116	0.1 (2.0)	-0.2 (-0.7 to 0.2)	0.341
Social relationships		121	-0.2 (3.0)	116	-0.1 (2.5)	-0.3 (-0.9 to 0.4)	0.375	
Environment		121	0.2 (1.7)	116	0.3 (1.7)	-0.1 (-0.5 to 0.3)	0.727	
HFS	Behaviour score	120	-1.2 (5.2)	116	-0.1 (5.1)	-1.0 (-2.1 to 0.2)	0.091	
	Worry score	121	-4.3 (12.5)	116	-3.3 (10.7)	-0.6 (-3.1 to 1.8)	0.602	
HADS	Anxiety score	121	-0.1 (3.2)	116	-0.3 (3.1)	0.2 (-0.6 to 0.9)	0.664	
	Depression score	121	-0.3 (3.3)	116	0.4 (2.9)	-0.5 (-1.2 to 0.2)	0.180	
EQ-5D	Utility Index	120	-0.03 (0.15)	113	-0.02 (0.17)	0.00 (-0.04 to 0.04)	0.876	

MCS, Mental Component Summary; PCS, Physical Component Summary; PWTSS, Preference-Weighted Treatment Satisfaction Score.

^a Calculated using mixed-effects regression adjusted for baseline QoL score, centre, DAFNE course and baseline HbA_{1c}. The SF-12 summaries are scored on a scale from 0 (poor) to 100 (good). The DSQOL domains and total score are scored on a 0 (good) to 100 (poor) scale and the treatment satisfaction is scored on a scale from 0 (poor) to 100 (good). WHOQOL-BREF domains are scored from 0 (poor) to 100 (good). The HFS behaviour score is scaled from 10 to 50 and the HFS worry score is scaled from 17 to 85; in both cases, higher scores represent more fear. HADS domains are scored from 0 (good) to 21 (poor) scale. The EQ-5D score is measured on a scale from -0.56 to 1.00 (good health).

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or functions at both 12 and 24 months: at 24 months the score had decreased by 9.6 points in the pump group compared with 3.6 points in the MDI group (adjusted MD -6.3, 95% CI -10.9 to -1.8; $p = 0.006$).

However, there was a wide spread of changes in DSQOL, with some patients in both groups reporting deterioration at 24 months compared with baseline, as shown in *Figure 19*.

TABLE 67 Quality-of-life secondary outcomes: MD in change from baseline at 24 months

QoL outcome	Domain	Treatment group				Adjusted difference ^a (95% CI)	p-value	
		Pump		MDI				
		n	Mean (SD)	n	Mean (SD)			
SF-12	PCS	122	0.3 (7.9)	112	1.0 (8.3)	-0.4 (-2.1 to 1.3)	0.657	
	MCS	123	2.1 (11.2)	114	0.5 (10.3)	1.6 (-0.7 to 4.0)	0.175	
DSQOL	Total score	123	-8.2 (13.1)	114	-4.2 (13.2)	-3.8 (-6.5 to -1.1)	0.006	
	Social relations	123	-5.7 (12.9)	113	-2.7 (14.8)	-2.5 (-5.4 to 0.4)	0.092	
	Leisure time restrictions and flexibility	123	-8.1 (17.0)	113	-3.6 (19.7)	-4.6 (-8.4 to -0.9)	0.016	
	Physical complaints	123	-8.7 (17.2)	113	-4.8 (16.6)	-3.6 (-7.3 to 0.0)	0.049	
	Worries about the future	123	-11.9 (23.3)	113	-7.8 (21.2)	-4.8 (-9.7 to 0.2)	0.058	
	Daily hassle or functions	123	-9.6 (21.2)	113	-3.6 (21.5)	-6.3 (-10.9 to -1.8)	0.006	
	Diet restrictions	123	-12.8 (19.5)	113	-6.9 (19.3)	-5.1 (-8.6 to -1.6)	0.004	
	Treatment satisfaction (PWTSS)	113	1.9 (4.5)	108	1.5 (5.4)	0.5 (-0.5 to 1.4)	0.317	
	WHOQOL-BREF	Physical health	123	0.5 (2.4)	114	-0.1 (2.2)	0.5 (0.0 to 1.0)	0.067
		Psychological	123	0.5 (2.5)	114	0.3 (2.4)	0.2 (-0.4 to 0.7)	0.567
Social relationships		123	0.0 (3.3)	114	0.1 (2.9)	-0.2 (-0.9 to 0.5)	0.627	
Environment		122	0.4 (2.2)	114	0.3 (2.0)	0.3 (-0.2 to 0.8)	0.211	
HFS	Behaviour score	122	-1.4 (5.6)	114	-0.6 (5.1)	-0.4 (-1.5 to 0.7)	0.442	
	Worry score	123	-6.7 (13.0)	114	-2.9 (12.5)	-3.4 (-6.0 to -0.8)	0.010	
HADS	Anxiety score	123	-1.0 (4.0)	114	-0.5 (3.5)	-0.5 (-1.3 to 0.4)	0.255	
	Depression score	123	-1.0 (3.8)	114	-0.2 (3.3)	-0.7 (-1.5 to 0.1)	0.105	
EQ-5D	Utility Index	123	0.00 (0.18)	113	-0.02 (0.18)	0.02 (-0.03 to 0.06)	0.464	

MCS, Mental Component Summary; PCS, Physical Component Summary; PWTSS, Preference-Weighted Treatment Satisfaction Score.

a Calculated using mixed-effects regression adjusted for baseline QoL score, centre, DAFNE course, baseline HbA_{1c}.

The SF-12 summaries are scored on a scale from 0 (poor) to 100 (good). THE DSQOL domains and total score are scored on a 0 (good) to 100 (poor) scale and the treatment satisfaction is scored on a scale from 0 (poor) to 100 (good).

WHOQOL-BREF domains are scored from 0 (poor) to 100 (good). The HFS behaviour score is scaled from 10 to 50 and the HFS worry score is scaled from 17 to 85; in both cases, higher scores represent more fear. HADS domains are scored from 0 (good) to 21 (poor) scale. The EQ-5D score is measured on a scale from -0.56 to 1.00 (good health).

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The HFS showed no difference in behaviour score but less worry about hypoglycaemia in the pump arm at 24 months only ($p = 0.01$). Higher treatment satisfaction by DTSQ was reported by pump users at all time points, and although this was not statistically significant at 6 months, statistical significance was reached at 12- and 24-month follow-up periods, although the absolute difference at 24 months was small at 4.0. EQ5D, SF-12, WHOQOL-BREF and HADS scores showed no differences between groups at any time.

TABLE 68 Quality-of-life secondary outcomes: DTSQ change from baseline at 6 and 24 months, DTSQc raw scores at 12 months

Follow-up (months)	QoL outcome	Treatment group				Difference ^a (95% CI)	p-value ^b
		Pump		MDI			
		n	Median (IQR)	n	Median (IQR)		
6	Perceived frequency of hyperglycaemia	126	-1 (-2 to 0)	116	-1 (-2 to 1)	0.0 (-1.0 to 0.0)	0.182
	Perceived frequency of hypoglycaemia	127	0 (-1 to 1)	116	-1 (-2 to 0)	0.0 (0 to 1.0)	0.296
	Treatment satisfaction	126	8 (3 to 12)	116	5 (1 to 10)	2.0 (1.0 to 4.0)	0.067
12	Perceived change in frequency of hyperglycaemia	121	0 (-2 to 1)	118	1 (-1 to 2)	0.0 (0.0 to 1.0)	0.131
	Perceived change in frequency of hypoglycaemia	121	-1 (-2 to 0)	118	-1 (-2 to 0)	0.0 (0.0 to 1.0)	0.345
	Treatment satisfaction (change)	121	16 (13 to 18)	118	12 (7 to 16)	-3.0 (-4.0 to -1.0)	< 0.001
24	Perceived frequency of hyperglycaemia	122	-1 (-2 to 0)	113	-1 (-2 to 0)	0.0 (-1.0 to 0.0)	0.071
	Perceived frequency of hypoglycaemia	123	0 (-1 to 1)	113	0 (-2 to 0)	0.0 (0.0 to 1.0)	0.504
	Treatment satisfaction	122	8 (3 to 12)	113	5 (0 to 9)	4.0 (2.0 to 5.0)	< 0.001

a Calculated as described in Newson 2006.¹³⁹

b Calculated using Wilcoxon–Mann–Whitney *U*-test. DTSQ treatment satisfaction is scored from 0 to 36 and DTSQc treatment satisfaction (change) is scored from -18 to 18; in both cases, higher scores represent better outcomes. DTSQ perceived frequency scores are scaled from 0 (infrequent) to 6 (frequent). DTSQc perceived change in frequency scores are scaled from -3 (less often) to 3 (more often).

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Per-protocol results

Some patients switched from pump to MDI and vice versa, and they may be atypical. We therefore carried out an exploratory per-protocol analyses of psychosocial outcomes after excluding those who switched, and obtained, the following results.

Both groups showed statistically significant improvements in DSQOL as shown in *Table 69*.

The findings were similar with HADS-anxiety – both groups showed small improvements but this reached statistical significance only in the pump arm (*Table 70*). Large improvements would not be expected because baselines scores were quite low (pump 6.8, MDI 6.1)

Hospital Anxiety and Depression Scale-depression scores improved in both groups but the change only reached statistical significance in the pump group (*Table 71*). Again, baseline scores were low (pump 4.4, MDI 3.7).

Qualitative interpretation: cross-cutting improvements in quality of life

We turn now to qualitative data to (1) help explain the general improvements found across most psychosocial outcomes for both treatment groups and (2) aid the interpretation of those findings that reached statistical significance at more than one time point (i.e. findings relating to treatment satisfaction, dietary restrictions and daily hassles of function).

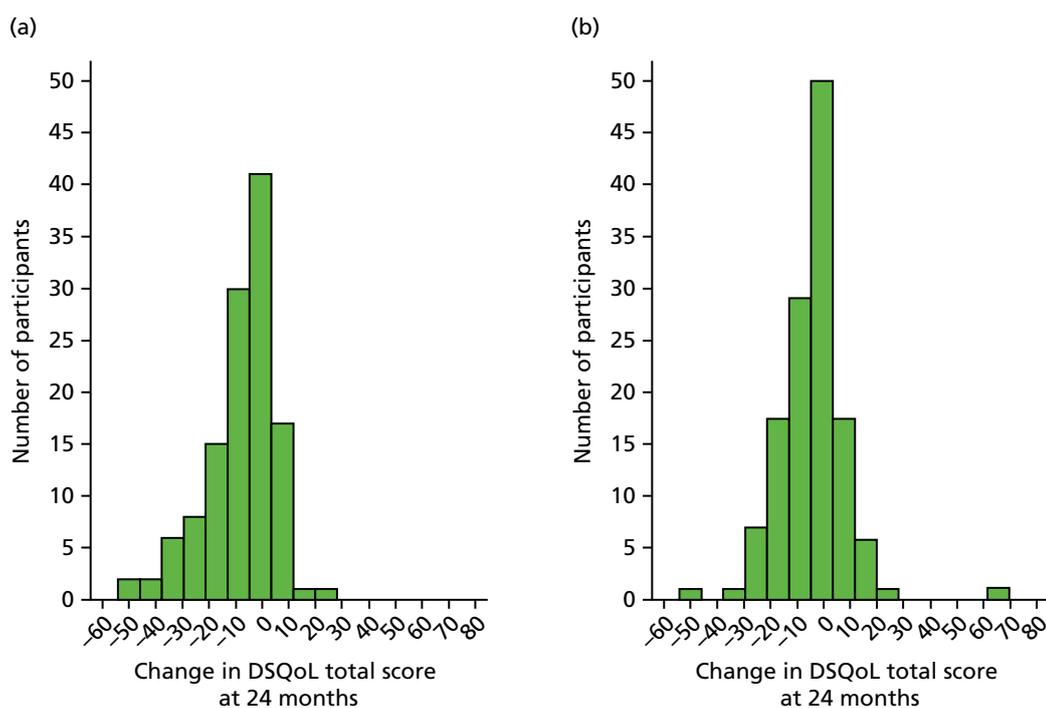


FIGURE 19 Changes in overall DSQoL at 24 months. (a) Pump; and (b) MDI.

TABLE 69 Overall change in DSQoL within arms at 24 months

Treatment group	n	Mean change (SD)	95% CI	p-value ^a
MDI	114	-4.16 (13.20)	-6.61 to -1.71	0.0010
Pump	123	-8.17 (13.07)	-10.50 to -5.84	< 0.00001

a Calculated using a paired *t*-test.

TABLE 70 Overall change in HADS-anxiety within arms at 24 months

Treatment group	n	Mean change (SD)	95% CI	p-value
MDI	114	-0.51 (3.49)	-1.16 to 0.14	0.1221
Pump	123	-0.95 (3.95)	-1.66 to -0.25	0.0087

TABLE 71 Overall change in HADS-depression within arms at 24 months

Treatment group	n	Mean change (SD)	95% CI	p-value
MDI	114	-0.15 (3.35)	-0.77 to 0.47	0.6355
Pump	123	-0.99 (3.79)	-1.67 to -0.31	0.0044

The overarching improvements in QoL observed in this study mirror those experienced by other cohorts of patients who have attended the DAFNE programme^{2,78,124,153} and, arguably, are largely attributable to conversion to a DAFNE approach. Indeed, when they were interviewed after their courses and 6 months later, patients in both arms reported very similar benefits and improvements to their lives. For example, patients in both arms – like other DAFNE graduates who have taken part in longitudinal qualitative research¹⁵⁴ – reported a renewed enthusiasm for managing their diabetes after attending their courses and being more open to discussing aspects of their condition and self-management practices with family and friends. As a consequence, patients also discussed being more open to seeking and accepting support from these family members and friends.

Patients in both arms – like other DAFNE graduates¹⁴³ – also reported feeling more in control of their diabetes/blood glucose levels and more committed to adhering to their treatment regimens (e.g. undertaking SMBG, administering insulin to cover the carbohydrate content of meals/snacks). Notably, however, although participants in the MDI arm tended to attribute these kinds of benefits and improvements to the education and instruction in DAFNE principles received during their courses, those in the pump arm – such as the participant quoted below – tended to accredit them to use of the insulin pump:

Because the pumps given me more awareness, like well if I do eat this and I give myself some insulin for it I'll need to know what my blood sugar is then, so I will test, so I've been doing more tests as a result of doing more insulin with the pump.

P43.2

In addition, patients in both arms reported similar improvements in QoL arising from use of their automated bolus advisors. As described in detail elsewhere,¹⁴³ patients who lacked confidence in their mathematical skills, or whose concentration could be compromised by high/low blood glucose, described the benefits and 'peace of mind' that arose from having the advisor to calculate their insulin doses for them. Those who were more confident about their mathematical ability also described liking and benefiting from using their advisor as these devices saved time and effort when calculating doses. Others still reported liking the data storage facility, as this reduced the burden of maintaining a paper diary.¹⁵⁵

Diabetes Treatment Satisfaction Questionnaire: treatment satisfaction (better for patients using pump therapy) After attending their course, patients in both arms reported high levels of satisfaction with their new regimens. Specifically, patients using pump and MDI – like other cohorts of DAFNE graduates¹⁴³ – described feeling more confident and in control of their condition by virtue of having been given what they saw as a more logical approach and a better toolkit for managing their diabetes:

And I think the DAFNE course gave, gave me the confidence to, to manipulate my dosing . . . be more consistent with corrections. And once, and better carb-counting so once the corrections . . . once you're right then it's, you don't need the corrections. I've found it much easier to maintain now.

M01.1

I'm testing me blood sugars a lot more, I'm counting, I've learnt how to count me carbohydrate properly. And I've learnt how to manage, if I ever get really sick, really bad sick days, I've learnt how to control them and deal with them a lot better, a lot better.

P13.1

However, patients using pump therapy also reported treatment benefits that were specific to using the pump, which helps explain the higher treatment satisfaction levels reported by those in the pump arm of the trial. For example, patients described how the pump delivered a drip-feed of insulin, which, as P04 suggested, enabled them to enjoy a more flexible lifestyle than had been possible using an injection

regimen because they no longer had to adhere to routines to maintain their supply of background insulin by injecting at similar times each day:

Having the basal has just been amazing, just having that constant [supply] and being able to see your sugars just so constant. And not having to get up at . . . like I used to try and take mine at ten in the morning and ten at night . . . Whereas now I can just, if I want to sleep in till midday and not eat anything and I can still wake up with blood sugars at 6 and 7 and be totally fine.

P04.1

Patients using insulin pumps also described liking and valuing having access to a method of insulin delivery that enabled them to avoid the pain and discomfort of injecting five or six times a day, as well as being able to administer insulin doses effortlessly and discreetly, and without the inconvenience of having to find somewhere private to inject:

. . . if I get taken out to lunch with a client or a supplier, then I don't need to excuse myself or I don't need to say sorry . . . I can do it from where I stand and, and taking something off your belt and so easy to do in so little time is, is, is great.

P17.1

I can just take my pump out of my pocket and key it, key it in and stick it back in my pocket. I don't have to, I don't have to get my needles out at dinner time and that's quite nice. And it is nice for it not to be such a big issue and not to have to get half undressed every time you, you want to have some insulin.

P01.2

Some patients who engaged in sporting activities described how the device provided them with a more effective self-management tool to undertake such activities than was possible with MDI. Specifically, such individuals described liking being able to use a regimen that allowed them to suspend or adjust the rate of insulin infusion, depending on blood glucose readings, both to take into account the effects of long-duration physical activity, or, in P09's case, to permit spontaneous visits to the gym:

Going skiing and having the pump . . . to have that and to be able to just tweak it constantly throughout the day if just great.

P04.2

Before if you were wanting to go to the gym you'd have to know hours and hours before it, before your last [background] insulin so that you could either reduce that . . . whereas now you can just say right I'm going to the gym I'll just reduce it now or . . . take it off even.

P09.2

The above accounts stood in contrast to those of some individuals in the MDI arm, who identified exercise and physical activity as areas in which they continued to struggle to manage their blood glucose effectively, despite making the changes recommended during their DAFNE course:

I wasn't given that much confidence with regard to doing physical activity and adjusting the dosage. Um, because my workout varies day in day out, so one time I go to the gym I might be there for an hour, um, but then one time I go to the gym on the weekend I might be there for an hour plus an hour in the pool or something like that. And it was just . . . the near enough generic way they give you of, um, adjusting your dosage, it's like drop it by 10% or something like that, I didn't find that that was effective [. . .] that side of things [exercise], it hasn't really had much of, any impact on.

M09.2

The greater treatment satisfaction found in the pump arm of the trial can also be explained by patients' perceptions of the added benefits of pump technology over MDI. These data are considered further under *Study aim 3*.

Diabetes-specific quality of life: dietary restrictions (more flexibility and freedom for patients using pump therapy) Mirroring the accounts of other cohorts of DAFNE graduates,¹⁴⁶ patients in both arms described how their newly acquired knowledge and skills had allowed them to be more flexible and spontaneous in their food choices. For instance, patients in both arms described feeling more confident about eating less carbohydrate (which, for some, eliminated a perceived need to eat a snack before going to bed) and, in certain circumstances, skipping consumption of carbohydrates entirely. Relatedly, patients also described being more able to alter the timing of meals, as they no longer feared hypoglycaemia if they did not eat at specified times:

I was so happy the first night I was thinking 'Oh I don't need to eat a snack, that's brilliant, I can just go to my bed if I want to go to my bed'. Whereas before I'd to wait till like 9, half past 9, to have my last insulin and have my snack before I went to bed and I was like 'This is fantastic! I don't even need to eat anything before I go to my bed!'.

P18.1

[I] was always very strict, 'this is what I need to eat, it's eight o'clock, I need to eat, otherwise there's going to be trouble' . . . I've definitely found some freedom in that I don't have to eat when I don't want to eat.

M07.2

However, patients in the pump arm highlighted additional benefits that appeared to be more specific to using an insulin pump, and which can be used to help explain the greater improvement in DSQOL diet restrictions in this arm of the trial. For instance, patients using the pump described how they could now eat a carbohydrate-based snack and administer a bolus accordingly, whereas, when using a MDI regimen, some reported having skipped a snack because they did not want to have a further injection:

I would rather have a pump than keep on injections and stuff, and it does mean I can have a snack. Um, you know, I don't, I don't really want to, let's say, have a bag, have a bag of crisps and then inject myself, it wasn't very appealing.

P31.2

Some such patients also discussed how, since moving on to pump therapy, they no longer had to restrict consumption of snacks containing carbohydrates to near to a mealtime in order to avoid having to inject more than once:

Before, if you were having something to eat, if you wanted something sweet, you'd have it with a meal, whereas it's a lot more flexible now. If you want to go out in the afternoon and have a cake or something, you could . . . you could have a cake and just have a bit of insulin for it.

P25.2

Patients also described feeling more confident and able to dine out because the pump afforded an easy means of administering a separate bolus for each course. As P27 observed, this made it easier to make an impromptu decision to have a dessert without the burden of also having to administer a further injection. Others, such as P33.2, described how the ease with which they could stagger their insulin doses during a meal meant that they no longer had to worry about hypoglycaemia, particularly if a course arrived later than expected:

The pump is good because you can make fine adjustments, fine-tuning. You go out for a meal in the evening and decide to have a dessert at the last minute, so you just take, you know, a few more units in the bolus. Far nicer than getting out the pen and all of that.

P27.2

Some people would take it [a single dose] before their meal and then if their meal doesn't come for so long, they sit and go, 'right, where's the cans of Coke' but I just feel as if you've got more freedom. You can actually stagger your insulin over a meal, which is good. I find, maybe if you're sitting for a long meal, a couple of hours, you can stagger your insulin so it's, you're not getting too much at once.

P33.2

Diabetes-specific quality of life: daily hassles of functions (better for patients using pump therapy)

Although there were no statistically significant differences at 6 months, patients did highlight factors and experiences in their 6-month interview accounts that might help to explain why the pump group also had better improvement in the DSQOL daily hassle of functions at both 12 and 24 months. Notably, patients using pump therapy reflected on how using a pump to administer insulin required less time and effort, and was 'less of a chore' (P25.2) than using pens. This was partly because pressing a button to administer insulin was a more convenient and expedient option than 'having the hassle and worry of getting the needle out' (P04) and 'having to crank it up on the pen and then inject' (P33.2). In addition, patients, including P30.2, highlighted the advantages of no longer having to take time out of their everyday activities to find private locations in which to inject (see also aim 4):

'Cos when I went to work, with pens, I'd often go into the locker room to inject myself. And now with the pump, I'll just take it out of my shirt pocket, type in what I am having, put it back in my shirt pocket and it's done.

P30.2

Some patients also described how pump therapy was a less burdensome and time-consuming option because of the ability to use, set and alter basal rates:

If I was on the pen, you know, I'd be having to take an extra insulin mid-morning, you know, if my blood sugar was rising . . . So for me it's just so much easier to be able to set things on a temporary basis.

P39.2

Cos I'm going to bed and I reach to take my insulin before I go to bed, and it's like, 'no, no that doesn't have to happen anymore', so it's good.

P40.1

Patients also highlighted the advantages of having 'less paraphernalia to lug around' (P06.2) by virtue of using the pump, whether this be when travelling to and from work (P03) or, in P04's case, when undertaking recreational activities, such as skiing on a recent holiday:

You've got that freedom with the pump, you can do anything whereas [with] the injections you've got to take your pen, you've got to take your needles, you've got to take your sharps bin, you've got to make sure you've got a spare pen in case that one don't work. Whereas with your pump, I always carry a spare quick inserter [cannula], a spare tube insert, just in case you've any problems or get a blockage or whatever . . . but they're nothing, they'll slip in a rucksack or in your pocket.

P03.2

There is no stress, it's there, it's attached. Going skiing and having the pump on was on me was just so much better than having pens, having to take pens and needles and stuff up the mountain . . . you've just got this thing attached to you and that's it done with now.

P04.2

Study aim 3

3. To understand and explore the added benefit (if any) of pump technology over MDI from patients' and educators' perspectives.

Qualitative data are drawn on to address this study aim; here we begin with patients' perspectives before moving on to those of staff.

Patients' perspectives

Preconceptions about insulin pumps

Many patients described having had misconceptions prior to the trial about how the pump worked and how it could be used to manage their diabetes. Specifically, some described how they had thought that the pump would be a small device implanted under the skin. Others had perceived the pump as being more akin to a closed-loop system, which would alleviate much of the burden of diabetes management by monitoring blood glucose and calculating and administering insulin doses:

I actually thought the pump was some kind of implant . . . and I thought it was something you connected . . . some kind of pipe or cannula and you filled up this implant and then once it was full you disconnected it and then you just had like a remote [control].

P09.1

I think my preconceived ideas were slightly wrong . . . I thought it would be a continuous monitoring system and adjust accordingly . . . And I didn't realise that you had to keep on testing yourself.

P14.1

Despite some such patients' initial hopes and expectations not being met, most of those who used pump therapy during the trial described the pump as offering benefits over a MDI regimen. Although some of the benefits described by these patients were also highlighted by those in the MDI arm of the trial (and, hence, arguably were due to the use of the DAFNE approach rather than pump therapy per se), some did appear to arise specifically from use of an insulin pump and these are considered below.

Drip-feeding basal insulin and altering basal rates

Most patients using pump therapy described feeling that they had better control over their blood glucose levels because the device supplied a constant drip-feed of basal insulin, which, as they suggested, more accurately mimicked the natural release of insulin by the pancreas.

Now, because it's such a little trickle, it's really, I think, that's made a huge difference, because it's made me operate, my body operates more like somebody that's got a, you know, a pancreas that works.

P24.2

Some patients also highlighted the benefits of being able to set different rates of basal insulin infusion during the day and night. This included P09, who described using a lower basal rate for a specific period of time to counter recurring nocturnal hypoglycaemia, and P19, who reported using higher basal rates to counter rises in blood glucose during periods of inactivity and lower rates when more active (e.g. at weekends):

. . . it's a lot easier, like, at the moment, my blood sugar tends to dip between midnight and four in the morning, so the pump slightly reduces the insulin . . . whereas on the pen [MDI] then I'd have to reduce the whole of the insulin from before I go to bed until I get up in the morning.

P09.2

[During the week] I'll sit at my desk until lunchtime, whereas obviously at the weekend I'll get up, have breakfast, and then I'll probably go out and about and do something active, so that was . . . weekends were my problem for blood sugar. But that, you know, now I've changed that, I've put on temporary, er, temporary basals for then, during the morning, and er, it's been fine.

P19.2

Others highlighted the clinical and personal benefits gained from being able to use a temporary basal rate to accommodate sporting and other physical activities (see *Study aims 1 and 2*) or, in P18's case, to minimise the risk of hypoglycaemia after drinking alcohol:

I'd set a temporary basal on it because I was having a drink and so I lowered the basal so as that I could, to stop me hypo-ing through the night sort of thing.

P18.1

Fine-tuning and administering small doses of bolus insulin

As well as being able to alter basal rates, some patients reported additional benefits arising from being able to administer very small and/or precise bolus doses of insulin. Reflecting back on their experiences using an injection regimen, such patients described how this feature had enabled them to more precisely match insulin doses to carbohydrate intake in order to fine-tune their blood glucose control:

I love that you can, you can just give 0.1 of a unit now and before I was on, like, you know, 1 unit, so the accuracy's much better . . . I'm excited that you can just fine-tune it so much . . . the control that it's given me already is just fab.

P04.1

. . . it's more clinical isn't it, so, you know, it's easier to be, to be able to drill down into it and to fine-tune it, which is, which is what really I need to do, it doesn't need to be massive changes, it just needs to be slight, you know, slight changes to make it that much better.

P19.2

As a consequence of being able to administer very precise and small doses, some patients who were sensitive to insulin also described how using the pump had lessened their perceived risk of hypoglycaemia:

If you're on the edge of going hypo[glycaemic] and you're having something to eat . . . so you take your insulin, that half a, extra half a unit can send you down again. Whereas on this [pump] you can, like I say, you can fine-tune it to half a unit, so you know exactly what you're taking. If you need one and a half units for a sausage roll, you're not trying to think, 'well, do I take 1 or do I take 2?'. You can take one and a half.

P13.1

Advanced settings: dual- and square-wave boluses

A small number of patients also suggested that they benefited from using advanced pump settings, such as the dual- or square-wave function, to offset the delayed effect of carbohydrate-dense foods, such as pasta, or when eating a meal over an extended period of time:

Then there was the dual wave, you know like when we've, if we've had pasta and you know your carb[ohydrate]s are going to be long acting and things like that, I think that's brilliant, whereas before when I were having injections, you just had your injection and then 3, 3 hours later your blood sugar would still be really high.

P05.2

At Christmas time, parties, right? Buffets and things like that, this is a lot easier because you can put it on a dual wave or a square bolus or something and you can forget, you know, right, I've dealt with

the insulin, and then you can just eat little bits over however many hours, um, and I did that and it worked . . . you couldn't do that with injections.

P07.1

Wearing the pump prompts patients to perform self-management practices

Although some patients described disliking being connected to the device (see *Study aim 5*) an additional benefit identified by some individuals was that the pump's presence prompted them to undertake DAFNE-specific self-management practices, such as SMBG:

. . . it's a very useful kind of physical manifestation of the fact that, ah, you have this, you have this condition and you're eating right now, and so do something about your blood test, do something about what you're eating . . . It's a very, kind of very useful as a, as a way of, er, reminding you to, you to employ the, er, the techniques . . . that we're that we're taught on the DAFNE course.

P23.2

No need to inject

Aside from perceived clinical benefits, many patients reported personal benefits arising from no longer having to inject. Despite having to insert a cannula every 2–3 days, most suggested that this procedure was much less onerous than having to inject five or six times a day:

I know you have to mess about with putting the cannulas in every 3 days, but that's the biggest hardship. It's still, you know, going from that . . . er, to like four injections a day, morning, lunchtime, teatime and night-time, when you're out you've got to pull the injection out, stick it in you and stuff like that, it's, it's totally different.

P10.1

As reported earlier, in *Diabetes Treatment Satisfaction Questionnaire: treatment satisfaction (better for patients using pump therapy)* and *Diabetes-specific quality of life: daily hassles of functions (better for patients using pump therapy)*, patients using pumps also described benefits and satisfaction arising from being able to administer insulin without having to inject in front of others and/or to find somewhere private to administer an injection when in a public place. As such, and like the adolescent pump users studied by *Lowes et al.*,¹⁵⁶ patients also described feeling less noticeable, stigmatised and, hence, detached from others as a consequence:

It's actually more discreet . . . one person thought it was an iPod [Apple Inc., Cupertino, CA, USA] . . . I find it more discreet because you can take a bolus before a meal without having to expose your skin, which, not everybody likes you injecting in public, it's easier to take your dose in that way, and it means it's much easier to fit in.

P12.2

Educators' expectations and perspectives

Educators' perspectives have already been reported in detail elsewhere;¹⁴⁷ hence, readers may wish to reference this work for more detail about particular findings or to access additional quoted material.

Added benefit of pump therapy

All staff were keen to emphasise that a MDI regimen, taught in conjunction with a DAFNE or similar educational approach, presented a very good and effective toolkit for undertaking diabetes self-management. Hence, educators also suggested that, if they were taught to use a MDI regimen effectively, most patients would neither need nor gain added clinical benefit from using pump therapy:

I think we can maximise most people on DAFNE and it's wonderful, we really are DAFNE advocates and we've had a lot of improvements and reductions in hypos.

D4

However, all educators also noted that, because of the constant drip-feed of insulin, the ability to alter basal rates, and also the ability to titrate and deliver very small insulin doses, pump therapy could potentially help certain groups of patients to improve and/or fine-tune their glycaemic control. As educators described, these individuals were principally those who met current NICE criteria for pump referral,¹³ such as those who suffered from the dawn phenomenon, were very insulin sensitive and/or who undertook a lot of sporting activities that exposed them to risk of hypoglycaemia:

People whose insulin requirements are really small, really low, where sort of injected longer-acting insulin, background insulin, you just can't adjust them finely enough . . . a pump is great for them because you've got the really, you know, minute basal adjustments.

N02

Those that are maybe quite intense when it comes to exercise, you know, there's definitely a potential for them. Equally, those that are maybe finding that they are on really small doses of insulin because it [the pump] does give them that opportunity to fine-tune.

D05

However, all educators pointed out that, to gain added clinical benefit from using a pump, patients had to be willing and able to use the pump's features otherwise, as N3 suggested:

They will just sit on the pump and use it as another method of delivering insulin and they'll be no better off than on injections.

N3

As is described further later (see *Study aim 4*), educators also highlighted the difficulties of predicting which patients, or groups of patients, would have this willingness and ability to use the pump to optimal effect.

Study aim 4

4. To look at why some patients may do better than others using pump therapy.

To address this aim, we begin by presenting quantitative data before drawing on educator accounts to reinforce and support the quantitative findings.

In addition to the pre-specified subgroup analyses presented in *Chapter 5, Subgroup analysis*, we undertook exploratory analyses investigating the relationship between continuous baseline variables and outcome, using scatter plots with superimposed regression splines (*Figures 20–22*).

Unsurprisingly, those with the highest HbA_{1c} at baseline tended to have the largest reductions in HbA_{1c} at 24 months in both groups. There were no clear associations seen between HbA_{1c} reduction and age at entry, duration of diabetes, BMI or age at onset in either group. As with HbA_{1c}, no clear patterns were seen between DSQOL at 24 months and mean age at baseline, duration of diabetes, BMI or age of onset. The biggest reduction was seen in those with highest DSQOL at baseline, who had more scope to gain.

The lack of association between duration of diabetes and benefit after DAFNE is an important finding, which supports the recommendation in the updated NICE guideline that structured education should be provided to all patients, not just those recently diagnosed.

We hypothesised that greater use of the facilities in the pump might be an indicator of engagement with self-management. However, we found no association between the number of basal rates used and change in HbA_{1c} (*Figure 23*).

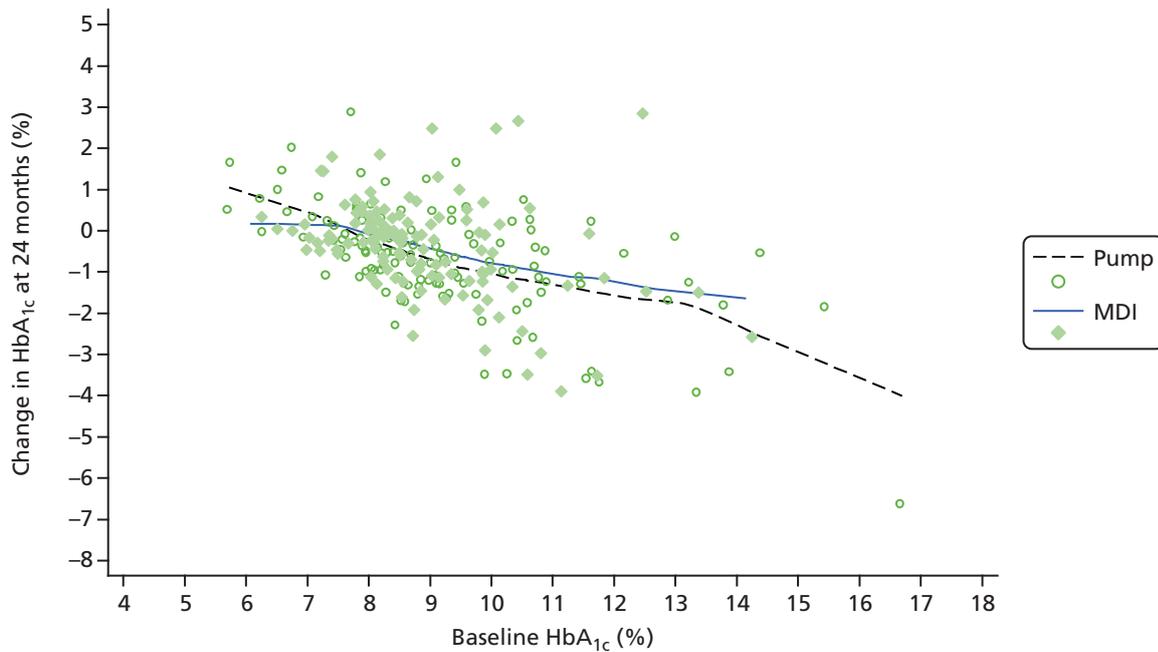


FIGURE 20 Relationship between baseline HbA_{1c} and change in HbA_{1c} at 2 years.

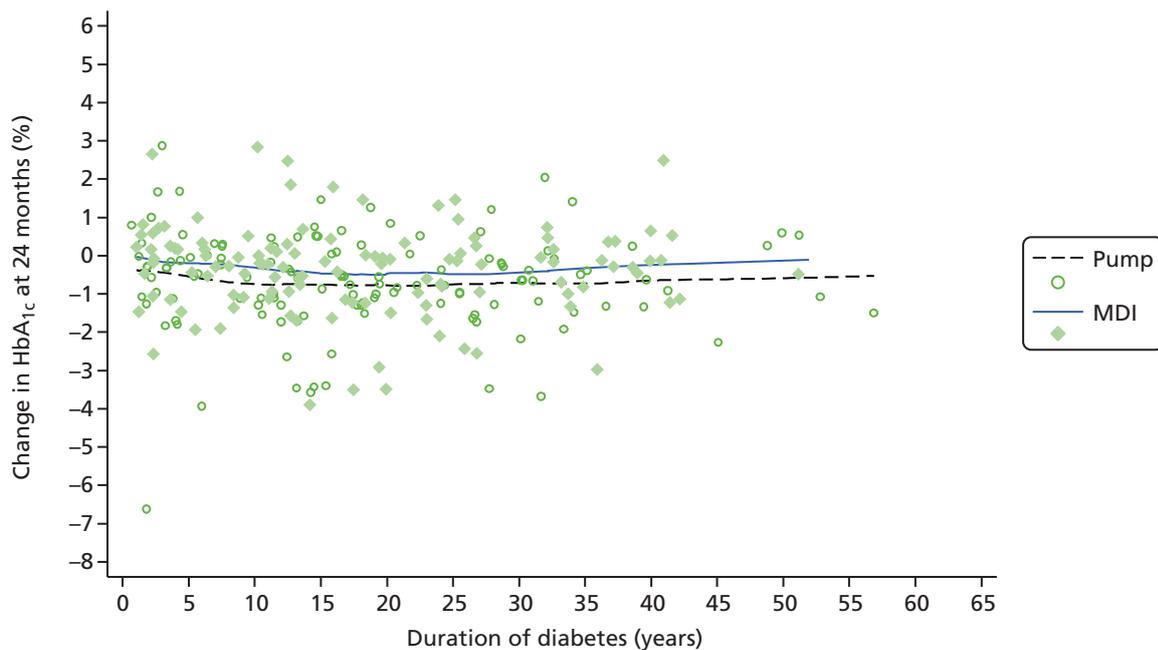


FIGURE 21 Relationship between duration of diabetes and change in HbA_{1c} at 2 years.

We found considerable variability of changes in both HbA_{1c} (see *Figure 4*) and DSQOL (see *Figure 19*), with some individuals making very considerable improvements and others deteriorating over time. However, exploratory analysis of factors that might be influencing the changes did not find anything of significance.

Qualitative findings: educator accounts

In advance of the trial, educators described holding certain preconceptions about who would do well on a pump and make full and effective use of its features to optimise glycaemic control. These preconceptions, as will be described, were subsequently challenged and revised in light of educators' trial delivery experiences.

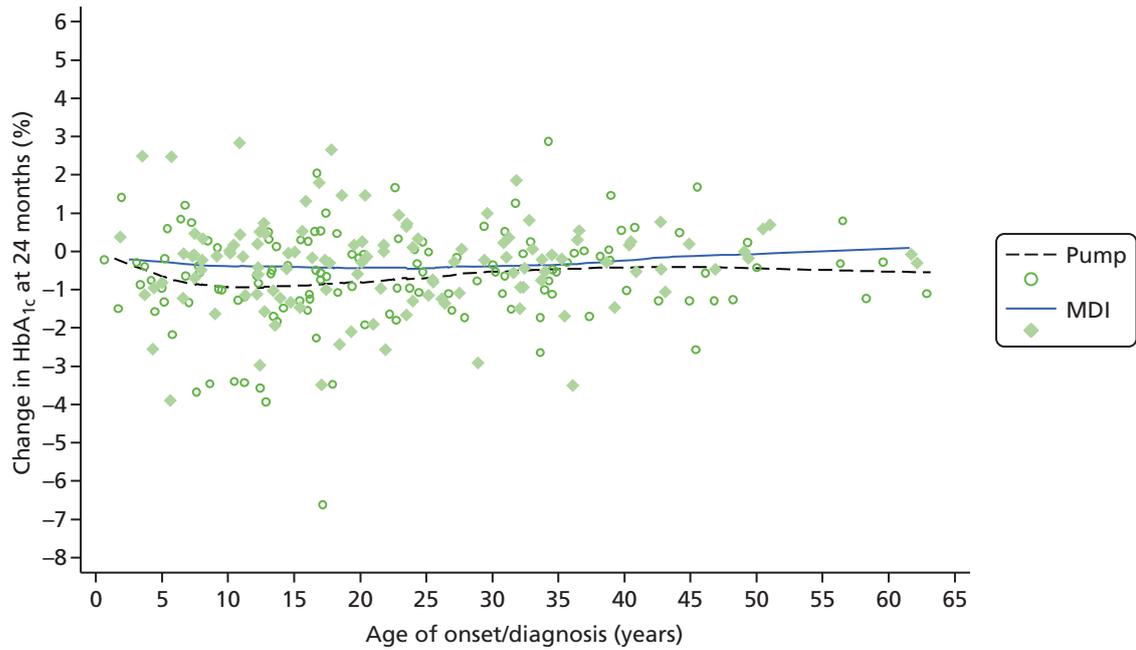


FIGURE 22 Relationship between baseline age of onset/diagnosis and change in HbA_{1c} at 2 years.

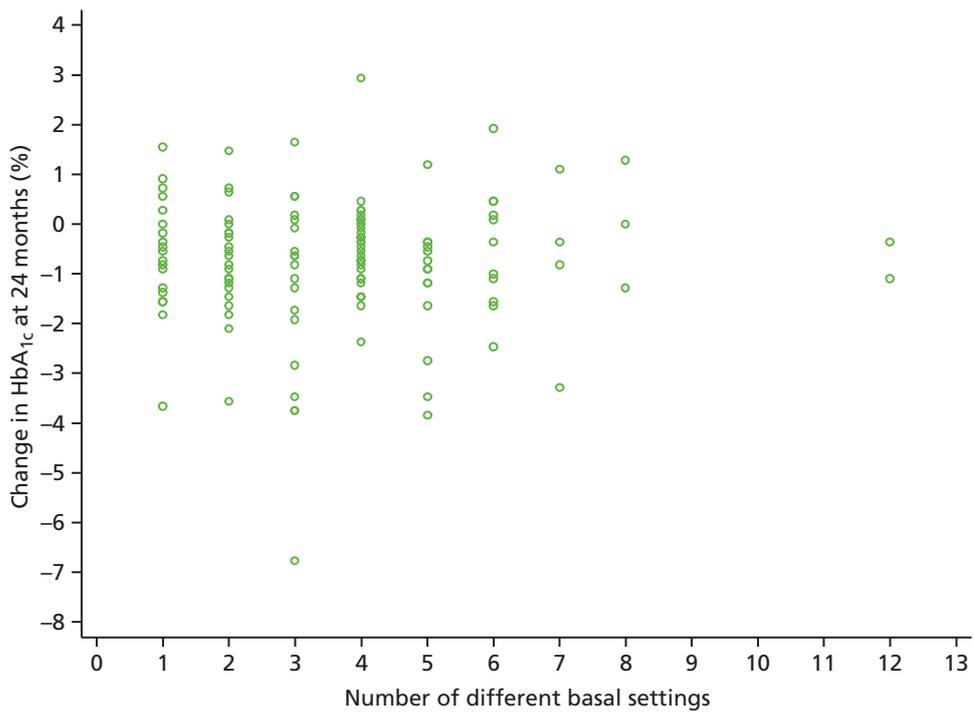


FIGURE 23 Change in HbA_{1c} (%) vs. number of different basal settings (pump group only).

Pre-trial views about pump candidacy

As indicated earlier (see *Study aim 3*) educators described having had preconceptions in advance of the trial about the kinds of individuals who would do well on a pump. Specifically, educators discussed how, in their routine clinical practice, in addition to using NICE and other clinical criteria, they had tended to recommend individuals for pump therapy based on tacit and informal assumptions about whether or not they

had the right aptitude and technical ability to use the pump to optimal effect. These individuals, as educators also noted, had tended to be those who were younger, technologically savvy and academically able:¹⁵⁷

... people who [are] more numerate and the more, the more intelligent, the more, you know, sort of educationally able to take on board all the information.

D03

For similar reasons, educators also described how, despite meeting clinical criteria for pump referral, they had not generally recommended individuals for pump therapy in routine clinical practice if they had a poor history of diabetes self-management, were older or were less academically able.¹⁵⁷ This was a result of their concerns that such individuals would be unwilling or unable to 'put in the extra work required to use a pump properly' (N11) and, hence, would not gain any added clinical benefit from the pump as compared with MDI.

Revising preconceptions as a result of trial participation

Educators also described how, as a result of their participation in the REPOSE Trial (for which a randomisation process rather than their own judgement was used to determine who was moved onto the pump), they had been exposed to individuals using pumps who they would not have put forward for this regimen in routine clinical practice. As educators further noted, this kind of exposure had led them to reconsider which kinds of people might gain clinical benefit from using a pump. Specifically, and as detailed elsewhere,¹⁵⁷ educators recounted experiences during which they had observed individuals during the trial 'doing really, really well on pump therapy who we would have predicted would have really struggled' (D2), as well as those 'such as the likes of the young lad who was desperate for a pump and he's just not using it' (N9). As a consequence, some educators described how they 'had stopped having preconceptions about who it will suit and who it won't' (N3), whereas others suggested that, in light of their trial experiences, they now thought that motivation – rather than age, technological aptitude or academic ability – should be used as the main criterion (alongside clinical criteria) for determining future pump referrals:

I've found that when you actually sit down, show them it, work way through it, actually they become more efficient. So in a way I don't think there's anybody that shouldn't do well on a pump as long as they are keen and motivated.

D4

Others still noted from their experiences of observing patients during the REPOSE Trial that use of a pump could itself act as a tipping point for increased disease self-management among some erstwhile seemingly demotivated patients. As a consequence, such individuals described having reached the conclusion that pumps 'should potentially be made available to everyone [meeting clinical criteria] because you simply can't predict, so maybe you need to give everyone a chance?' (D1).¹⁴⁷

Summary

Educator accounts thus highlight the difficulties of identifying and using patient characteristics to predict potential clinical success using an insulin pump, thereby reinforcing the findings of the quantitative analysis, which showed that it is not possible to determine which patients, compared with others, are likely to do better on the pump.

Study aim 5

5. To explore acceptability of, and reasons for, discontinuing (pump) treatment.

To address this study aim, we draw on the interview accounts of patients in the pump arm of the trial.

Acceptability

As described in *Study aims 1 and 2*, very high levels of treatment satisfaction were reported by patients using pump therapy. However, at baseline, and over time, a small number of individuals did describe

having struggled to adapt to the presence of the pump and discussed how they had disliked being attached to the device, as it acted as a constant reminder of their disease state:

... it just makes me feel like I've got, I know I have a disease, but like a diseased person with this thing, a machine attached to me.

P12.2

Although most patients found the pump to be a discreet form of treatment, a few also reported feeling self-conscious when using the device in public settings:

... before, obviously, you've got nothing ... there's nothing on you to say, 'I'm a diabetic' and now you've got this pump, people are a little bit more ... inquisitive.

P09.2

In some cases, and mirroring findings reported by Hayes *et al.*,¹⁵⁸ patients described how they had found the pump inconvenient to carry on their person and awkward to stow in their clothes, both during the day and when in bed. Others spoke about having experienced pain if they had accidentally bumped the site where the cannula had been inserted and/or if they had caught the cannula needle/tubing when performing everyday activities. This included occasions when patients had been in bed asleep, driving, playing with children, wearing tight-fitting clothing, having sex or undertaking sporting activities:

... sometimes when I've lifted the kids they've caught themselves on the tubing ... and having to say to them 'you need to watch mummy's pump' so they don't kick it or something when we're carrying on.

P18.2

It's not nearly as convenient ... it's in the way. And it's also awkward at night ... So I'm still getting to grips with that, and as I, when I played tennis this week I took it off, when I play golf I tend to put it in the pocket and the same with gardening.

P11.1

Despite many patients reporting having experienced practical difficulties, most also indicated that they had quickly adapted to wearing the pump. To do this, patients described having altered where they had stowed the pump or having adapted clothing to ensure the device was more secure or tubing less likely to snag:

I'm mostly wearing it tucked into a belt. And one of the things I have changed recently is I now tend to wear it at the side or even slightly behind the side.

P11.2

I think at first it's obtrusive because it's there, isn't it and it's in bed and 'where do the, where the hell do I put it ... and it's been under my pillow. But now I've got used to it. And as I say, I've got some elastic to get it tucked away at night-time.

P05.1

Furthermore, although many patients described how the pump could be a 'bit of a nuisance sometimes' (P14.2), most also suggested that the practical inconvenience of having it attached to their body was outweighed by their perception that the device had enabled them to achieve better glycaemic control, and a more flexible lifestyle than was possible using a MDI regimen (see *Chapter 9, Research question 3*):

I thought 'oh I'm not sure I'm going to like having something attached to my body the whole time'. But I think, after doing the week [DAFNE course], you can see the benefits that it had in terms of being able to manage your diabetes and make subtle changes in the amount of insulin you have that you can't really do with pen injections, you know, that kind of outweighed for me the fact that I'm

going to have . . . and you just get used to it, like I don't really feel it on me now so you just kind of get used to it.

P21.1

Similarly, patients who described difficulties siting and inserting a cannula contrasted this level of inconvenience with a MDI regimen, which they considered to be much more cumbersome:

When it comes time for me to change the pump [cannula], I'm like, I can't be bothered doing this! But then I think to myself, 'well, it's either do this or else do six injections a day' and then I just have a wee argument with myself and tell myself to shut up [laughs]!

P18.2

Limiting the use of the pump

Although none of the patients who participated in the qualitative study reported having discontinued using the pump entirely, there were two individuals, both young women, who reported struggling with disruption to their body image: 'it's like having a colostomy bag attached to you' (P01.1), 'I think I was like, "oh, this thing's attached to me and I'm getting fed up with it, I need a break from it otherwise it'll drive me insane"' (P04.2).

As a result, both of these individuals described temporarily reverting to MDI on some occasions during the 6-month period of study. They also identified specific trigger points, similar to those reported by Hayes *et al.*,¹⁵⁸ which had resulted in them disconnecting the pump, including when there was little time available to change a cannula or when a tight-fitting dress had had to be worn and 'every lump and bump' was visible. However, despite the unease they had experienced when wearing the pump, both women reported removing the device for only relatively brief periods of time before subsequently reattaching it because, as P04 explained, 'all the positives outweigh the negatives'.

Study aim 6

6. To enhance understanding and assist in the interpretation of trial outcomes (e.g. differences in HbA_{1c} between the two arms).

As there were no significant differences in HbA_{1c} between the two arms, we are unsurprisingly cautious in drawing any major contributions from the psychosocial work in relation to these outcomes, although it should be noted that, because of our restricted funding, we were limited by our inability to interview patients beyond 6 months. The perceived benefits of the pump user group, both in terms of the qualitative work and the limited benefits in terms of treatment satisfaction and some DSQOL domains, are described in detail within study aims 1–5.

Summary

We used a mixed-methods approach with questionnaires and interviews, and had a good response to questionnaires, with approximately 94% completion in the pump group and 86% in the MDI group. There was also a very good response to invitations to take part in interviews, and attrition in this part of the study was low with only three of 45 recruits not completing the round 2 interviews.

We found little difference in quantitative psychosocial outcomes between the pump and MDI arms, largely because improvements were observed in both following DAFNE. There were some statistically significant differences in the subdomains of the DSQOL in favour of pump therapy, those being leisure time restrictions and flexibility, daily hassle and dietary restrictions.

Treatment satisfaction also improved in both arms, but statistically significantly more in the pump arm. These observations were supported by findings from the qualitative interviews. There was also a greater reduction in the 'hypoglycaemia worry' score in the pump arm. The qualitative findings were that patients in both arms felt more in control of their diabetes.

Patients in both arms reported benefiting from automated bolus advisors, although, as reported elsewhere, there may be unintended consequences to giving people access to this technology.¹⁵⁵

A recurrent theme was that after doing the DAFNE course, patients in both arms felt more in control and more confident in self-management. However, those on the pump reported some additional benefits from the pump, mentioning increased flexibility of lifestyles, avoidance of the frequent injections with MDI, more effective self-management around sporting activities and dietary variations, and the ability to administer very small doses of insulin, with different basal rates, at different times of day and night.

Chapter 8 Discussion

Statement of principal findings

We carried out a randomised trial of pump versus MDI in a group of adults with T1DM referred for structured training in flexible insulin therapy because of suboptimal diabetes control. Both groups received training ensuring that education was balanced across the arms. The main results were:

- The pump group had a slightly greater mean reduction in HbA_{1c} of 0.85% (9.3 mmol/mol) than 0.42% (4.5 mmol/mol) on MDI. After adjusting for baseline difference and accounting for missing data, the MD at 2 years did not reach statistical significance -0.24% (95% CI -0.53% to 0.05%) or -2.7 mmol/mol (95% CI -5.8 to 0.5 mmol/mol).
- Overall, participants in the trial achieved a clinically worthwhile fall in HbA_{1c} of 0.6% (7 mmol/mol) at 2 years.
- Some patients switched treatments during the trial and the per-protocol analysis showed a statistically significant MD of -0.36% (95% CI -0.64% to -0.07%) or -3.9 mmol/mol (95% CI -7.0 to -0.8 mmol/mol) in favour of pump therapy ($p = 0.015$). The 95% CI includes the 5% clinically important effect and so we cannot claim equivalence of pump and MDI in this population.
- The proportions achieving HbA_{1c} of $\leq 7.5\%$ at 24 months were relatively low in both groups at 25% on pump and 23% on MDI.
- The frequency of severe hypoglycaemia fell in both groups, although more so in the pump group during months 12–24.
- At 24 months, there were no significant differences in BMI, insulin dose or lipid levels.
- Both groups demonstrated improved psychological outcomes over a range of different scales, which included treatment satisfaction and DSQOL. Treatment satisfaction and two subdomains of the DSQOL (daily hassle, diet restrictions) improved to a greater extent in those allocated to pump therapy both at 12 months and 2 years.
- The qualitative work found that patients in both arms felt more in control of their diabetes and benefited from automated bolus advisors. A recurrent theme was that after undertaking the DAFNE course, participants in both arms felt more in control and more confident in self-management. Those on pump therapy reported some additional benefits from the pump, including increased flexibility of lifestyles, more effective self-management around sporting activities and dietary variations, and the ability to administer very small doses of insulin. These findings are reflected in the differences in the quantitative outcomes, but did not result in significant differences in glycaemic control.

Thus, in terms of the primary outcome, there were no significant differences in change from baseline to 24 months between those randomised to pump therapy or those using MDI, indicating that pump treatment provided no significant additional biomedical benefit over DAFNE skills training.²³

Rates of severe hypoglycaemia were halved in both groups, a benefit maintained to 24 months with no difference between the groups in this or in rates of moderate hypoglycaemia.²³ However, we noted that between months 12 and 24, rates of severe hypoglycaemia were lower in the pump group, although this comparison had not been pre-specified. There were no other differences in biomedical outcomes apart from slightly greater reductions in insulin doses in those randomised to pump treatment.²³ Contrary to most previous studies, insulin dose fell in the MDI arm.

Summary of trial- and model-based estimates of cost-effectiveness

Both the trial- and model-based estimates of cost-effectiveness showed that the addition of pump therapy to a structured training course was not cost-effective compared with the £20,000–30,000 per QALY gained threshold used by NICE.²² These results were robust to all scenario analyses.

In the base-case EFACT, the addition of insulin pump therapy to structured education for adults with suboptimally controlled diabetes was dominated by current practice as, on average, it produced fewer discounted QALYs over the 2 years (−0.004) at a higher discounted cost (£2959). The lowest ICER was observed in the scenario analyses, in which a 50% reduction in the cost of insulin pumps and insulin pump consumables in the per-protocol population was conducted. The ICER of this strategy was £552,866, indicating that, even with substantial discounts in price, insulin pump therapy was not a cost-effective addition to structured education for adults with suboptimally controlled T1DM.

Any differences in the rates of diabetic complications in the long term are not included in the estimates of cost and QALYs in a within-trial analyses, as they will occur after the last follow-up period. To address this issue, the lifetime costs and QALYs were estimated using the Sheffield Type 1 Diabetes Policy Model.

In the long-term modelling, the addition of insulin pump therapy to structured education for adults with suboptimally controlled diabetes generated more incremental discounted QALYs (0.1447) at a higher incremental cost (£20,448), producing an ICER of £141,312 per QALY gained. The lowest ICER was observed in the scenario in which the prices of insulin pumps and insulin pump consumables were reduced by 50%. The ICER of this strategy was £46,578, again indicating that even with substantial discounts in price, insulin pump therapy was not a cost-effective addition to structured education for adults with suboptimally controlled T1DM.

Strengths and weaknesses of the research

Our study had a robust, multisite design, involved larger participant numbers and had a 2-year follow-up period, which was longer than previous trials of pump therapy and therefore more clinically meaningful. Participants in both arms used analogue insulins and bolus calculators.²³ The study was conducted in secondary care centres, reflecting a range of experience delivering pump therapy and involving attendance at a structured training intervention that has consistently shown improved biomedical and psychological outcomes and is well established across the UK. It included a main outcome measured in a central laboratory and a comprehensive psychological evaluation with high levels of data completeness. The pragmatic study design thus provides good external validity, particularly as participating in the educational course led to sustained improvements in glycaemic control, reduced rates of severe hypoglycaemia and improved psychological outcomes across a range of scales.²³

The follow-up period, although longer than other studies, could have been lengthened to 3 years, as evidence from some previous studies indicates a waning of the effect of pumps over time.⁶³

It is not possible to blind a trial in which insulin delivery systems are fundamentally different, and this could lead to a bias in any RCT involving pumps. A trial studying individuals who have expressed a desire for pump treatment is likely to struggle to recruit participants if one arm continues on MDI. Those randomised to MDI may also either drop out or exhibit poor outcomes due to 'disappointment' and lack of motivation. We studied individuals who had not specifically requested pump therapy, but who were awaiting a course in diabetes self-management to help them improve their glycaemic control. Thus, our aim was to determine any added benefit of pumps above MDI while controlling for the training itself.²³

An important additional limitation is that those randomised to pump treatment might have been insufficiently motivated to make the most of any technological benefit, as they had not expressed a particular wish to use a pump. Anecdotally, one common reason given by patients for not wanting to participate was reluctance to use an insulin pump. However, educators encouraged participants to use pump features and provide additional input if this was requested. Overall, we reasoned that as participants had signed up for a course to improve their glucose control, any additional benefits of pump treatment would emerge.²³

Comparison with other research

Two appraisals of pumps by NICE have reviewed the evidence on clinical effectiveness and cost-effectiveness. The first¹⁴ noted that there were no trials of pumps against 'best MDI' with long- and short-acting analogue insulins; some trials had unequal amounts of education in the arms (with more in the pump arms); and the trials had focused on easily measurable outcomes, such as HbA_{1c}, rather than on benefits in terms of flexibility of lifestyle and QoL. The report recommended trials of pumps against analogue-based MDI. A more recent report⁹ found only three trials in adults: one a pilot and the second involving 39 adults with T1DM, already on pump therapy, who were randomised to stay on pump therapy or to switch to glargine-based MDI; patients had 4 months on each form of treatment. A third trial recruited 57 adults who were randomised to pump or analogue MDI in an equivalence study. None showed any difference in HbA_{1c}. Thus, the evidence base from trials for comparing pumps and 'best MDI' was weak in terms of numbers, with a total of only 103 patients and short follow-up. (This paragraph is reproduced from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.)

The literature on the cost-effectiveness of insulin pump therapy has solely been based on comparisons of insulin pump therapy to MDI rather than 'optimised MDI'. A recent systematic review on the cost-effectiveness of pump therapy in different countries identified four studies that were conducted in a UK setting, three of which presented an ICER.¹⁹ The base-case ICERs in these studies ranged from £37,712 to £11,461 per QALY gained. These ICERs are much lower than those estimated in the analyses based on the REPOSE Trial data. However, the ability of these studies to determine the cost-effectiveness of insulin pump therapy as a treatment for all adults with suboptimally controlled T1DM is limited, as the effectiveness used in these analyses does not compare insulin pump therapy to 'best MDI'. Hence, the REPOSE health economic study is the first known evaluation of insulin pumps in the type of individuals enrolled in the REPOSE Trial.

There is limited evidence on the increases in HbA_{1c} that adults with T1DM may experience beyond the trial period. Much of the existing evidence is based on observational studies of adults with T1DM, who received either best-practice MDI or insulin pump therapy. None of these long-term observational studies made a comparison between those adults with T1DM who received MDI and those who received insulin pump therapy. The applicability of this evidence to the individuals in the REPOSE Trial may be limited, especially as, by design, we excluded patients with a clinical indication for a pump as recommended by NICE.¹³ Thus, information presented in the observational studies is probably the best available evidence to inform long-term trends in HbA_{1c} for the economic modelling.

The advantage of the observational studies of adults switching to pumps for clinical indications lies in measuring change in glycaemic control and hypoglycaemia in those who have most to gain. These studies showed improved HbA_{1c} of the order of around 0.5%. Bias in observational studies is more of a problem and results must be treated with caution.²³ Furthermore, of 48 observational studies, only nine reported QoL. Study numbers were small, with, at most, 35 patients, and duration was usually short, often ≤ 6 months. The longest study noted that initial benefits from pump therapy might not be sustained. The REPOSE Trial has thus addressed a number of these concerns, with large numbers in an adequately powered trial and a virtually complete data set for both biomedical and psychological outcomes.²³

Discussion of results

Our study suggests that extending the availability of pumps to adults with T1DM with suboptimal glycaemic control and no firm desire to use this form of insulin delivery is unlikely to result either in lower levels of glycaemia as measured by HbA_{1c} or lower rates of hypoglycaemia, or be cost-effective. The results would appear to support the current clinical pathway as proposed by NICE,¹⁸ in which people desiring improved diabetes control should undertake structured education in flexible insulin therapy with MDI alone.²³

Clearly some patients improved more than others in terms of glucose control or hypoglycaemia and we explored whether or not there were any demographic differences in those who did particularly well. There was no reliable evidence of any plausible subgroup effects or interactions between the pump and MDI group, and the baseline characteristics of those whose glycaemic control improved to < 7.5% during the trial were no different from the pump population as a whole. (This text, from 'Clearly' to 'whole', is reproduced from The REPOSE Study Group 2017.²³ This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.) Those using insulin pumps did show some QoL benefits, reporting fewer restrictions in diet and daily hassles in the DSQOL, and greater treatment satisfaction. Nevertheless, the differences were modest and observed in comparison to a group given no novel technology. As they were not associated with other positive treatment outcomes, they are probably insufficient to justify a major alteration in guidelines for the use of pumps.²³

One of the more striking results of this trial was the generally high level of HbA_{1c} among adults in the UK enrolling for self-management training in flexible insulin therapy. Participation in the courses produced significant and sustained improvement, but still fell well short of the target recommended by NICE, recently reduced from 7.5% to 6.5%.¹⁵⁹ There is an urgent need to explore the barriers to successful self-management in adults with T1DM in the UK and understand why referral for appropriate training is often left so long. This was also the conclusion of our recently completed research programme, funded by NIHR.²⁷ The results of the REPOSE Trial show that these problems cannot be overcome merely by providing additional technology in the form of pumps.²³

The possible lack of engagement among some individuals assigned to pump therapy may also explain the increased numbers of episodes of DKA in those randomised to insulin pumps. In the earliest trials of insulin pumps in the 1980s, rates of DKA were also raised among those who had agreed to try a pump when offered. A psychological analysis, undertaken at the time, suggested that those who experienced DKA expressed less personal responsibility for their care. Importantly, in the REPOSE Trial, both MDI and pump courses included instruction in 'sick day rules', designed to prevent the development of DKA in the case of illness. Pump courses also included specific guidance in dealing with an interruption of the insulin infusion, although there was no guarantee that participants would follow these.

A detailed review of DKA cases indicated that:

- more patients on pumps had multiple episodes (five vs. two)
- differences were confined to the first year; there were comparable numbers of episodes (four in each group) during year 2
- three episodes occurred in two patients switching to pump and one in a single person switching to MDI
- most DKA episodes were due to infections; in pump patients, 18% were due to 'set failure'
- only five episodes occurred when all sick day rules were implemented.

Implications for health care

The NICE Type 1 diabetes guideline¹⁵⁹ states:

1.3.1 Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis.

1.3.2 If a structured education programme has not been undertaken by an adult with type 1 diabetes by 12 months after diagnosis, offer it at any time that is clinically appropriate and suitable for the person, regardless of duration of type 1 diabetes.

The REPOSE Trial provided DAFNE to both arms, and we observed significant improvements in both arms, which persisted for the 24 months of the study. The improvements were both in glycaemic control, as reflected by HbA_{1c}, falls in severe hypoglycaemia and measures of QoL, providing support for NICE recommendation 1.3.1.

We found no relationship between duration of diabetes and benefit from DAFNE, which supports NICE recommendation 1.3.2 – that all patients should be offered structured education.

The recent update of the T1DM guideline recommends that people be supported to aim for a tight target of glycaemic control in recommendation 1.6.6¹⁵⁹ [6.5% (48 mmol/mol)], which is lower than the treatment target of 7.5% set when the REPOSE Trial was being run. Despite recent evidence dissociating lower HbA_{1c} in T1DM from increasing severe hypoglycaemia rates, fear of hypoglycaemia remains a barrier. The combination of recommendations 1.6.6 and 1.6.8 will be challenging, and is likely to require an increase in the use of insulin pumps as approved under the current NICE technology appraisal guidance.¹³ However, we would point out that DAFNE structured training also reduces rates of severe hypoglycaemia.

The REPOSE Trial excluded patients who met the NICE criteria for a pump. We also excluded patients who had a strong desire to use an insulin pump. Therefore the results of REPOSE are not relevant to the recommendations of TA151,¹³ they apply to a group of patients with a lower level of need.

The results of the REPOSE Trial showed improvements in both arms. The pump group showed slightly greater improvements than the MDI arm, but most of the differences were not statistically significant, and the difference in HbA_{1c} did not reach a clinically meaningful level. Our cost-effectiveness analysis shows that in the type of patients in REPOSE, pumps will not be cost-effective.

It is important to note that the REPOSE Trial may be reported as a 'negative trial' of pumps, but the failure to show a significant benefit of pump over MDI was because both groups improved following DAFNE training. The results indicate that, in adults with high levels of HbA_{1c}, training them to self-manage their diabetes with structured training programmes is more useful than providing them with insulin pumps.

Implications for the National Institute for Health and Care Excellence

The implications for NICE guidelines and guidance are:

1. The guideline on the importance of providing structured training programmes is reinforced. Considerable evidence has been found for the effectiveness (and cost-effectiveness) of offering evidence-based structured education to individuals with T1DM.
2. There are no implications for TA151 on insulin pumps. The REPOSE Trial results do not apply to the patient groups to which TA151 refers.

Future research needs

There remains a clinical and economic need to improve the glycaemic control of adults with suboptimally controlled T1DM. The results in the UK, for example in terms of proportions of people reaching HbA_{1c} targets, are poorer than in some other European countries. We need to explore the differences in clinical practice and patient behaviour that underlie these differences. The DAFNEplus programme of research is

aiming to develop and evaluate the current DAFNE course (based on previous research, behaviour change theory and technological support). This programme is not expected to report until September 2021.

In both arms of the REPOSE Trial there were marked variations in HbA_{1c}, with some people showing marked improvement and others showing deterioration. Further research is needed to explain why some people do so well, whereas others do not.

We found no relationship between duration and benefit from structured education. This raises a question as to why patients who have been attending diabetic clinics for many years – even decades – have not been offered structured training in diabetes self-management.

More extensive qualitative research should be considered to:

1. explore the issues that influence patients' use and rejection of technologies, such as insulin pumps and CGM
2. examine patients' perspectives on both the impact of withdrawal of technology (e.g. pumps and CGM), both at the end of trials and in clinical practice when they are deemed not to meet NICE criteria
3. compare the views of both professionals and patients in other European countries that appear to achieve far better glucose control.

The Cochrane review of pumps by Misso *et al.*³¹ is now well out of date and should be replaced by an up-to-date, but much more focused, review of pump versus analogue MDI, which would include the REPOSE Trial.

Conclusions

In conclusion, people with T1DM might be better served by ensuring far greater availability of high-quality, structured self-management training, which is currently accessed by < 10% of adults with T1DM in the UK.¹⁶⁰ Participants may recognise the limitations of insulin delivery by MDI only once they are attempting to maintain flexible intensive insulin therapy following training. Those individuals could then be offered pump therapy to help them reach the stringent glucose targets that are necessary to achieve an optimal HbA_{1c} or overcome problematic hypoglycaemia.²³

Chapter 9 The challenges of closing out a clinical trial after which treatments may be withdrawn: qualitative study of staff involved in closeout of the REPOSE Trial

Background

Clinical trials are considered the 'gold standard' method for assessing the efficacy and safety of pharmaceutical treatments and other health-care interventions. It is common practice for qualitative research to be undertaken with patients and staff who are involved in clinical trials.^{161,162} This research usually takes place during a trial's pilot or early phases to improve recruitment, patients' understanding of trial processes and the solicitation of informed consent.^{163–168} Qualitative research has also been undertaken during trial delivery to explore adherence to trial protocols and treatments, and aid interpretation of trial findings.^{169,170} Although the closeout of a trial potentially presents challenges for both patients and health professionals, especially when patients may be required to stop using the treatment(s) under investigation, this aspect of trial participation and delivery remains surprisingly under-researched. The limited work undertaken to date suggests that patients may experience a form of trial bereavement on closeout,¹⁷¹ and some may wish to continue using trial treatment(s) despite the trial failing to show clinical benefit.¹⁷² How staff address closeout issues with patients, and what their own information and support needs are, remain unknown.

Closing out REPOSE

Recruitment to the REPOSE study commenced in November 2011 and the first trial centre began to close out patients [i.e. commenced 2-year (final) follow-up appointments] in April 2014, with the final centre closeout appointment in June 2015. The insulin pumps used during the REPOSE study were provided free of charge by Medtronic, with a warranty that covered only the trial's 2-year duration. After extensive negotiations, pump consumables were funded at a local or national level (e.g. by the DH, Chief Scientist Office or a primary care trust) for the duration of the trial and on the understanding that pump therapy would be withdrawn post trial unless a clinical benefit could be demonstrated for individual patients and local funding provided. This was communicated to potential trial participants in the patient information sheet for the trial (see *Appendix 8*). On closeout, each REPOSE centre was advised (as per the trial's SOP for closeout; see *Appendix 15*) to make their own clinical decisions about which patients should remain on a pump and who should revert to a MDI regimen, with centres having to find local funding for patients who remained on pump therapy.⁸⁶ It was also agreed (as formalised in the SOP) that the patients would not be told whether or not they would keep their pump until after their data had been collected at the final 2-year appointment because of concerns that this knowledge might influence how they completed their questionnaires.

Early reports from trial staff and ongoing review of trial data indicated a large variation in closeout practices between the REPOSE centres (listed in *Table 11*). Although, in some centres, most or all patients remained on pump therapy, in others, the majority of patients had pump therapy withdrawn and were reverted to a MDI regimen. Early anecdotal reports from staff also indicated that patients' emotional reactions to withdrawal of pump therapy were variable, with some presenting major challenges to staff. Specifically, some staff expressed concerns about the lack of guidelines, procedures and support structures for themselves to manage and support patients effectively at closeout when withdrawing pump therapy. In light of these reports, it was decided to systematically evaluate staff experiences of closeout to generate insights and recommendations to support the conduct and closeout of future trials, especially those where

an expensive health technology is being tested that may be withdrawn at the end of the trial period. A case was made to the funder to undertake this additional piece of qualitative work using some underspend within the grant. Approval from the funder for this substudy was given on 13 April 2015.

Aims

This qualitative study drew on the experiences, understandings and views of health professionals who were involved in closeout of the REPOSE Trial in order to:

- better understand variations in practices between trial centres on closeout and establish whether or not, and to what extent, these arise from local clinical guidelines and practices, individual physician/health professional beliefs and/or other factors and considerations
- inform guidance and support for staff involved in the closeout of future clinical trials, particularly those in which investigated treatment(s)/device(s) may be withdrawn.

Research questions

1. What are health professionals' experiences of closing out the REPOSE Trial? What (if any) practical/ethical/other issues arose for staff, and how did they attempt to address these?
2. What factors and considerations informed health professionals' decisions to continue or discontinue pump treatment in individual patients?
3. What processes and procedures do staff think should be put in place to support patients and staff involved in the closeout of future clinical trials, especially those where expensive health technologies are being investigated and may be withdrawn?

Overview

The qualitative work was completed to plan and on schedule, enabling a comprehensive investigation of staff members' experiences of closeout in the seven main REPOSE centres. Although it had originally also been our intention to include patients' views, we were unable to involve this group because of the limited time available to gain NHS research ethics and R&D approvals at the REPOSE centres, and undertake the data collection and analysis. One journal article has been accepted for publication, which reports key findings from the following analysis (Lawton *et al.*¹⁷³).

Study design and methods

In-depth interviews were used to collect data about staff experiences of study closeout, as these afforded the flexibility needed for participants to raise and discuss issues that they perceived as being salient, including those unforeseen at the study's outset.^{142,174} The use of one-to-one interviews also afforded privacy, allowing participants to share their views about the processes and procedures for closeout at their study centre. The study was informed by the principles of Grounded Theory¹⁴⁰ and entailed simultaneous data collection; this allowed the areas explored in the later interviews to be revised in light of emerging findings.

Recruitment and sample

Working closely with the CTRU to identify relevant individuals, we targeted all staff members (physicians, diabetes specialist nurses and dietitians) in the REPOSE centres, who were thought to have been actively involved in closeout appointments. Staff were recruited from seven of the eight participating centres. The eighth centre was not included because it was a reserve centre that was added at the end of the trial to deliver two courses only, and this centre had only one patient using a pump at the end of the trial.

Staff were recruited via written (e-mail) invitations accompanied by information sheets and opt-in forms. When staff had opted in, NH contacted them to arrange an interview.

Data collection and analysis

The University of Edinburgh's Centre for Population Health Sciences, Ethics Review Group granted ethics approval for this study in June 2015. The interviews took place between June and August 2015. Participants were offered the choice of a telephone or face-to-face interview at a time/place most convenient to them; only six (29%) staff members requested a face-to-face interview.

Interviews were informed by a topic guide that was developed in light of literature reviews and findings from qualitative research conducted earlier in the trial,^{147,155} and were revised in light of emergent findings from the early interviews. The final version of the topic guide is appended to this final report (see *Appendix 16*). Interviews lasted for ≈60–90 minutes. The key areas in the topic guide were covered and explored in depth in all interviews. Interviews were digitally recorded (with consent) and transcribed in full for in-depth analysis. By the time recruitment and interviewing had stopped, data saturation had been achieved, that is, no new findings or themes were identified in new data collected.

The interviews were analysed thematically by NH and JL using the method of constant comparison.¹⁴⁸ Individual interviews were read through repeatedly to look at differences and similarities in individuals' perspectives and experiences before being cross-compared to identify common issues and experiences across and within study centres. NH and JL wrote separate reports before meeting (both during and after data collection) to discuss and reach agreement on key themes, identify emerging findings requiring more detailed exploration and develop a coding frame. The qualitative analysis software package NVivo10 (QSR International, Warrington, UK) was used to facilitate data coding and retrieval. Coded data sets were subjected to further, in-depth analysis to identify subthemes and illustrative quotations.

The findings presented below are structured under our original research questions. To safeguard participants' confidentiality, pseudonyms for individuals, Dr X (diabetes specialist) or EDX (DAFNE educator – diabetes specialist nurse/dietitian), and centres (A–G) are used throughout this report, and all identifying information has been removed or deliberately altered.

Findings

Participants

Twenty-four staff members were invited to participate. In one case a staff member said that they had no direct experience of closeout/end-of-trial consultations. Two others opted in, but an interview could not be arranged at a convenient time, hence 21 (87.5%) staff members were interviewed. Full details of the final sample are provided in *Appendix 17*.

As can be seen from *Appendix 17*, we achieved good representation of different types of staff: clinical diabetes specialists, diabetes specialist nurses and dietitians. Between two and five (mode three) members of staff were interviewed at each centre. With the exception of centre A, at least one DAFNE educator and one diabetes specialist was interviewed from each centre.

Staff experience of delivering DAFNE varied from 5 to 17 years (mean 10 years). There was also variability with regard to individuals' experience of pump therapy, ranging from 2 to 37 years (mean 10 years). It should be noted that the majority of staff interviewed at centres D and E had relatively little experience of pump therapy prior to delivering REPOSE. Although many staff had previous experiences of working on clinical trials, few had been involved with studies that had required new technologies to be withdrawn at the end of the trial. The main exceptions were those staff members ($n = 5$) who belonged to the three study centres that had been involved in the delivery of a DAFNE pump pilot study. This 12-month study²⁷ – 6 months' recruitment and 6 months' follow-up – had taken place between 2009 and 2010.

In order to understand staff members' experiences of closing out REPOSE, it is necessary to provide an account of what happened at the end of the trial in the various centres. Thus, prior to answering the research questions, we will describe the variations in closeout practices that staff described in the different centres.

Background: closeout practices in REPOSE centres

As noted above, the CTRU issued a SOP for closeout (see *Appendix 15*), which outlined what was to happen up to the point at which all trial procedures were completed (i.e. final blood samples were taken, QoL measures collected and data from the pump downloaded). What happened to trial participants afterwards – whether or not they remained on MDI/pump, whether or not they had pump therapy withdrawn or initiated – was a clinical decision, taken by staff at the individual centres. In other words, the decision to leave patients on, start or terminate pump therapy was not a trial decision. However, many of the staff involved in delivering REPOSE experienced these post-trial treatment decisions and, more specifically, patients' reactions to them, as part of their trial experience. Thus, for the purpose of this chapter, we will talk about post-trial treatment decisions as part of the closeout process because this is how the staff perceived and interpreted them.

To ensure that resources (i.e. pumps) were allocated appropriately and fairly at the end of the trial, most centres put site-specific procedures in place for closeout (i.e. what would occur after the final downloads had been logged). Some centres adopted very formalised operational procedures for decision-making about post-trial treatment. In these centres, decisions about individual participants were made at a multidisciplinary team (MDT) meeting, involving all of the research team and other staff members, and which took place a couple of weeks before the closeout of each of the groups. The MDTs' decisions were governed by strict NICE/Scottish Intercollegiate Guidelines Network (SIGN) criteria (see *Research question 2*) and (normally) documented. Each patient then attended a post-trial consultation with a clinician/educator after the final data collection session to discuss his/her treatment plan.

Other centres took a less formal approach to closing out their patients. Dr H described what happened in one such centre (centre B):

I guess it wasn't a formal MDT. But yeah it was just a chat with the educators and myself about each individual patient as they were coming up for the end of the study, about who/what the best way forward was for them.

In some of these centres, the whole research team met in advance of the post-trial appointments to discuss what might happen in individual cases; in others, the educators briefly spoke to the clinician after the patient had provided their final download and before they went in for their post-trial consultation. In these centres, although some, or all, trial team members had some input into post-trial treatment decisions, it was individual clinicians who made the final decision during the post-trial consultation, often taking the patient's views into account:

We started a fairly neutral conversation about how it been and what would they want to do if the option were that they could keep it. And then if they said well you know, they'd really like to stay on pump therapy then I said 'OK, well you know, let's have a look at how you've got on with it' and obviously I'd got a feel for that already. So before they came in [educator] and I sat down and looked through and looked at how they'd got on, and what had happened to hypoglycaemia frequency, what had happened to HbA_{1c} and then obviously they came through and told us how they felt in terms of, the impact on quality of life and things.

Dr G

In all of the centres, the clinical appointment to discuss post-trial treatment occurred after the final appointment to collect trial data. In some cases, patients were seen on the same day on which they came in for their final trial appointment; in others, this clinical appointment occurred a couple of weeks later.

Research question 1

- What are health professionals' experiences of closing out the REPOSE Trial? What (if any) practical/ethical/other issues arose for staff and how did they attempt to address these?

What are health professionals' experiences of closing out the REPOSE Trial?

Staff who had been involved in follow-up appointments during the trial, primarily the educators, said that they had become increasingly aware that withdrawal of pump therapy at closeout/the end of the trial would be difficult. This was a result of their observations (see ED7 below) that patients were becoming increasingly emotionally attached to their pumps as the trial progressed, an issue which became particularly apparent from the 12-month follow-up appointment onwards.

... at the kind of the routine REPOSE follow-ups when we asked them how they were feeling about the pump, they all reported that they loved the pump, that they felt it was making their life so much easier, and that they couldn't imagine going back to having to inject multiple times a day... So they were all very vocal that they really wanted to stay on their pump. And that they would be prepared to fight for it, if needs be.

ED7

For this reason, some staff reported worries and concerns about how patients might react to the withdrawal of the pump at the end of the trial: 'I knew it was going to be difficult and I wasn't looking forward to it' (ED11).

Dealing with stressful situations

The ways staff experienced these post-trial consultations varied, and was related to whether or not patients were able to remain on their preferred therapy and, as will be described later [see *What (if any) practical/ethical/other issues arose for staff and how did they attempt to address these?*], whether or not staff had put pre-emptive measures in place to manage and prevent problems arising from the withdrawal of pump therapy. In some cases, when patients who wanted to remain on a pump were told they would have to revert to MDI, staff members, including Dr C, described situations that had been stressful and difficult to manage because patients had become upset and/or angry:

I had trouble in the course, because one lady when she came to the end of her trial, her HbA_{1c} was appalling. I mean it was appalling. There was no way you could justify leaving her on pump, because she was getting no benefit from it biomedically. What she needed was a complete change in how she managed her life. And she was very upset to have the pump removed. But what was fascinating was she did not say that at the closeout interview... Next thing I know she's written streams of letters of complaints to all and everybody, because we removed the pump from her, and refused to give her any supplies after 3 months.

Dr C

Later in the interview, Dr C reflected on how this and other similar experiences had '... kind of tainted the whole study for me, because it was really quite difficult for a little while. It was very uncomfortable'. Dr B reported a similarly stressful encounter with a patient:

The one locally that really didn't go well, was a gentleman whose control had got worse on the pump. And I was explaining that in fact on balance it was actually more dangerous for him to remain on pump. And he was the one that walked out. He didn't shout or give me any indication. He just stood up and said 'OK' and walked out.

Dr B

Like Dr C, Dr B had been taken aback by this experience: they had been ill prepared for it, primarily because, like the other clinicians in the study, they had been less involved in the trial follow-up visits, which had been mainly carried out by educators.

Smooth transitions

However, the withdrawal of pump therapy was not always experienced as generating such negative reactions; indeed, a small group of patients, across the centres, were described as having been 'happy' to revert to MDI, with some requesting this transition at the end of the trial. Moreover, in another centre (centre A) at which pump therapy had been withdrawn from the majority of patients, staff said that closeout had been relatively straightforward and non-confrontational. As will be described further later [see *What (if any) practical/ethical/other issues arose for staff and how did they attempt to address these?*], this appeared to be due to staff having put procedures in place to pre-empt, prevent and manage disappointment among those patients.

In approximately half of the centres, patients received the treatment that they wanted at the end of the trial, and closeout, as a result, was experienced as raising few issues for staff. This was particularly the case in Scottish centres where, in 2012, the Scottish Government had made funding available for pump therapy, with a target of $\approx 5\%$ of patients with T1DM to be using pump therapy between 2013 and 2015. As Dr E reflected, because of the Scottish Government's largesse, closeout was very straightforward in that centre because the majority of patients were able to remain on pump therapy if they wished to do so:

Our closeout has probably been less complex than most places. And that's because of this impetus to increase the number of people with pumps . . . Happily for us, because the timing was just perfect, so that the end of the trial was within this expansion up, we were actually able to fairly straightforwardly continue with pumps on a routine NHS way for all of the patients who wished to.

Dr E

ED3, from another resource-rich centre, similarly said 'I think it [closeout] went well. There was nothing certainly from our side in [site D]. I don't think there were any issues for us'.

Staff at the Scottish centres did comment that, had government funding not been put in place during the trial, closeout would have been more challenging and problematic:

Well I guess we would have been in the same situation as other centres where there was no funding stream to continue patients. And we would have had to say: 'sorry. We don't have any money for you to continue on this'. And I think it would be very difficult. I mean obviously I would imagine in other places it's caused a bit of damage to the doctor or health-care professional relationship . . . I guess people having invested a lot of time in it over the course of the study you'd feel a bit let down if somebody's told that there's no money. Sorry, give it back.

Dr H

Although staff at such centres did not generally have to manage patients' reactions to the withdrawal of the pump, they did have other issues with which to contend. First, as Dr E noted, they had problems providing timely training for all MDI patients who were offered, and accepted, pump therapy at the end of the trial: 'Most of our control patients were really quite keen to go on pumps, afterwards. And the, you know, there's a degree of work just dealing with that'. Second, even though patients usually received the therapy they wanted after closeout, the staff said they still had to reassure and 'calm down' patients when they came in for their final downloads because they were anxious about losing their pumps:

On the day of their final visit I think they were all extremely heightened, they were very worried I think most of the patients who came in. We kind of had to almost calm folk down a little bit. We had quite a few who were walking in the door at that final visit very, very scared because they knew it was the end of the trial and they didn't know what was going to happen now.

ED6

As ED6 commented, dealing with patients' anxiety throughout the trial was particularly difficult in their centre, as although staff realised that most people would have their pump therapy funded after the trial, they still had to follow the trial SOP, which required staff to be more circumspect when patients asked about post-trial treatment during follow-up visits.

Differences of opinion within multidisciplinary teams

Finally, with regard to their closeout experiences, some staff indicated a lack of consensus within some research teams regarding the decision to keep particular individuals on pump therapy at the end of the trial:

And I think there was a difference in how some of the team viewed it as well, in that some seemed to say: well, it's a trial for 2 years. And then they come off the pump and we see how they do. And then we may put them back on the pump. Whereas others are saying: well no there's been significant improvement, So we'll keep them on the pump. So I had kind of extremes.

ED12

I think others (in our site) were much more, I . . . I think that they thought that they were going to stick to the letter of the law and they'd take pumps away and that would be tricky . . . but then that's their individual practice it's not for me to tell colleagues particularly consultants how they should practice, and the practice is very different it's such a personal thing.

Dr A

This particularly applied to those centres that had adopted less formalised closeout procedures, specifically where final decisions were taken by clinicians alone. In such centres, not only were disparities in decision-making between different team members noted, but also some team members described having not always agreed with their colleagues' decision to keep individual patients on pump therapy. Several staff commented that they were not always convinced that patients were benefiting over and above what could be achieved using a MDI regimen and DAFNE education. Indeed, some such staff indicated that they would rather have used stricter guidelines for pump allocation at the end of the trial to ensure that NHS resources were distributed in a fair and transparent way in their centre (see *Research question 3*).

In summary, the interviews confirmed differences in staff experiences of closeout across the study centres. First, in centres at which pump therapy was routinely withdrawn from all but a few patients, staff had needed to manage some of the patients' negative emotional reactions and some had felt ill prepared for this experience. Second, there was evidence that some centres had managed patient expectations about post-trial treatment more successfully than others, thereby pre-empting patients' disappointment at having pump therapy withdrawn (see *Research question 2*). Finally, in centres where ample funding for pump therapy was available, the issues arising at trial closeout focused on calming anxious patients before final data collection and providing timely training for MDI patients commencing pump therapy.

What (if any) practical/ethical/other issues arose for staff and how did they attempt to address these?

Staff identified a couple of issues that may have affected their own and patients' experience of the trial and closeout; these included the length of the trial and the ethical challenges arising from withdrawal of the pump. Although some of these issues had been identified and addressed prior to, or during, the main trial, others emerged only during the interviews, as staff reflected upon their trial experiences.

Length of trial

Some staff, as already indicated, reported that they did not really start picking up on patients' anxiety about the removal of pump therapy until they attended their 12-month follow-up. Thus, the length of the trial, or, specifically the length of time spent on pump therapy, was identified as an issue by a number of staff who questioned that this may have affected patients' emotional reactions at closeout:

I have been involved with trials where the treatment has been withdrawn, but it's been a shorter period of time. I think 2 years is quite a long time and people get very used to things, don't they. And then they do start to think that the pump's theirs. So I think that's more difficult. When I've been involved with other trials of equipment it's been more like a few weeks, 6 weeks or something like that. And so patients are very aware that it's just for that trial period.

ED11

Although ED11, like others, saw the length of time spent on the pump as affecting patients' reactions at closeout, ED1 regarded the trial's relatively long duration as indirectly influencing some of clinicians' decisions to continue pump therapy for certain individuals in their centre:

The REPOSE SOP for the end of the study was based on what we did for the pilot. And the only thing I could say, I hadn't really thought about that until just this morning. And whether there was something to do with the length of the trial, the duration, which made it more difficult to make that decision [to remove pump therapy] at the end.

ED1

Learning from experience gained during the pilot study

Three of the centres in the main trial had been involved in the pilot,²⁷ and staff who had taken part in the pilot talked about how these earlier experiences had influenced the ways that they approached the main trial. These staff described how they had entered the trial with some, but perhaps not enough, awareness that terminating pump therapy at closeout might be problematic, and how this had led them to putting some pre-emptive measures in place to prepare patients for removal of their pumps:

When we did the pilot . . . some people were really devastated that they couldn't keep the pump, even though we told them. So we were much clearer we think, this time round with: you're not, you know – although everything was signed – with the fact that they needed to give the pump back. And I think we were before. But I think we just reiterated it throughout the process more.

ED10

Indeed, in one such centre (centre A) staff designed a clear formal protocol for ending the trial, which not only set out criteria for who was to stay on pump therapy (see *Research question 2*), but also helped them to manage patients' expectations throughout the trial and their emotions at closeout. This centre had reverted the majority of patients to MDI at closeout and they had followed strict procedures for this including explaining why pumps were being removed, what removal meant and how reversion to MDI might be a temporary state of affairs, which could be revisited in the future. This centre also provided patients with spare consumables so that they could continue to use their pumps in the immediate short term before reverting to MDI at a convenient time, thereby giving them a chance to adjust psychologically and practically to the transition. These strategies appeared to work, for although this centre had withdrawn pump therapy from most patients, the staff reported that this had gone reasonably smoothly:

So that we didn't switch them there and then on that 24-month visit. We reminded them, we had a few people were quite upset and grumpy about it. And we said: look, how can we? We have some kit we can give you that can tide you over for another month or 6 weeks, while we sort out your pens and getting you back – to switch you back onto MDI and doing it in a supportive as way as possible. We didn't rip the pump off them at that appointment and say: there's your pens back, off you go. And so having that discussion at the meetings [MDT] before for all of them just helped us come up with a kind of individual plan to sort of, damage limitation really.

ED14

Leaving the door open to revisit patients' eligibility for a pump

Although centre A was the only centre to consistently allow patients a lead-in period to revert back to MDI, staff in other centres described how they had tried to manage anxiety and disappointment by making patients aware that they could make a case for them to have the pump reinstated in the future if they struggled to manage their diabetes using DAFNE + MDI:

And we did say to him, as we said to others. This is does not mean that pump therapy is completely closed to you. You know, what you need to do now is go back on injections, really apply DAFNE. You know, monitor, keep records, make adjustments, and you know, down the line, if you're still not managing to achieve an HbA_{1c} or you're getting hypos, then we can consider a pump again. But you need to put the work in.

ED1

Staff in all of the centres, but especially those in pilot centres, also talked about how they had tried to manage patients' expectations about closeout throughout the trial, particularly the likelihood that they may not continue on the pump:

Cause we did – had done the pilot as well we'd sort of expected – we knew what to expect, cause you know, we'd done the pilot before REPOSE. So we'd been involved and the same sort of thing had happened: people you know, of course if they liked the pump, they like the pump and want to keep it. So it was really about just reminding people of the rules and we tried to do that each time we met them as well, just to remind them that this was about the trial, this was about seeing if the pump was effective and if they didn't meet NICE criteria the pump would go back. So we tried to talk about that at each meeting time as well, not just leave it to the end.

ED11

In a couple of centres, in addition to raising the issue of withdrawal of the pump during trial visits, patients in the pump arm were given encouragement several weeks before closeout to use the remaining period of the trial to demonstrate that they could use their pumps more effectively by the time of their final download or, as Dr H described, to prepare patients for closeout and ease their disappointment if a clinical benefit could not be evidenced:

I think we just felt better that we'd given them the opportunity. You know if you're pre-warned that there's going to be an exam[ination] result in another 3 months kind of thing, then if you don't do so well in it, you think: oh well, at least they told me kind of thing. I think we were just thinking that a warning shot is quite a good idea. And might make the that's all, no you can't have a pump any more discussions easier.

Dr H

The ethical challenges of withdrawing pump therapy

For some staff closing out the REPOSE Trial was seen as throwing up distinctive ethical challenges not only because the patients had time to get used to pump treatment, but also because of the nature of the treatments involved. As Dr H noted, unlike drug trials through which treatments might be replaced by seemingly similar forms of therapy, REPOSE required the withdrawn treatment to be replaced by a very different therapeutic option, which, as they noted, may be seen by some patients as not really an option at all:

I mean it doesn't really have parallels to other studies. I mean I guess if you're on a new tablet for x, y or z at the end of the study you might not be able to continue it, but there's usually an alternative. And it's you know tablet versus tablet instead of you know, pump versus another way of giving insulin which is very different . . . as I say it's not like this is trying one pump versus another pump, and you at the end of the study you go back to the old pump. But you take away the new fancy one. This is like something, getting something versus getting nothing.

Dr H

Dr A raised further ethical issues regarding the withdrawal of pump therapy. This clinician, like others, argued that if individuals were benefiting, or even perceived themselves as benefiting, in ways that went beyond the clinical criteria outlined in the NICE/SIGN guidelines then it would not be right to remove pump therapy at the end of the trial period, not least because these individuals had given their time to take part in a research project. In other words, as long as patients were using their pump safely then they had the right to keep it after the trial had finished:

Just because we're doing a research project doesn't mean you don't continue to have a therapeutic relationship with people and I mean you can call me a softy, but I think we owe it to our patients who participate in research to do the best by them, and as I said at the beginning you can get a pump for anybody if you want, and I just think making a judgement that they don't benefit therefore they should stop. If they think they're benefiting, then I'm not comfortable saying I know better than you.

Dr A

Dr A, like others, also stressed that removing pump therapy at the end of the trial could potentially undermine an ongoing therapeutic relationship with a patient – especially as was the case for this doctor, when health professionals delivering the trial were also responsible for providing patients' routine diabetes care.

Although Dr A was based in a centre at which access to funding for pump therapy was limited and some patients had pump therapy removed at the end of REPOSE, ED5's centre, in contrast, had plenty of funding available and the majority of patients had stayed on the pump following closeout. ED5, however, was acutely aware of the different funding situations across the trial centres and commented that the removal of pump therapy at the end of the trial in some centres and not others was just further evidence of the existence of what they regarded as an unethical 'postcode lottery':

That's the state of the NHS that really at the end of the day if the patient's benefiting then I feel it's quite sad that someone can remove something from someone that they're benefiting from. And I think that it just highlights in the NHS a bit of a postcode lottery really regarding pumps, and that hopefully in the future that's going to be more standardised. Because your care really wherever you are should be equitable.

ED5

In summary, staff in all of the centres anticipated that closeout and the withdrawal of pump therapy might be an issue for patients and, hence, had developed a range of potential solutions to address these, including developing strict protocols for managing expectations and emotions, and reminding patients that pump therapy was a research intervention whenever they attended trial visits. In addition, staff identified a couple of ethical issues, such as the problem of withdrawing treatment from patients who perceived themselves as benefiting from it, potentially compromising an ongoing therapeutic relationship, and the inequity of the postcode lottery for funding treatments in the UK.

Research question 2

- What factors and considerations informed health professionals' decisions to continue or discontinue pump treatment in individual patients?

Variability between centres

The number of patients staying on pumps after closeout varied markedly between centres and, as noted in *Research question 1*, it was clear that the staff in the different centres, including ED10, were aware of this:

ED10: And there are always going to be clinical judgement and exceptions. But it feels a bit like people [sites] have done things slightly differently at the end.

I: What did you do at the end?

ED10: We said to everybody, you have to give it back.

Ultimately, it was the availability of resources, specifically the availability of funding to keep/move patients on to pumps in routine clinical practice, which determined what happened to individual patients at the end of the trial. In centres E, B, D and F, for which generous funding was available, the majority of REPOSE patients stayed on/commenced pump therapy if they wanted to:

So we were very fortunate in that sort of financially there wasn't going to be any problem here about asking patients for the pump back at the end of the study. It was agreed that it would be daft to do that and then restart them again on a pump 3 months later or something. So although the patients didn't know and obviously we wouldn't say to them, because that wasn't, that wouldn't have been good. You know within the group it was realised that there was a sort of secure funding stream to continue those that were benefiting from the pumps at the end of the study.

Dr H

In centres A, C and G, for which funding was scarce, staff were acutely aware that pump therapy needed to be rationed and restricted to those patients who demonstrated a clinical need or benefit, independent of the patient's wishes:

[Dr] was quite cut and dried about it. Unless there was a medical reason or unless they met NICE [criteria] already from a hypo[glycaemia] point of view they had to come off. And you know if there was any, you know, trouble, they would come down and talk to the patient themselves if necessary.

ED14

Different interpretations of National Institute for Health and Care Excellence/ Scottish Intercollegiate Guidelines Network criteria

The interviews suggested that staff in resource-rich and resource-limited centres tended to use different criteria when making decisions about individual patient's post-trial therapy. Two resource-limited centres adopted very strict criteria for allocating pump therapy at the end of the trial so that, in general, only those patients with a clinical need who met NICE/SIGN criteria,^{13,175} as tightly defined (namely, HbA_{1c} > 8.5%, attempts to reach target with MDI resulting in disabling hypoglycaemia), continued using pump therapy following closeout. The remaining patients in these centres were informed that they would revert to MDI:

My view was that if they had shown significant benefit in terms of HbA_{1c} and, and/or reduction in hypoglycaemia frequency, then we would continue them on pump therapy. And that's effectively what we did . . . they had to effectively fulfil what NICE would expect. So the NICE guidance is based on an expectation of a 0.9% reduction in HbA_{1c} and I felt that was what they should be achieving for us to say that they should continue pump therapy.

Dr G

There were some that we knew had done really well on the pump. We knew that they'd really enjoyed being on the pump, that we knew that because they had never had, kind of from a NICE guidance point of view, a period of time having had what we would consider a, you know having done DAFNE and seeing if DAFNE works first, before putting them on a pump, and had never seen that, we couldn't justify it from a hypo[glycaemia] point of view. They had done really well no doubt. But we couldn't justify it from NICE to keep them on the pump.

ED14

This approach contrasts with that adopted by resource-rich centres that applied a much looser or subjective interpretation of the NICE/SIGN criteria when determining who remained on pump therapy. In one of these centres, nearly all of the patients in the pump group were allowed to remain on the pump when the trial finished, with some individuals, such as Dr F, justifying their decision by referring to the ambiguity inherent in the NICE/SIGN criteria:

Yeah. I think it was difficult to remove something that somebody's doing well with, and wants to continue. If you know you have that funding available. And as I say SIGN and NICE are very vague. So you know, you, I felt I could justify it.

Dr F

Using quality-of-life criteria to inform decisions

These centres frequently took QoL issues, as well as biomedical criteria, into account when deciding who should remain on pump therapy. Dr F, for example, commented that they took into consideration how 'well' people were doing on pump therapy when making treatment allocation decisions in their centre:

I: What do you mean by doing well?

Dr F: It's interesting isn't it. So doing well might be having good blood glucose values. But doing well might just be engaging with their diabetes better than they did before. So we had a couple of quite chaotic people who don't have perfect glycaemic control, but they're testing, they're entering information and they're keeping in touch with us in a way that before they weren't. So I guess you know, doing well can be something over and above what their blood sugar's telling us. And certainly their control, it's not perfect, it's better and safer than it was before. So I think that's what I would sort of class as doing well.

Likewise, Dr H, from another resource-rich centre, described how decisions about post-trial therapy at their centre were governed by the team's 'global impressions' about how individuals had coped on pump therapy:

We didn't have any sort of hard criteria. It was going to be more just a sort of global impression taking into account of all the team's views. You know, for instance this guy . . . early on in the study I think everybody would have said if he ever makes it to the end of the study, when he gets there he shouldn't be on a pump. But he eventually got there with using it. So the people kind of relaxed a bit more about it. But I think he was the only person potentially that we would have taken off.

Dr H

Ensuring patient safety

Finally, independently of the availability of resources to fund pump therapy, decisions around individuals' continuation on pump therapy following the trial were primarily affected by consideration of safety issues. As ED3, who was based in a well-resourced centre, indicated:

So as a team we reviewed all the people on pumps and made the decision about whether we felt, based on the information that we had and their downloads etc. they were using the pump first of all safely, cause that's the key priority really is, the safeness and then whether they were getting any benefit from it.

ED3

Indeed, in resource-rich centres, safety appears to have been the only reason for removing people from pump therapy at the end of the trial, unless patients requested to come off the pump:

Oh it was definitely individual, definitely. I mean if we had funding but thought that person wasn't safe. It wouldn't have mattered if the funding was in place.

ED4

In summary, post-trial treatment decisions in all centres were influenced by assessments of patient safety and efficacy plus the availability of funding for pump therapy. Access to resources ultimately dictated the decision-making strategy that was adopted by the different centres; in resource-limited centres individual treatment decisions were NICE/SIGN-guideline driven and based on strict, objective efficacy criteria, whereas in resource-rich centres, decisions about individuals were based on looser, subjective views of efficacy or patient benefit and a desire to safeguard an ongoing therapeutic relationship.

Research question 3

- What processes and procedures do staff think should be put in place to support patients and staff involved in the closeout of future clinical trials, especially those where expensive health technologies are being investigated and may be withdrawn?

Strategies used in REPOSE

As already outlined above (see *Research question 1*), staff had developed some strategies either proactively or during REPOSE to manage and prepare patients for potential withdrawal of the pump. In the main, staff

saw these strategies as having been helpful, effective and appropriate, and said they would use them (and recommend them to others for use) in future trials of a similar nature to REPOSE. Such strategies included preparing patients for closeout by reminding them, at the outset, that pump therapy was only funded for the duration of the trial:

... it's about the expectations those people had from the start. And I do think that if you're very clear from the outset, if people's expectations are at a certain level, then those conversions (post trial) are much easier. But it's about being very clear from the outset.

ED14

In addition, staff recommended that patients be given reassurance that they will be monitored to determine whether or not they needed a pump in the future so that a case could be made for them to access one; separating (ideally in space and time) the clinical appointment to discuss post-trial treatment from the final trial appointment and, if possible [see *What (if any) practical/ethical/other issues arose for staff and how did they attempt to address these?*] giving patients a window of time after closeout to adapt before therapy was removed:

You know maybe there should have been a wash-out period or something afterwards, you know like this is the end of the trial maybe you'll have 2 or 3 months or something to discuss with your team the way forward or whatever rather than people thinking right on the day it finishes and that's it, it's very difficult to just whip something off somebody and say here you are go back to your pen so I think that might have been the only thing, and that's just feedback from the patients really.

ED6

Staff also identified two general areas in which they felt that their practice could have been improved and which could help support patients and staff involved in closing out future trials involving potential withdrawal of treatment. These were formalising post-trial procedures and improving communication between/within teams and with patients.

Formal post-trial procedures

Staff at a number of centres commented that the post-trial period is relatively neglected in trial planning compared with trial set-up and delivery. In light of their experiences of working on REPOSE, these staff members highlighted a need to acknowledge and prepare for the ending of a trial from the outset:

Maybe if I'd been in a trial where something had been taken away, we would have formalised this a bit more ... But it's difficult to envisage that when you're writing a protocol so far in advance isn't it? At that point the major thing is: can we get enough people into the study. That's always the major hurdle. And in hindsight we probably ought to have sorted out the closeout in more detail once we were up and running. And set aside time to actually do that. With amendments or whatever it needed.

Dr B

There was widespread acknowledgement that thinking about closeout in advance and adopting a more detailed or formalised set of procedures for decision-making about ending/continuing trial therapy would have been helpful for staff managing this process. Some staff commented that appropriate costings/resources would also be required for this and to ensure staff had dedicated time to manage the closeout effectively rather than trying to fit it into already busy work schedules:

And that we had enough time for it – I think one of the issues as well is, because we're such a busy clinical team and this was kind of fitted in as part of our clinical work as well. Although there was some backfill and things it was still a very busy time for us. So making sure that we did have the time and it was given to that

ED13

Staff in resource-limited centres, in particular, highlighted a need to develop a more formalised process with regard to decision-making about post-trial therapy, suggesting that this would enable staff to support each other when making difficult treatment allocation decisions and communicating them to patients:

But the final decision [post-trial treatment] was made by different people. In hindsight potentially I think all of the educators and the PI should have been probably together for all of them. And discussed them . . . I would have definitely met and gone through the SOP and gone through everything and checked that everyone was clear with what we were doing. And probably together supported each other and probably have continual meetings with those people particularly involved in the trial.

ED10

Local guidelines

As indicated earlier, staff also thought that having local guidelines in place was important to avoid inconsistent practices within centres and to help promote parity in decision-making, fair allocation of scarce resources (pumps) and also to help prevent potential disagreements and tensions within the team.

Staff in resource-rich centres also suggested that having more formalised procedures at the end of the trial could be useful and result in more transparent and accountable post-trial treatment decisions:

Would I have put something in at the end to kind of reassess, to kind of see whether or not there was, was it right to allow a participant who'd been given a pump to remain on a pump . . . So perhaps something that perhaps brought a bit more structure into that . . . But that perhaps would have been one thing to kind of do a fuller or a more structured assessment about whether or not it was the right thing to keep them on a pump.

ED8

The staff speculated that adopting more formalised procedures for closing out patients would ensure that staff with the requisite skills were available following closeout to train patients to use different technologies, if required, as well as provide emotional support:

When I saw the patients my team weren't there. So, and that was a technical problem, because I had to teach people how to use MDI and how to use the bolus calculators . . . I struggled a bit, 'cause I'm not a trained educator . . . And it just wasn't done properly. And that's entirely my fault, because we didn't set it up to do it. We didn't think it through I don't think. And they were the last patients. So we didn't get the chance to improve it.

Dr C

Finally, some staff also indicated an explicit need for training/role play to deal with patients' emotional reactions at closeout and suggested that this training could be usefully incorporated into the costings and design of future trials:

And I guess maybe yeah, just kind of sort of, kind of how to deal maybe with – if people are being – if something's being withdrawn from the person as well, in terms of a sort of a therapy, how to kind of sort of handle that as well, and what kind of the, so maybe a little bit of training about kind of the best way to kind of present that to people.

ED13

Improving communication

Finally, nearly all of the interviewees talked about the need for better communication about closeout at the end of the trial. As Dr C said, 'Most of our problems came from breakdowns in communication, I think'. First, many staff noted that better communication across trial centres would have been helpful in

the REPOSE Trial, as this would have enabled staff in the different centres to prepare for, and alert others to, patients' reactions and develop more consistent protocols and/or guidelines for good practice:

I think the only thing I might have done better is we might have had more of a discussion about the scenarios and shared the experiences so people got a more consistent message.

Dr A

Consensus and communication within centre teams was also seen as important for managing closeout effectively. Some staff noted that there had been a communication breakdown in their centre, with the result that some team members were not aware when pump therapy was scheduled to be withdrawn, and that this had caused problems for the staff and patients involved.

I think that was, that was, that was all not – we didn't manage that very well, if I'm honest, because Dr did it on a day when I was on leave. And Dr didn't – I didn't know Dr was going to take the pumps off them there and then. So I would have, I would have liked to have seen them to have gone through their regimes on pens with them. And to have given them a bolus calculator meter, which would be like the bolus calculator on their pumps that they were used to. So we didn't – I didn't know they were going to walk into the consultation with a pump and leave without one.

ED12

Other staff members at this centre commented that better communication within the team would have enabled them to better support each other through the closeout process:

I think probably there should have been more of a team effort at the close. Because there was a lot of people involved in the team, but it was more or less left to you know, the educators and the dietitian. And then the consultant saw them later. But I think you know, if the whole team were involved there wouldn't have been so much awkwardness at the close.

ED10

Finally, staff argued that closeout of these sorts of trials would be potentially easier if there was better communication with research participants. As indicated earlier, some advocated continually reminding participants that pump treatment was funded only for the trial's duration [see *What (if any) practical/ethical/other issues arose for staff and how did they attempt to address these?*]. Others, who supported adopting more formalised end-of-trial processes, suggested that these could be explained to patients so they are made aware in advance of how decisions about their post-trial therapy would be made:

You need to let the patients know this, you know, you could have some fixed set criteria for whether they keep the pump or not. Or we say, at the end of the trial, you come off the pump for 3 months. And after the 3 months your diabetes control will be reviewed again to see if the pump therapy is suitable for you. So that they actually – and that might be the better way to do it – so that everybody knows they're going to come off the pump for 3 months. And then they'll get a review, rather than this.

ED12

As noted earlier [see *What (if any) practical/ethical/other issues arose for staff and how did they attempt to address these?*], staff made a related point when they argued that it might be useful to make patients aware during the trial when they were currently not reaching the criteria for post-trial treatment (pump) so that they were prepared for the possibility of their treatment being withdrawn:

If we'd had the same conversations all along: your HbA_{1c}'s no better. You only bolus twice a day. And you have that conversation three or four times, then the patient is going to come to the conclusion: yeah I'm not going to keep the pump. I can't do this. They would have got to that point themselves.

Dr B

Dedicated trial clinics

Although all staff regarded communication between staff and patients as a crucial factor in facilitating trial closeout, some acknowledged that developing relationships with trial participants is difficult, particularly in the larger trial centres. To overcome this, one member of staff suggested that, in the future, trials should set up clinics for trial participants, which, they reflected, would have been helpful in the REPOSE Trial when communicating with patients, particularly when terminating pump therapy:

Whoever finished the trial with the patient and communicated to them the decision should have known the patient. Just so that it was a – it was much more of a more – the way you would clinically, . . . the person who did know the patient should have been there at the time [the end] to support the patient through the transition. I don't think we really realised how the patient would perceive the difficulty of the transition . . . unlike other studies that I've done I personally didn't feel that I was engaged with the study's subjects, which probably is correct from the point of view of the outcomes, but it did make the ending of the study a bit more difficult.

Dr C

As Dr C further suggested, having dedicated trial clinics would result in continuity of care across the trial and thus make it easier at closeout because staff involved would be known to the patients and vice versa: 'I think the person who is terminating the study should have been involved throughout it – that would have made all of the difference'.

Dr B similarly commented that involving educators who were known to the patients in the post-trial consultations was helpful when it came to communicating with, and managing, patients' emotional reactions:

I think, she [educator] knew some of the patients better than I did because she'd done the course with some of them. And so she was warning which ones might be tricky. And you know, she is a good judge of character. So that was really helpful I guess. I think one of the other times we ran into a problem where it, the doctor that didn't know the background to the patient. You know, so if you, I suppose not had the pre-warning, if we've not had that discussion beforehand, it would come across, or could be, come across really quite cold and so I think that was helpful.

Dr B

Role of the Clinical Trials Research Unit

Finally, one member of staff, ED11, suggested that CTRUs have a major role to play in communicating and co-ordinating information about trial closeout by offering/co-ordinating training, hosting meetings/teleconferences to allow staff to share experiences of closeout, offering examples of good closeout practices, making sure that there is adequate resourcing to do the closeout/post-trial appointments properly and reminding centres that closeout is approaching so that they can make preparations, particularly for potential negative reactions to the withdrawal of treatment:

I think everyone should have been advised to have those difficult conversation – you know had the conversation about not being able to keep the pump at the end, being advised to do that at every visit and every opportunity, so that people had their expectations managed. [And] . . . maybe a reminder that we needed to meet and discuss who was going to stay on the pumps and who wasn't. You know, so just a reminder to say: have you had that conversation with your team? Has the patient been primed? Something like that would have been helpful.

ED11

During the trial there were opportunities for staff to share experiences during regular TMG meetings involving local PIs and some lead educators from all of the centres, as well as during regular educator teleconferences. However, these teleconferences primarily focused on issues relating to trial delivery. Although closeout was discussed in advance in both types of teleconference, the educator teleconferences were stopped just before the start of the closeout period, as it was thought that, by this point, further

meetings would not be necessary (a decision that may have been partly due to a lack of awareness of the problems which would arise for some staff at closeout). Hence, there were limited opportunities for some staff members at the different centres to share and discuss the difficulties they went on to encounter when withdrawing treatment.

In summary, although most staff did not regard themselves as having needed support for the closeout of the REPOSE Trial, they outlined a number of ideas that they felt would facilitate closeout in trials when treatments are withdrawn. In addition to the strategies they had already developed during REPOSE, staff suggested that more formalised procedures for ending trials should be adopted; specifically, procedures for post-trial treatment decision-making and for transitioning research participants back into clinical care. Second, they advocated for improved communication among trial staff both between and within centres and with patients.

Key findings

This study has highlighted and explored differences in staff members' experiences of closeout, both within and across the REPOSE centres. In most of the centres with limited funding for pump therapy, all but a few patients were reverted to MDI at the end of the trial. In some such cases, staff had had to manage patients' negative emotional reactions to the withdrawal of pump therapy. In other centres at which funding for pumps was more readily available, all patients who were safely using the pump, who wished to continue using it and who were benefiting, as broadly defined from pump therapy, were allowed to continue this treatment following trial closeout. As patients in these centres were able to remain on the pump if they wanted to, closeout in these centres was perceived as less challenging.

Most staff, but particularly those involved in the pilot phase, anticipated that the withdrawal of pump therapy might be an issue for patients, and hence had developed a range of potential solutions to address this. These included developing strict protocols for managing patients' expectations and pre-empting potential disappointment/anger by reminding patients that pump therapy was a research intervention that may terminate at the end of trial whenever they attended trial appointments.

All centres developed site-specific procedures for decision-making about post-trial treatment, although some were more formalised than others. These decisions were influenced by assessments of patient safety and efficacy plus the availability of funding for pump therapy. Access to resources ultimately dictated the decision-making strategy adopted by the different centres (and, in some cases, by different individuals within those centres); in resource-limited centres individual treatment decisions were NICE/SIGN-guideline driven and based on objective efficacy criteria, whereas in resource-rich centres the treatment decisions were based on more subjective views of efficacy or patient benefit and a desire to safeguard an ongoing therapeutic relationship.

Staff described a number of ethical questions and issues concerning the withdrawal of treatment, which they felt had emerged in closing out the REPOSE Trial. These included whether or not it was right to remove a therapy if patients were deriving some benefit, or perceived themselves as benefiting, from it; the fact that removal of therapy might undermine the trust and confidence in an ongoing therapeutic relationship; and the existence of inequity in funding for post-trial treatment.

Staff identified a number of things that they felt could facilitate closeout of future trials when treatments may be withdrawn. In addition to the particular strategies they had developed during the REPOSE Trial, staff suggested that more formalised procedures for ending trials should be adopted; specifically, procedures for post-trial treatment decision-making and for transitioning research participants back into clinical care. Second, they advocated for improved communication among trial staff, both between and within centres, and with patients. In addition, staff highlighted the potential value of having several team members involved in post-trial consultations, including staff who had contact with patients during the trial.

Key recommendations

1. Planning for closeout should begin at a trial's inception. Closeout should be addressed in the risk assessment for the trial, and consideration given to whether or not there may be ethical and practical issues related to removing a trial treatment.
2. Ensuring that the necessary resources, training and protocols are in place will require that realistic costings for closeout (e.g. training for staff, making sure they have dedicated time for post-trial clinic appointments and MDTs) are included in the grant application or are negotiated with trusts during the planning stage.
3. Having formal closeout procedures for decision-making about post-trial treatment and transitioning patients back into clinical care/other therapies may increase accountability and transparency, and aid the communication of treatment decisions to patients.
4. Consensus and communication within centre teams is important for managing closeout effectively.
5. If closeout is staggered across/within centres then regular meetings/debriefs during the closeout period would allow staff to share and learn from each others' experiences.
6. If a treatment may be withdrawn at the end of the trial, trial staff should communicate this to patients at every opportunity during the trial to prevent/pre-empt disappointment.
7. Information about the potential withdrawal of treatment should be included in formal trial materials (e.g. the patient information sheet, see *Appendix 8*), as occurred in REPOSE, as well as informal trial communications (e.g. trial newsletters). Participants could also receive a separate (local) closeout information sheet before the end of the trial, which explains the timescales involved, the training/support provided and arrangements for future monitoring of (new) treatment. Consideration could also be given to whether or not a statement about the potential withdrawal of treatment should be included on the consent form.
8. Continuity of care across the trial could be encouraged; this could take the form of running dedicated clinics for trial participants or, at the very least, ensuring that staff closing out the trial are known to the patients.
9. Research appointments to collect trial data and clinical appointments to discuss post-trial therapy should be distinct; if possible, these should occur at different times and in different places.
10. Allowing patients a period of time after the trial is ended to continue on trial therapy and adjust to the idea of the withdrawal of treatment may be valuable. Funding for this period of adjustment may need to be included in the grant application.
11. Examples of good and bad practice at closeout could be documented and used to create scenarios for role play/training staff involved in the closeout of future trials involving potential withdrawal of treatments.

Strengths and limitations

This study had very high opt-in levels from staff, providing us with a sample size sufficient to achieve data saturation and allowing good representation of a diverse range of views. Recruitment from the seven main trial centres enabled us to identify a number of variations in practice in closing out the trial and the impact of contextual (e.g. availability of funding for pumps), as well as individual, factors (previous experience of delivering pilot, exposure/lack of exposure to patients during follow-ups, etc.) on closeout experiences and practices. This wide-ranging approach also enabled us to identify broader cross-cutting ethical issues and challenges, experienced in most/all of the centres.

There are, however, a couple of limitations that must be considered. First, in some cases there was a time lag between closeout and the interviews; hence, some of the accounts may have been subject to a recall bias. Second, the interviews required staff to reflect on what proved, for some, to be sensitive experiences. This may have impacted on staff willingness to discuss these issues in too much depth, although this was not evident in the interviews. Third, the fact that all of the staff interviewed come from a relatively small research community has affected the material that we are able to report because of our ethical mandate

to safeguard confidentiality. Finally, one major limitation of this study is that we were unable to interview REPOSE patients about their closeout experiences because, as noted above, there was insufficient time available to secure ethical and other approvals and to collect the data.

In summary, the REPOSE Trial, presented an opportunity to undertake research on the experiences, views and information/support needs of staff members involved in the closeout of a trial, which potentially involved the withdrawal of trial treatments, thereby allowing us to provide data on a much neglected topic. All of the objectives of this qualitative study were achieved, and all of the original research questions answered. A peer-reviewed journal article is in press.¹⁷³

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The REPOSE Study Group

Simon Heller was the chief investigator.

Norman Waugh was the deputy chief investigator.

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Cindy Cooper, Gemma Hackney, Diana Papaioannou, Emma Whatley and David White provided central trial management, oversight and monitoring.

Mike Bradburn, Michael Campbell, Munya Dimairo and Ellen Lee contributed to the statistics.

Hasan Basarir, Alan Brennan, Simon Dixon and Daniel Pollard contributed to the health economics.

Nina Hollowell, Jackie Kirkham, Julia Lawton and David Rankin designed and undertook the qualitative work.

Katharine Barnard provided expert input to the quantitative psychosocial work.

Timothy Chater and Kirsty Pemberton provided data management.

Fiona Allsop and Lucy Carr provided central administration.

Pamela Royle conducted literature searches and exploratory analyses.

Gill Thompson and Sharon Walker provided central DAFNE support.

Pauline Cowling conducted the fidelity assessment.

W Henry Smithson provided user input to the design and implementation of the trial.

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Nina Hallowell conducted the qualitative substudy on the challenges of closing out a clinical trial.

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Data sharing statement

Requests for patient-level data and statistical code should be made to the corresponding author and will be considered by the REPOSE TMG, which, despite the fact that specific consent for data sharing was not obtained, will release data on a case-by-case basis following the principles for sharing patient-level data as described by Smith *et al.*¹⁷⁶ The presented data do not contain any direct identifiers; we will minimise indirect identifiers and remove free-text data to minimise the risk of identification.

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Appendix 1 Search methods

The Ovid MEDLINE search strategy was adapted, as appropriate, to the other databases.

1. ((continuous or subcutaneous) adj3 insulin adj3 infusion).mp.
2. (csii or insulin pump*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. (insulin and pump*).m_titl.
4. Insulin Infusion Systems/
5. 1 or 2 or 3 or 4
6. Diabetes Mellitus, Type 1/ or type 1.mp.
7. random*.tw.
8. randomized controlled trial.pt.
9. 7 or 8
10. 5 and 6 and 9
11. limit 10 to yr="2007-Current"

The searches yielded 1341 records, and 749 remained after duplicates were removed. After screening the titles and abstracts to exclude studies not in adults, 180 records remained, and the titles and abstracts of these were screened by two authors. Only 128 were RCTs. We excluded trials for the reasons reported in *Chapter 2* (see *Methods*). Twenty-three papers were included in the table of previous trials. Some trials were reported in more than one paper.

We also checked inclusion lists of six past systematic reviews (Colquitt *et al.*,¹⁴ Cummins *et al.*,⁹ Pickup *et al.*,²⁸ Monami *et al.*,¹⁸ Fatourechi *et al.*²⁹ and the Cochrane review by Misso *et al.*³¹).

Searches were run in Ovid MEDLINE for observational and audit studies of insulin pumps from 2012 to 7 January 2016.

The search strategy was

1. ((continuous or subcutaneous) adj3 insulin adj3 infusion).mp.
2. (csii or insulin pump*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. (insulin and pump*).m_titl.
4. Insulin Infusion Systems/
5. 1 or 2 or 3 or 4
6. *Diabetes Mellitus, Type 1/
7. type 1 diabet*.tw.
8. 6 or 7
9. 5 and 8
10. limit 9 to yr="2012-Current"
11. (editorial or letter or randomized controlled trial).pt.
12. (10 not (editorial or letter or randomized controlled trial)).pt.

This retrieved 603 records and, after screening, 33 were retained for screening by a second reviewer. Of these 22 were included.

Appendix 2 Regulatory approvals

Research Ethics Committee approval was obtained for the study from the Liverpool East REC on 26 April 2011. MHRA approval was received on the 26 May 2011.

The relevant R&D departments were approached and approval was given for the relevant primary care trusts/trusts on the following dates:

R&D department	Date of approval
Sheffield Teaching Hospitals NHS Foundation Trust	27 October 2011
NHS Greater Glasgow and Clyde	10 January 2012
King's College Hospital NHS Trust	13 January 2012
Cambridge University Hospitals NHS Foundation Trust	26 October 2011
Harrogate and District NHS Foundation Trust	20 January 2012
NHS Dumfries & Galloway	24 October 2011
NHS Lothian	5 January 2012
Nottingham University Hospitals NHS Trust	31 October 2012

Appendix 3 Consent forms

re/pose Consent Informed Consent

FOR OFFICE USE ONLY			
Screening Number	<input type="text"/>	-S	<input type="text"/>
Candidate Initials	<input type="text"/>	<input type="text"/>	<input type="text"/>

Investigating Whether Insulin Pumps are More Effective in Treatment of Type-1 Diabetes than Multiple Insulin Injections when Combined with Diabetes Education (Dose Adjustment for Normal Eating – DAFNE).

Today's date

Thank you for reading the information sheet about the REPOSE trial. If you are happy to participate then please complete and sign the form below.

Please initial the boxes below to confirm that you agree with each statement:

	Please initial box
I confirm that I have read the patient information sheet dated 4 th September 2012 (version 05.1) for the REPOSE trial. I have had the opportunity to ask questions and have had them answered to my satisfaction.	<input type="text"/>
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	<input type="text"/>
I understand that sections of my medical notes and data collected during the study may be looked at by research staff or regulatory bodies. I give permission for these individuals to have access to my records.	<input type="text"/>
I agree to my GP being informed of my participation in the trial.	<input type="text"/>
I am happy to have my contact details passed on and to be contacted by an interviewer in order to be invited to participate in some interviews.	<input type="text"/>
I am happy to participate in the trial.	<input type="text"/>

Name of participant (Capitals) Signature Today's date

Person obtaining witness
(Educator/consultant) Signature Today's date

One copy to be kept by patient with information sheet, Original copy to be kept in the REPOSE trial site file, One copy to be kept in the clinical notes.

Version 6.1, 04SEP2012

FOR OFFICE USE ONLY

Consented to DAFNE research database Yes No DAFNE number /

re/pose Consent
Informed Consent

FOR OFFICE USE ONLY	
DAFNE number	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>
Participant Initials	<input type="text"/> <input type="text"/>

Please could you fill out your contact details below:

Full name	<input type="text"/>
House number and street	<input type="text"/> <input type="text"/>
City/town	<input type="text"/>
County	<input type="text"/>
Post code	<input type="text"/> <input type="text"/>
Mobile	<input type="text"/>
Landline home	<input type="text"/>
Landline work	<input type="text"/>

Please could you fill out your GP details below:

Full name	<input type="text"/>
House number and street	<input type="text"/> <input type="text"/>
City/town	<input type="text"/>
County	<input type="text"/>
Post code	<input type="text"/> <input type="text"/>
Telephone number	<input type="text"/>

Please turn over

FOR OFFICE USE ONLY	
DAFNE number	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>
Participant Initials	<input type="text"/> <input type="text"/>

Ethnicity

White

- English/Welsh/Scottish/
Northern Irish/British
- Irish
- Gypsy or Irish Traveller
- Any other White background
(please specify):

Mixed / multiple ethnic groups

- White and Black Caribbean
- White and Black African
- White and Asian
- Any other Mixed / multiple ethnic
Background (please specify):

Asian / Asian British

- Indian
- Pakistani
- Bangladeshi
- Chinese
- Any other Asian background
(please specify):

Black / African / Caribbean / Black British

- African
- Caribbean
- Any other Black / African / Caribbean
Background (please specify):

Prefer not to say

Other ethnic group

- Arab
- Any other ethnic group
(please specify):

Version 6.1, 04SEP2012

V3, 07Feb2012



Qualitative Study

Informed Consent

FOR OFFICE USE ONLY

Candidate Initials

REPOSE Qualitative Study - Interview sub-study

Today's date

Thank you for reading the information sheet about the interview sub-study. If you are happy to participate then please complete and sign the form below.

Please initial the boxes below to confirm that you agree with each statement:

- | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>I have read and understand the information sheet dated 7th Jan 2011 (version 01) for the above study and have had the opportunity to ask questions.</p> <p>I have received satisfactory answers to all of my questions.</p> <p>I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.</p> <p>I am willing to have my interview tape-recorded.</p> <p>I agree to take part in the above study.</p> | <p>Please initial box</p> <p><input type="text"/></p> <p><input type="text"/></p> <p><input type="text"/></p> <p><input type="text"/></p> <p><input type="text"/></p> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Name of participant

Today's date

Signature

Person obtaining consent

Today's date

Signature

FOR OFFICE USE ONLY

DAFNE number /

Appendix 4 Sample of data collection booklet: 24-month follow-up

FOR OFFICE USE ONLY					
DAFNE number	<input type="text"/>	<input type="text"/>	<input type="text"/>	/	<input type="text"/>
Participant Initials	<input type="text"/>				



REPOSE STUDY
Data Collection Booklet

24 month



04/02/2014 v1

repose 24 month
Data Collection

FOR OFFICE USE ONLY	
DAFNE number	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>
Participant Initials	<input type="text"/> <input type="text"/>

Please find below the checklist for the 24 month data collection visit. Please read the checklist carefully and ensure that all of the items have been addressed by the end of the visit.

<p>Checklist for 24 month data collection visit:</p> <p><input type="checkbox"/> Taken blood and urine samples</p> <p><input type="checkbox"/> <u>Updated on-going data collection booklet - checked that all severe hypos, contacts and AEs have been recorded; where applicable end dates for AEs should also be provided (may need to check patient notes)</u></p> <p><input type="checkbox"/> Checked for any unreported SAEs (check patient notes)</p> <p><input type="checkbox"/> Collected the psychosocial questionnaire. If the participant has not brought it to the appointment ask them to fill in a questionnaire now (They may also hand you a 'permission for future contact' slip. If so please return to CTRU; please send in a separate envelope to the questionnaires)</p> <p><input type="checkbox"/> Downloaded previous week data from Bolus calculator</p> <p><input type="checkbox"/> Completed the 'Study Completion / Discontinuation' form (If the participant has attended their 24m follow-up visit they have completed the study)</p>	FOR OFFICE USE ONLY
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------

04/02/2014 v1

repose 24 month
Data Collection

FOR OFFICE USE ONLY

DAFNE number /

Participant Initials

Are you currently using an insulin pump? Yes No

Date that you started to use the insulin pump /

Treatment details

Please record details about the MDI / Pump treatment (e.g. any temporary breaks from allocated treatment), including dates and reasons where applicable. For example: Break from Pump 12/03/2012-15/03/2012, patient on holiday

MDI only

Current MDI insulin regimen (REPOSE ratios of Quick Acting (QA): Carbohydrate Portion (CP) and Background Insulin (BI) doses, use previous day's doses):

Current MDI insulin regimen	Typical daily dose <small>(based on use in the last week and using diary entries/expert meters)</small>	Number of injections per day
Quick acting (QA)	<input type="text"/> <input type="text"/> i.u.	<input type="text"/> <input type="text"/>
Background insulin (BI)	<input type="text"/> <input type="text"/> <input type="text"/> i.u.	<input type="text"/>
Pre-mixed insulin (Mix)	<input type="text"/> <input type="text"/> <input type="text"/> i.u.	<input type="text"/>

Is the participant using ratios? Yes No

QA:CP Ratios: . :lb . :lm . :le . :ls

Pump users only

Current pump regimen (REPOSE ratios of Insulin: Carbohydrate and Basal Insulin (BI) regime, use previous day's doses):

(All questions relating to dose should be calculated based on use in the last week and using diary entries/expert meters)

Typical/usual daily bolus total: . i.u.
(Note: whole number NOT range)

24 hour basal dose: . i.u.

Average number of boluses per day (based upon 'usual' day)

Is the participant using ratios? Yes No

QA:CP Ratios: . :lb . :lm . :le . :ls

04/02/2014 v1

re/pose 24 month
Data Collection

FOR OFFICE USE ONLY	
DAFNE number	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>
Participant Initials	<input type="text"/> <input type="text"/>

Insulin type

QA: Human Animal Novo Rapid Humalog Apidra

Method of delivery: Syringe Reusable pen Disposable pen Pump

BI: Human Animal Lantus Levemir

Method of delivery: Syringe Reusable pen Disposable pen

Mix: Human Animal Analogue

Method of delivery: Syringe Reusable pen Disposable pen

Appearance of injection sites - is Lipohypertrophy present? Yes No

Medication

Lipid lowering (Statin; Fibrate; Ezetimibe) Yes No

Antiplatelet agent (Aspirin; Clopidrogel; Dipyridamole) Yes No

Medication for depression (exclude antidepressants for neuropathy) Yes No

Have you been pregnant since your last REPOSE visit? Yes No

Are you pregnant now? Yes No

Current gestation (weeks)

04/02/2014 v1

re/pose 24 month
Data Collection

FOR OFFICE USE ONLY

DAFNE number /

Participant Initials

Moderate Hypoglycaemic Episodes (to be completed by educator with patient)

Moderate hypoglycaemia is defined as **any** episode which could be treated by that individual, but where hypoglycaemia caused significant interruption of current activity, such as having caused impaired performance or embarrassment or having been woken during sleep.

They do not necessarily need to be confirmed by a blood glucose measurement although the person should be confident that their symptoms were due to hypoglycaemia.

How many moderate hypoglycaemic episodes have you had during the last 4 weeks?
(use BG diary entries)

Please give details of moderate hypos, where known, in the log below:
(use continuation sheet on page 11 for additional records)

Approximate date	Reason for Hypo (i.e no food, exercise, illness, alcohol etc)	Woken from sleep (Y/N)	Blood Glucose Level (mmol/L)	Measured before or after treatment	Confirmed by educator as moderate hypo*	
					(✓)	Educator Initials
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	
<input type="text"/>			<input type="text"/> . <input type="text"/>		<input type="checkbox"/>	

* Educator must be certain that the patient was able to treat the episode of hypoglycaemia themselves.

04/02/2014 v1

re/pose 24 month Data Collection

FOR OFFICE USE ONLY	
DAFNE number	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>
Participant Initials	<input type="text"/> <input type="text"/>

Severe hypoglycaemic episodes We will use a standard definition of severe episodes: an episode leading to cognitive impairment (confusion or inability to think straight) that is either sufficient to cause a coma or requires the assistance of another person to recover.

Has participant had any severe hypos since the last REPOSE visit? Yes No

Adverse Events Have any of the following occurred?

- An increase in frequency of hypoglycaemia that is suddenly noticeable to the patient/patient's relatives;
- Blood glucose reading >30 mmol/L;
- Unexplained constantly raised blood glucose readings (defined as three consecutive readings > 20mmol over 12 hours);
- Suspicion of pump malfunction (adjudicated by the educator). Note: Medtronic must be notified via their technical helpline;
- Pregnancy (so that any ARs may be identified if and when the child is born);
- Infection at pump cannula site / pump site infection
- Other, please specify

Has participant had any adverse events since the last REPOSE visit? Yes No

Phone / clinic contacts Have contacts occurred since the last REPOSE visit?

Has there been any contacts since the last REPOSE visit? Yes No

If yes to any of the above, please check that these events have been reported and are in the on-going data collection booklet

Please also review all on-going Adverse Events and where applicable enter the end date

FOR OFFICE USE ONLY	
DAFNE number	<input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/>
Participant Initials	<input type="text"/> <input type="text"/>



REPOSE STUDY
On-going Data Collection Booklet

This booklet contains the severe hypo log, adverse event / reaction log and diabetes related contact log

- 1) At Baseline, please record a 12 month history of severe hypos.
- 2) At the 6, 12 and 24 month visits please ensure that the severe hypo, adverse event / reaction and diabetes related contact logs are up to date. (This may involve transposing any loose severe hypo, adverse event / reaction and contact forms onto their respective logs).

Beware of double counting events

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repose 24 month
Data Collection

FOR OFFICE USE ONLY	
DAFNE number	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/>
Participant Initials	<input type="text"/> <input type="text"/>

Complications (conditions and events) since the last **REPOSE** visit? Yes No

If yes, please record below which conditions are present and the date of onset for each:

Condition (tick if present)	Date of onset
<input type="checkbox"/> Hypertension	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Painful neuropathy	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Foot ulcer	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Retinopathy	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Proliferative	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Registered partially sighted	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Registered blind	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Microalbuminuria (Female = greater than 3.5 on 2 occasions, at least 1 early morning urine) (Male = greater than 2.5 on 2 occasions, at least 1 early morning urine)	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Proteinuria (Dipstick positive and/or ACR greater than 30 on 2 occasions and/or greater than 300mg/l in 24 hours)	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Erectile dysfunction	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

If yes, please record below which of the events have happened and the date of the most recent occurrence for each.

Event (tick if present)	Date of event
<input type="checkbox"/> MI	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Heart failure	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Coronary revascularisation	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Peripheral revascularisation	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> CVA	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Amputated toe	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Amputation above toe level	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Laser Rx	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Dialysis	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
<input type="checkbox"/> Renal transplantation	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>

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re/pose 24 month
Data Collection

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Participant Initials

Total number of **diabetes related** inpatient episodes since the last **REPOSE** visit

Bolus calculator

How often does the patient use their bolus advisor/calculator for the following functions:

	Never	Rarely (about 25% of the time)	Sometimes (about 50% of the time)	Often (about 75% of the time)	Always
Calculation of insulin dosage					
Calculation of correction doses					
Any other activities (e.g. exercise, menstruation)					

Where the bolus calculator advisor is used for the calculation of insulin boluses for food, how frequently is the advice given used?

	Never	Rarely (about 25% of the time)	Sometimes (about 50% of the time)	Often (about 75% of the time)	Always

Previous one week download data collected from bolus calculator Yes No

How many admissions due to Diabetic Ketoacidosis (DKA) have you had in total?

Total number ever

Total number since the last **REPOSE** visit

Number of telephone contacts regarding your diabetes with **any** healthcare professional since the last **REPOSE** visit

Number of face to face/clinic contacts regarding your diabetes with **any** healthcare professional since the last **REPOSE** visit (exclude any inpatient hospital admissions)

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re/pose 24 month
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DAFNE number				/	
Participant Initials					

Please note the number of blood tests...

performed in the last 2 weeks

recorded (e.g. written down) in the last 2 weeks

Do your symptoms of hypoglycaemia usually occur at a blood glucose level of:

- Greater than/equal to 3mmol/l
- Less than 3mmol/l
- Do not feel symptoms

Please record the method of data collection (more than one can be selected where necessary):

- Face to face
- Telephone
- Hospital records

Data collected by
(Print name)

Signature

This is the end of the 24 month data collection booklet. Please now ensure that the checklist items on page 2 have been addressed.

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repose 24 month
Data Collection

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DAFNE number / Participant Initials **Additional notes**

Please use this section to make any additional notes (e.g. expansion on checklist items)



04/02/2014 v1

Appendix 5 Blood glucose diary: pump arm

repose

Pump Diary

**Type 1 Diabetes: Less guesswork.
More freedom. Better health.**



Name: _____

Address: _____

Hospital contact number(s): _____

DAFNE contact number(s): _____

HbA1c level at commencement of diary: _____

HbA1c level at completion of diary: _____

Personal goal: _____

Key to Diary

CP = Carbohydrate Portion Bolus = Insulin given with CP's or for corrections

BG = Blood Glucose Basal = Insulin to cover background insulin requirements

Guidelines for Bolus Insulin

Each individual has different insulin needs. You will learn to calculate your own requirements.

As a general starting guideline 1 unit insulin covers 1 CP. Most adults will require between $\frac{1}{2}$ - 2 units per CP, depending on the time of day.

Your personal calculated amount of insulin: CHO bolus ratio

Breakfast = units/CP

Lunch = units/CP

Evening Meal = units/CP ↴

Other = units/CP

18

Corrections

1 unit of insulin can **LOWER** BG by 2-3 mmols

1 CP can **INCREASE** BG by 2-3 mmols

Your personal calculated correction factor:

1 unit of insulin lowers blood glucose levels by mmol/l

Blood Glucose Levels

Recommended Targets

Pre breakfast 5.5 - 7.5

Other meals 4.5 - 7.5

Pre bed 6.5 - 8.0

Your individual Targets

Pre breakfast

Other meals

Pre bed

Ready Reckoner Sick Day Rules

TDD	10%	20%
15	1.5	3
20	2	4
25	3	5
30	3	6
35	4	7
40	4	8
45	5	9
50	5	10
55	6	11
60	6	12
65	7	13
70	7	14

TDD = total daily dose of insulin

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	Comments
Date																									
Time																									
CP																									
BG																									
Bolus																									
Basal																									
Time																									
CP																									
BG																									
Bolus																									
Basal																									
Time																									
CP																									
BG																									
Bolus																									
Basal																									
Time																									
CP																									
BG																									
Bolus																									
Basal																									

Appendix 6 Ongoing data collection booklet

FOR OFFICE USE ONLY					
DAFNE number	<input type="text"/>	<input type="text"/>	/	<input type="text"/>	<input type="text"/>
Participant Initials			<input type="text"/>	<input type="text"/>	<input type="text"/>



REPOSE STUDY

On-going Data Collection Booklet

This booklet contains the severe hypo log, adverse event / reaction log and diabetes related contact log

- 1) **At Baseline, please record a 12 month history of severe hypos.**
- 2) **At the 6, 12 and 24 month visits please ensure that the severe hypo, adverse event / reaction and diabetes related contact logs are up to date.** (This may involve transposing any loose severe hypo, adverse event / reaction and contact forms onto their respective logs).

Beware of double counting events

28/05/2012 v2.1



Severe Hypo Log

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Participant Initials

Severe Hypoglycaemic Episodes – Severe hypoglycaemia is defined as an episode leading to cognitive impairment (confusion or inability to think straight) sufficient to either cause coma or requiring the assistance of another person to recover.

#	Date reported	Occurred prior to Baseline (✓)	Description of Hypo		Did family/friend administer Glucagon? (Y/N)**	Required paramedic assistance (Y/N)	A&E attendance (Y/N)	Hospitalisation (Y/N)***	Unconsciousness (Y/N)	Lowest Blood Glucose at time of severe hypo (mmol/L)	Measured before or after treatment†	Confirmed by educator as Severe hypo	
			Date (if day is not known, please provide month and year)	Reason*								(✓)	Educator initials
1	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>
10	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="checkbox"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>

*No food, illness, exercise, alcohol, other (please specify)

** **Confirm** family/friend assistance was required for recovery (if the participant could have administered glucagon themselves if no one was around this is not a severe hypo)

*** If the participant was hospitalised this hypo **must** be reported as a serious adverse event using the SAE form within four weeks of finding out about it.

28/05/2012 v2.1



Adverse Event / Reaction Log

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Participant Initials

#	Category* Choose from below	Start date	Ongoing (✓)	End date	Related to study drug	Serious** See right for how to assess if AE serious
1		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
2		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
3		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
4		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
5		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
6		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
7		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
8		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
9		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
10		dd/mm/yy	<input type="checkbox"/>	dd/mm/yy	Yes <input type="checkbox"/> No <input type="checkbox"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>

**** Assessing Severity**
 Rated as serious if meets any of the following criteria:

- results in death;
- is life-threatening^a (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation^b
- results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect
- is another important medical event that may jeopardise the subject^c

^a "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

^b Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

^c Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

*Category
 1 = An increase in frequency of hypoglycaemia that is suddenly noticeable to the patient/patient's relatives;
 2 = Blood glucose reading >30 mmol/L;
 3 = Unexplained constantly raised blood glucose readings (defined as three consecutive readings > 20mmol over 12 hours);
 4 = Suspicion of pump malfunction (adjudicated by the educator). Note: Medtronic must be notified via their technical helpline;
 5 = Pregnancy (so that any ARs may be identified if and when the child is born);
 6 = Infection at pump cannula site / pump site infection
 7 = Other, please specify

All serious adverse events or reactions must also be reported using the SAE form

FOR OFFICE USE ONLY

DAFNE number /

Participant Initials



Diabetes related contact log

#	Contact date and time (24 hour)		Contact type			Duration of contact (to the nearest 5 mins)		Notes		
1	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
2	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
3	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
4	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
5	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
6	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
7	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
8	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
9	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
10	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
11	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
12	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
13	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
14	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	
15	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="checkbox"/> Telephone	<input type="checkbox"/> Face to face / clinic	<input type="checkbox"/> Email	<input type="checkbox"/> hours <input type="text"/> mins	

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Appendix 7 Individual characteristics for the simulated cohort in each of the pre-specified subgroup analyses

TABLE 72 Baseline individual characteristics used in the health economic modelling (n = 5000): continuous variables

Characteristic	Full cohort	Baseline HbA _{1c} ≥ 58 mmol/mol	69 mmol/mol > baseline HbA _{1c} ≥ 58 mmol/mol	80 mmol/mol > baseline HbA _{1c} ≥ 69 mmol/mol	Baseline HbA _{1c} ≥ 80 mmol/mol	Baseline HbA _{1c} < 69 mmol/mol	Baseline HbA _{1c} ≥ 69 mmol/mol	Per-protocol population
Baseline HbA _{1c} , mmol/mol (SD)	76.1 (18.8)	78.5 (17.0)	63.3 (3.0)	73.3 (3.1)	96.6 (16.3)	60.3 (6.8)	85.9 (17.0)	75.5 (17.5)
Age, years (SD)	40.3 (13.3)	40.4 (13.1)	43.0 (12.3)	40.6 (13.2)	37.7 (13.0)	42.6 (13.2)	39.5 (13.2)	40.6 (13.0)
Diabetes duration, years (SD)	18.0 (12.5)	17.9 (11.8)	19.3 (12.2)	19.0 (11.7)	16.1 (11.4)	19.3 (13.9)	17.4 (11.7)	18.3 (12.5)
Triglycerides, mmol/mol (SD)	1.3 (1.0)	1.4 (1.0)	1.3 (0.9)	1.2 (0.6)	1.6 (1.3)	1.3 (0.9)	1.4 (1.1)	1.3 (0.8)
TC, mmol/mol (SD)	4.9 (0.9)	5.0 (0.9)	4.8 (0.9)	4.8 (0.8)	5.3 (1.0)	4.8 (0.9)	5.1 (1.0)	4.9 (0.9)
HDL cholesterol, mmol/mol (SD)	1.6 (0.4)	1.5 (0.4)	1.5 (0.4)	1.6 (0.5)	1.5 (0.4)	1.6 (0.4)	1.5 (0.4)	1.5 (0.4)
LDL cholesterol, mmol/mol (SD)	2.8 (0.9)	2.8 (0.9)	2.7 (0.9)	2.7 (0.8)	3.0 (0.9)	2.6 (0.8)	2.9 (0.9)	2.8 (0.9)
Systolic blood pressure, mmHg (SD)	131.3 (16.3)	131.6 (15.9)	133.7 (18.1)	130.6 (13.6)	130.3 (16.1)	132 (17.7)	130.7 (15.0)	131.4 (15.9)

TABLE 73 Baseline individual characteristics used in the health economic modelling (n = 5000): categorical variables

Characteristic	Full cohort, %	Baseline HbA _{1c} ≥ 58 mmol/mol, %	69 mmol/mol > baseline HbA _{1c} ≥ 58 mmol/mol, %	80 mmol/mol > baseline HbA _{1c} ≥ 69 mmol/mol, %	Baseline HbA _{1c} ≥ 80 mmol/mol, %	Baseline HbA _{1c} < 69 mmol/mol, %	Baseline HbA _{1c} ≥ 69 mmol/mol, %	Per-protocol population, %
Sex								
Female	41.0	41.0	34.8	38.1	47.0	36.2	43.0	40.5
Male	59.0	59.0	65.2	61.9	53.0	63.8	57.0	59.5
Physical activity								
Low	24.9	28.0	17.0	28.7	34.9	17.1	31.6	25.6
Medium	48.8	48.9	53.7	54.8	39.7	28.9	47.3	50.4
High	26.4	23.1	29.3	16.5	25.4	56.4	21.1	24.1
Smoking status								
Current	19.2	20.6	16.0	17.3	27.2	14.7	23.7	20.0
Former	26.3	26.4	28.9	22.9	24.6	28.9	24.9	26.4
Never	54.5	53.1	55.0	59.8	48.2	56.4	51.4	53.5
Ethnicity								
White	99.1	99.3	98.5	100	99.2	98.9	43.0	99.3
Black	0.9	0.7	1.5	0	0.8	1.1	57.0	0.7
Nephropathy								
No complications	92.2	92.0	88.7	94.7	92.4	88.7	94.2	91.5
Microalbuminuria	4.7	4.7	6.6	3.8	3.6	7.1	3.5	5.0
Macroalbuminuria	2.7	2.9	3.3	1.5	4.0	3.0	2.3	2.9
Dialysis or transplant	0.4	0.4	1.3	0	0	1.2	0	0.6
Neuropathy								
No complications	90.7	91.9	94.6	97.2	85.3	92.2	90.5	91.8
Neuropathy or foot ulcers	9.3	8.1	5.4	2.8	14.7	7.8	9.5	8.2

continued

TABLE 73 Baseline individual characteristics used in the health economic modelling (n = 5000): categorical variables (continued)

Characteristic	Full cohort, %	Baseline HbA _{1c} ≥ 58 mmol/mol, %	69 mmol/mol > baseline HbA _{1c} ≥ 58 mmol/mol, %	80 mmol/mol > baseline HbA _{1c} ≥ 69 mmol/mol, %	Baseline HbA _{1c} ≥ 80 mmol/mol, %	Baseline HbA _{1c} < 69 mmol/mol, %	Baseline HbA _{1c} ≥ 69 mmol/mol, %	Per-protocol population, %
Retinopathy								
No complications	56.0	54.6	50.3	52.7	59.6	54.0	56.7	54.8
Background diabetic retinopathy	34.8	35.6	40.5	36.7	28.8	38.0	32.9	35.6
Proliferative diabetic retinopathy	9.3	9.8	9.2	8.6	11.5	8.0	10.4	9.6
MI								
No complications	97.8	97.8	98.6	95.8	98.6	98.9	97.0	98.0
MI	2.2	2.2	1.4	4.2	1.4	1.1	3.0	2.0
Stroke								
No complications	99.7	99.6	100	100	99.0	100	99.3	99.5
Stroke	0.3	0.4	0	0	1.0	0	0.7	0.5
HF								
No complications	99.4	99.6	99.0	100	100	99.2	100	99.5
HF	0.6	0.4	1.0	0	0	0.8	0	0.5
Angina								
No complications	98.8	99.0	98.6	98.5	100	97.8	99.2	98.8
Revascularised	1.2	1.0	1.4	1.5	0	2.2	0.8	1.2

Appendix 8 Participant Information Sheets

Participant Information Sheet – Main Study

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PATIENT INFORMATION SHEET FOR THE REPOSE TRIAL

Investigating whether insulin pumps are more effective in treatment of type-1 diabetes than multiple insulin injections when combined with diabetes education (Dose Adjustment for Normal Eating – DAFNE).

We are inviting you to take part in a research project to test the benefit of insulin pump treatment on people with Type 1 Diabetes. Before you decide whether to take part it is important to understand why the research is being undertaken and what will be involved. Please take time to read this information and discuss it with friends, family and your GP if you wish. Please feel free to ask questions if anything is unclear or if you would like more information.

What is the Purpose of the Study?

Insulin pumps, which are about half the size of a mobile phone and inject insulin continuously under the skin through plastic tubing, are becoming popular, particularly in the USA as a way of taking insulin in Type 1 diabetes. However, it is unclear whether they are better than insulin injections to control blood sugar and improve quality of life. Some professionals think that pumps have major advantages while others don't believe they offer much more than training in the skills of insulin adjustment, as offered by a standard DAFNE course using multiple daily insulin injections.

We already know that the standard DAFNE course, using multiple daily insulin injections, helps people to look after their own Type 1 diabetes more effectively. We now want to see if teaching people to use pumps as well as learning DAFNE, during the same week, helps people to get better glucose control and have less hypoglycaemia, than doing a DAFNE course and continuing on injections. In other words, do pumps offer added benefit over DAFNE alone to people with Type 1 diabetes.

The people who take part in the study need to be prepared to do either the course with standard injections or to do the course while using a pump instead of injections for 2 years.

Why have I been chosen?

We are asking you because you have Type 1 diabetes and may benefit from undertaking a DAFNE course. We are contacting all people in Sheffield, Harrogate, Cambridge, South London, Nottingham, Edinburgh, Dumfries and Galloway, and Glasgow who are already waiting to do a DAFNE course or who may benefit from a DAFNE course to see whether they might be prepared to join this study.

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Do I have to take part?

No. It is for you to decide whether or not to take part in the study. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. You will be free to withdraw from the study at any time, without giving a reason. This will not affect the standard of care you receive from the hospital staff or delay your participation in a regular DAFNE course. The only difference in the study from the standard care you would usually receive through DAFNE, is that you may be asked to include using an insulin pump to deliver your insulin during and for 2 years after your DAFNE course.

What will happen to me if I take part?**Before the Course:**

Before starting the course you will meet with one of the local DAFNE research team to discuss the course and the trial in detail. If you agree to participate we will ask you if you are happy to take part in various tests, such as checks of your weight, a HbA1c test obtained by blood sample and albumin creatinine ratio by urine sample. During this visit we will ask you to start checking your blood glucose regularly and you will also discuss your insulin treatment so that any changes to your usual dosing regimen can be agreed, as would happen on any standard DAFNE course. At this time you will be given your insulin pump if you were one of the participants allocated to have one.

We will also ask you to fill out a number of questionnaires. One of the questionnaires will be filled out at the visit with the member of the research team present and the rest will be given to you to take home and fill out in your own time. The other questionnaires will allow us to measure how you feel about your diabetes and how it affects your life and mood. These questionnaires will probably take about 15 minutes to complete. We ask you to return these questionnaires when you come to do the course. We will also ask you to keep a diary of any hypos (episodes of low blood sugar) for 2 weeks and to return this with the questionnaires.

The course:

Half the people who participate will have been allocated to do a standard 5 day DAFNE course and the other half will do a DAFNE course but will also be taught to use an insulin infusion pump. You will not be able to choose which therapy you are offered. You will find out which therapy you will receive approximately 2-3 weeks before the DAFNE course. People allocated to pump therapy will start using it immediately before the DAFNE course and be asked to continue to use pump for the following 2 years. You will receive support and advice in making sure you know how to adjust and keep to either treatment plan and you will be able to contact someone whenever you have a question or a problem on either treatment. The teaching on the pump course will be no different to a standard DAFNE course except for training on using a pump. The same educators who teach the standard DAFNE course will also deliver the pump course and it will be held in the same place.

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Ongoing evaluation after the course:

You will receive the usual support from the DAFNE team, the same as other DAFNE graduates and will continue to be able to contact someone whenever you have a question or a problem on either treatment. For 2 years after the course, we will evaluate both forms of treatment. We will ask you to keep a simple record of any hypos you have throughout this period and we will ask you to visit DAFNE staff 6 months, 1 year and 2 years after the course where you will have the same tests as before the course. The questionnaires will be sent out to your home address 2 weeks before you are due to visit in order that you would have time to fill these out and bring them back during your visit. As with the questionnaires at the start of the study, these should take about 15 minutes to complete.

As part of the REPOSE evaluation you can, if you wish, take part in an extra element of the study and agree to be interviewed. When you sign the consent form you will be asked whether you are happy for an interviewer to contact you regarding the interview element of the study, and to ask you whether you would like to participate. If the interviewer chooses to contact you for interviews then they will give you a patient information sheet to tell you all about this and there will be a separate consent form.

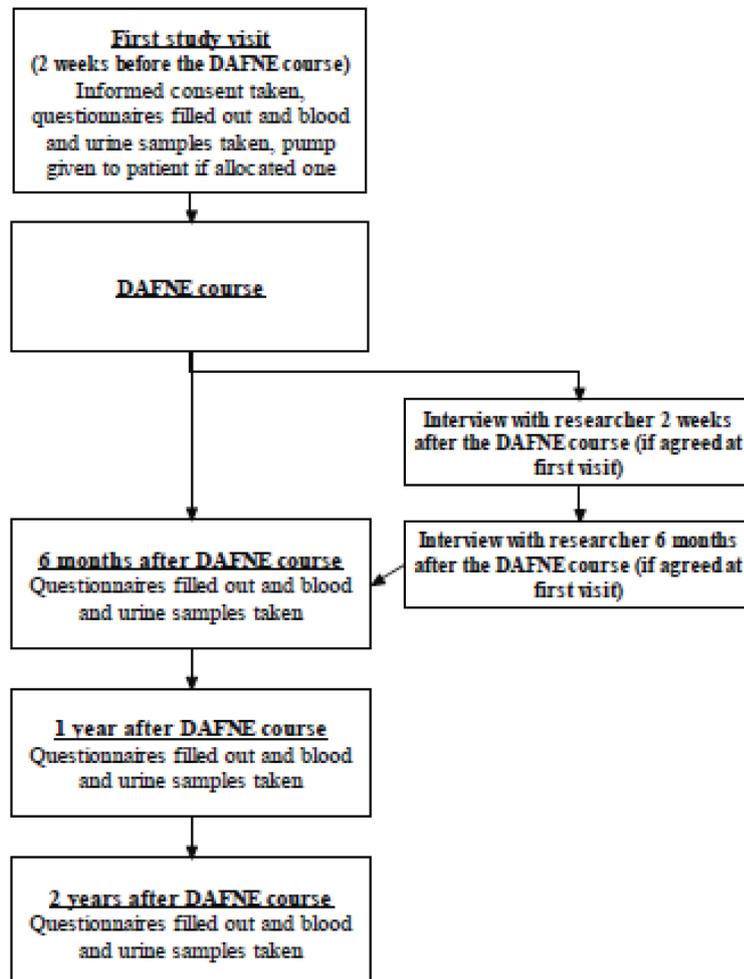
As part of the ongoing evaluation of DAFNE courses running within the UK, you will be invited to have your data included on a national database of DAFNE course participants. This would involve some of your data being copied and imported from the REPOSE database to the DAFNE database. There is also a separate patient information sheet and consent form for this.

After the 2 year evaluation:

Those who have been allocated to pump therapy will be asked to return the pump and we will provide you with the extra training you may need to transfer the skills in insulin management back to the use of injection therapy. If after 3 – 6 months of using DAFNE principles and injection therapy, you find your control less good than with the pump, we will tell the doctor responsible for your care. They will want to discuss this with you and may approach the people in your area who are responsible for funding and request finances for you to continue pump therapy. We cannot guarantee that this will be forthcoming but if you did achieve benefit on pump and DAFNE that is not sustained on DAFNE with injections, you may have a strong a case to have these funded permanently. For patients who were allocated to injection therapy at the start of the trial, the usual NHS criteria will apply for progressing to pump therapy (usually problems in achieving good overnight control without hypoglycaemia).

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The flow chart below is a simplified diagram to explain the process that you would go through if you were to take part in the study.



What are the benefits?

There may not be any benefits over and above that anticipated from attending a standard DAFNE course. All those who complete a DAFNE course should feel more confident about managing their diabetes and be able to adjust their insulin dose correctly to suit their choice of food. This should mean greater freedom, improved quality of life and improved blood glucose control. The study will allow us to give the Department of Health a much clearer idea of who benefits from an insulin pump and who does not. This could mean that everyone in the country who would benefit from a pump will be able to try one.

Once you have decided that you would like to take part and would be happy to return for your data collection visits and to fill out the questionnaires, we will send you a £5

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gift voucher after each follow up visit (6 month, 1 year, 2 years) in order to show our appreciation of your participation.

Are there any risks?

Previous experience shows that many people who use pumps prefer them, but this doesn't apply to everyone. Many trials have involved people who either wanted pumps or were advised by their medical teams to try them. It is often a matter of personal preference. There are small risks of infection with insulin pump use where the cannula is placed on the skin, but these are reduced by proper use of the device, which we will teach you. Because the pump only contains very short acting insulin which is given at a very slow rate between meals and at night, there is in theory, an increased risk of loss of diabetes control with high blood glucose concentrations and possibly even ketones in the urine (ketoacidosis). This means pump users do have to keep monitoring their blood glucose regularly, but this turns out to be no more frequently than the number of tests used to help DAFNE users achieve best outcomes. With modern pumps and methods of using them, this risk seems to be not much different than with standard treatment. Some people find wearing the pump intrusive or uncomfortable.

Will I be able to keep my pump at the end of the trial?

Since we are having to obtain the pumps especially for the trial, people will not be able to keep them at the end. The standard criteria the NHS uses in deciding who is given pump therapy will apply to you, whether or not you were allocated to a pump in the trial. It will be for your own GP (in England) or Health Board (in Scotland) to provide support if you decide you want a pump permanently and to obtain the necessary funding. We cannot guarantee that this funding will be forthcoming but if you did achieve benefit on pump and DAFNE that is not sustained on DAFNE with injections, you may have a strong case to have these funded permanently. In this instance every reasonable effort will be made to assist you.

What happens if I don't want to continue with the study?

You are free to withdraw from the study at any time. This will not affect your clinical care including the follow up support from the DAFNE team. If you have been using a pump, you will need to first contact your DAFNE educator to organise the switch from pump treatment and to receive advice and support concerning standard injection regime. We would ask you to consider completing the study questionnaires and having the blood test as you did at the beginning, but you are not obliged to.

Will it cost me any money?

No. Doing either course is free of charge and food will be provided each day. You will not have to pay for either the pump or the running costs.

What happens if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (contact details below). If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure. Details can be obtained from the hospital.

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed due to

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someone's negligence then you may have grounds for legal action and compensation against the University of Sheffield or [XXX hospital] but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

If you consent to take part in the research, some information may be taken from medical records, including details of the disease and treatment. We will inform your GP and usual diabetes care team that you are participating. All information that is collected about you during the course of this study will be kept strictly confidential and will be secure. When you sign the informed consent form we will ask you to provide your personal contact details. We ask for these so that we may contact you to arrange your visits. Information will only be accessed by the research team and regulatory authorities. All identifiable information will be destroyed 15 years after the end of the study.

What will happen to the results of the study?

We will publish the results in a scientific journal and produce a report that is freely available to anyone who wishes to read it. You will not be personally identified in any report or publication we produce. Please contact us using the details below if you would like to see a summary of the results when the trial is completed.

Who is organising and funding the research?

The research is organised by the University of Sheffield and funded by the Department of Health.

Who has reviewed the study?

This study was given a favourable opinion for conduct in the NHS by the Northwest 3 Research Ethics Committee-Liverpool East

Contacts for further information:

If you have any further questions you may ask **PI** (details below) or the DAFNE lead educator, **EDUCATOR**. You will be given a copy of this information sheet and a signed consent form for you to keep.

[local PI details]

[local educator details]

If you wish to speak to somebody who has no involvement in the trial, and would therefore not influence you in taking part in the trial you may contact:

[local patient advice service details]



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Qualitative Study Interview sub-study

Educator information sheet

What is the purpose of the research?

We would like you to take part in an interview study which is exploring people's experiences of the REPOSE trial. To do this, we are interviewing patients and educators who are taking part in the trial. This work is being undertaken in order to better understand the outcomes of the REPOSE trial and to improve future courses, information and support given to patients.

Why have I been chosen?

You have been chosen because you are the educator who is taking part in the REPOSE trial, and we would like to learn about your experiences of delivering courses during the trial.

What would taking part in the research involve?

If you decide to take part, you will be interviewed once in a place of your choosing and at a time most convenient to you. With your permission, your interview will be tape-recorded. We estimate that each interview will up to an hour, although this will depend on what you have to say.

Do I have to take part in the research?

It is entirely up to you whether you take part in this study or not. If you do decide to take part, you are still free to withdraw at any time without giving a reason.

Will my taking part in the research be kept confidential?

Yes. All information that is collected about you during the course of the research will be kept strictly confidential. All the information you provide will be kept in a locked filing cabinet and stored on a password-protected computer within a locked office at the University of Edinburgh, under the supervision of the research team. All personal information will be removed from these computer files and they will not be shown to anyone outside the research team. When we type up the recordings made during interviews and write about the results of the research, all your personal details will be removed so that no-one will know who you are.

What will happen to the results of the research?

The results will be published in scientific and policy journals and presented to key groups of health professionals, voluntary organisations and groups involved in the care of people with diabetes. The results will be used to help to develop and improve education courses for people with diabetes and the methods used to evaluate them.

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Are there any benefits to taking part in the research?

Although there may be no direct benefits to you personally, we hope that you find the research an interesting experience. Taking part will help us develop and improve education courses for people with diabetes.

Are there any disadvantages to helping with this research?

Your interview may take up to one hour of your time.

Who is funding the research?

The research is funded by the HTA (Health Technology Assessment).

Who has reviewed the research?

The research has been approved by [name of] independent research ethics committee.

What do I need to do next?

If you agree to take part, the Research Fellow [name to be added] will contact you to arrange to interview you. You will be asked to sign a consent form at the start of the interview.

Thank you very much for taking the time to read this. In the meantime, if you would like more information or want to ask any questions about this research please contact:

[Name of researcher]
University of Edinburgh
Centre for Population Health Sciences
Medical School, Teviot Place
Edinburgh EH8 9AG
Tel:
Email:

Thank you for taking the time to read this information sheet.

Copies: 1 for participant, 1 for researcher

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REPOSE Qualitative Study Interview sub-study

Patient information sheet

We would like you to take part in an interview study which is exploring people's experiences of taking part in the [name of trial]. Before you decide whether or not to take part in this interview research, it is important that you understand why it is being done, and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

Please ask if anything is not clear (contact details are given at the end of this form). Taking part in this interview research is voluntary and your medical care will not be affected if you decide you do not wish to take part.

What is the purpose of the research?

We are interviewing people about their experiences of taking part in the REPOSE trial. This is so that we can get a better understanding of what people like and dislike about the courses they attend during the trial. We also want to look people's experiences of managing their diabetes after they have attended their courses. The research will help us to understand the findings of the REPOSE trial and be used to improve future courses, information and support given to patients.

Why have I been invited?

You have been invited because you have agreed to take part in the trial. We would like to learn about your experiences of, and views, about your course, and how you manage your diabetes after you have been on the course.

What would taking part in the research involve?

You would be interviewed in a place of your choosing and at a time most convenient to you. With your permission, your interview would be tape-recorded. We estimate that each interview would last about an hour, although this would depend on what you have to say.

Do I have to take part in the research?

It is entirely up to you whether you take part in this interview study or not. If you do decide to take part, you will be free to withdraw at any time without giving a reason. You can take part in the trial without having to take part in the interview study.

Will my taking part in the research be kept confidential?

Yes. All information that is collected about you during the course of the research will be kept strictly confidential. All the information you provide will be kept in a locked filing cabinet and stored on a password-protected computer within a locked office at Edinburgh University. This will be under the supervision of the research team. All personal information will be removed from these computer files and they will not be shown to anyone outside the research team. When we type up the recordings made during interviews and write about the results of the research, all your personal details will be

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removed so that no-one will know who you are.

What will happen to the results of the research?

The results will be published in scientific and policy journals and presented to key groups of health professionals, voluntary organisations and groups involved in the care of people with diabetes. The results will be used to help to develop and improve education courses for people with diabetes.

Are there any benefits to taking part in the research?

Although there may be no direct benefits to you personally, we hope that you find the research an interesting experience. Taking part will help us develop and improve education courses for people with diabetes.

Are there any disadvantages to helping with this research?

Your interview may take up to one hour of your time.

Who is funding the research?

The research is funded by the HTA (Health Technology Assessment).

Who has reviewed the research?

The research has been approved by [name of] independent research ethics committee.

What do I need to do next?

If you agree to take part, a member of the research team will contact you to arrange to interview you. You will be asked to sign a consent form at the start of the interview.

Thank you very much for taking the time to read this. In the meantime, if you would like more information or want to ask any questions about this research please contact:

[Name of Research Fellow] Centre for
Population Health Sciences
University of Edinburgh
Teviot Place
Edinburgh, EH8 9AG
Tel & Email: to be added

If you wish to speak to somebody who has no involvement in the study, and would therefore not influence you in taking part you may contact.

[Insert Local Advisor Contact details here]

Thank you for taking the time to read this information sheet.

Copies: 1 for participant, 1 for researcher.

Appendix 9 Qualitative substudy topic guides

Qualitative substudy – topic guide for patient interviews at baseline.

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DAFNE pump study (REPOSE) Interview sub-study

Patient ID:..... Location:..... Date:.....

Interview Topic Guide for Patients – Post course

Note: the contents of the topic guide might be revised in light of issues identified during an on-going analysis of interview data. This is standard procedure in a qualitative study employing an emergent design.

Background and history of diabetes

- Background: can you tell me a bit about yourself, such as who you live with and what you do? When did you first find out you had diabetes?
- Support needs:
 - What contact have you had with health services and healthcare professionals (HCPs) since diagnosis?
 - How have you felt about past advice and support from HCPs?
 - What types of support have you received from family/friends?
 - Have you sought any additional information and support? From where?
- Living with and managing diabetes since your diagnosis:
 - What sorts of things have you done to manage your diabetes over time? (*e.g. taking insulin, SMBG; food/alcohol, physical activity*)
 - Has your treatment (i.e. type of insulin and timing of injections etc) changed over time? In what ways? How did you feel about this?
 - Before DAFNE, what was your self-management of diabetes like?
 - Over time, what things have affected your diabetes self-management?
 - Tell me about your experiences and responses to episodes of hypoglycaemia in the past?

Food choices, dietary patterns and physical activity (pre-course)

- Background food choices before starting DAFNE:
 - Can you tell me about the types of foods you usually eat, starting with the first meal of the day (*Explore meal contents, when/where eaten, variation in choices, snacking, routines*)?
 - Who chooses and prepares your food? Are there any exceptions to this?
 - Are there any circumstances that impact on mealtimes and dietary patterns? (*Explore family-, social-, work-life*).
 - When did you normally choose to inject surrounding eating?
- What types of sports/physical activities were you involved in before your course?
 - How did you manage your diabetes when you were doing these activities?

Decisions to attend DAFNE, pre-course

- Approaches regarding DAFNE and decision to enrol
 - How and by whom were you approached?

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- What did you hope and expect to gain from the course? Why did you decide to attend?
 - What did you think when told it would be a group education course?
 - Had you previously received any education on or relating to any of the information you received on the DAFNE course – e.g. carb counting?
-

Views about the trial and decision-making surrounding attendance

- At what point in the process of waiting to hear about your place on a course were you invited to take part in the trial?
 - How were you approached and what did you think/feel at the time?
 - What was your understanding of the purpose of the trial?
 - Why did you agree to take part?
 - When informed about the trial, did you have a preference for attending a standard DAFNE course or a pump course? (*probe to establish whether patients had ever talked to HCPs about the possibility of moving onto a pump prior to being approached to take part in the trial*)
 - How did you feel after finding out which course you had been allocated to?
 - At any point did you consider withdrawing from the trial? Why?
 - Any other hopes, expectations or concerns about taking part in the trial?
-

Views on the course attended

- Looking back at the course you've just attended, which aspects did you find helpful and unhelpful? (*e.g. timing /duration of course, specific aspects of the curriculum*)
 - Did the course fulfil your initial expectations? (*Explore any assumptions made regarding course type in advance of randomisation*).
 - [If relevant, why did the participant not feel able to complete the full course?]
 - What new skills did you learn when attending the course?
 - What barriers might affect your use of specific skills taught on the course (*e.g. carb counting, SMBG, diary keeping, using a pump (if relevant)*)
 - *What kinds of adjustments did you make to your treatment (e.g changes to ratios) during the course? How did you feel about making these changes?*
 - Views on group education and comparisons with previous experiences
 - What aspects of the group education format did you like and dislike? (*explore normalising / sharing of experience, emotional support given and received, increased self-efficacy, pro's/cons of group?*).
 - How did you feel about the review sessions and group environment?
 - How able were you to participate and have an active role?
 - How does DAFNE training compare with your past experiences of educational instruction?
-

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- Views on how diabetes is managed following the course attended
 - Following your course, have you made any changes to how you think about and self-manage your diabetes? What are these changes?
 - What impacts do think the skills and education received on the course might have on your daily life in the coming months? (*e.g. meal choices, family life, social life*)
 - Have you made any immediate changes to dietary patterns? What changes have you made, and why?
 - How do you think using the DAFNE principles will fit within your everyday life? (*e.g. impact of family-life, pressures of work*)
 - How do you feel about continuing to record your CPs and BG readings in the diary?
 - What were the goals that you set during the course? How did you decide upon these? Have any of them changed since the course? How realistic / achievable are they?
 - Has your approach to managing hypos changed at all following the DAFNE course? Why?
 - After DAFNE, have there been any changes in how you approach food / exercise / injection timing? Might this change in future?

 - What is the main message you took from your course?
 - How, if at all, do you see your diabetes impacting upon your health in future?
-

For patients who attend the pump course

- What's it been like moving onto a pump? How do you think using a pump compares with experiences of managing your diabetes using injections?
 - Has using the pump been different to what you imagined it would be like
 - Any unanticipated benefits/problems to using the pump
 - Impact on lifestyle compared to previous experiences of injection regimens
 - How have other people reacted to you moving onto a pump?
 - Are you wanting and willing to remain on a pump (for the duration of the trial, in the long term), why?
-

Future developments

- Do you have any ideas/suggestions for how the course you've just attended could be improved?
- What support might help you to continue using the skills and training received on the course? (*Explore support from HCPs, family and friends*)
- What are your hopes and expectations for the future
- Is there anything else you would like to add that you think I haven't covered?

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DAFNE Pump study (REPOSE) Interview sub-study

Patient ID:..... Location:..... Date:.....

Interview Topic Guide for Patients – 6 month follow-up

N.B. the follow-up interviews will be tailored to individual patients and in light of their specific responses in their previous interview.

Introductory questions:

- What's been happening in your life since we last spoke?
 - Have there been any changes in your circumstances – job, family, living arrangements – *tailor for those you have knowledge of*. Do you have any significant events coming up in the near future?

Living with diabetes post-course

- Can you tell me what it's been like for you in managing your diabetes since we last spoke in *[month]* when you had completed the course?
- How, if at all, has your management of diabetes changed over the last six months since attending the course?
- To what extent are you testing your BG and keeping a DAFNE diary (BGs and CPs)? What affects your testing regimen and diary keeping? If recording/testing: How manageable have you found this to be?
- How are you determining CPs? What has got in the way? Do they use the course book at all? How?
- How, if at all, have you made adjustments to insulin doses over time? *[Check for changes to background insulin and/or QA ratios. Are adjustments being made short-term – corrections, or are they following a stepwise approach? If completing diaries then do they use these to determine patterns? If not, why not?]*
- Do you look for patterns? What has helped/hindered you in making adjustments? *(i.e. understanding of insulin peaks/profile; pattern spotting/recording; support)*.
- Do you feel that you are following DAFNE or adapting its rules for yourself?
- How, if at all, do the DAFNE targets feature in your management?
- Can you remember the goals that you set following the course? How have you progressed with regards this goal? Have you set any further goals?
- How much of the information do you remember from the course?

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- What have been the main successes of your approach? And what have been the main challenges you have encountered? *Explore any 'disappointments'.*
- What do you feel is the impact of diabetes on your daily life now? What about the impact of diabetes on significant others (partner/family/friends)?
- How do you feel about your role in managing your diabetes, six months after completing the course? Has it changed?
- How have you felt about being able to continue using the DAFNE principles?
- What is your current experience of hypoglycaemia and how are you currently treating your hypos?
- Are there specific aspects of the education received on the course which you have put into practice to help you manage your diabetes? (*hypo treatment; sick day rules, correctives*) Any aspects that you had more difficulty in implementing? Why?
- Have you had any recent HbA1c readings taken? When was this? Why did you have the test done at this point in time? [Why did you hold off having it?] What was this? What effect, if any, did this reading have for you? *Explore in relation to the patient's previous results? Are they better/worse?*
 - What effect has your HbA1c reading had on your views of DAFNE?
- Can you think of any ways in which your current diabetes management has affected your life/lifestyle? What are these / why?

Tailored questions for pump users

- Explore likes/dislikes of using a pump; how this compares with previous experiences of managing diabetes using injections
- If relevant, explore reasons for discontinuing pump usage

Food, exercise and lifestyle in general

- Have you made any changes to your food choices since attending your course? What are these changes and what prompted them? (*Explore: food cooked in the house; eating out; daily routines and at weekends; snacking behaviour*).
- Have there been any changes to the way that you relate to food / the sorts of foods that you eat? What are these? Why?
- Tell me about your food choices for breakfast, lunch and dinner?
- DAFNE also contained advice on exercise. Have you found the advice that was offered to be of use? In what ways? How do you now approach exercise?
- How have you managed with alcohol and the DAFNE guidance provided?

Support structures and environment

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- Can you tell me about the follow-up support – did you attend the meeting? If so, then of what use was it to you? Why/why not?
 - How did you find meeting up with the group again at the follow-up event? How were others doing? How did this affect you?
 - Any further contact with any of the group outside of DAFNE? What did this consist of and did you find it beneficial?
 - Over the last six months, what experiences/contact have you had with healthcare professionals? (*Who, are they DAFNE trained? DAFNE educators; for pump users – have these HCPs been familiar with pump usage*)
 - Have you had contact with other HCPs outside of DAFNE? What effect, if any, has your DAFNE training had on these encounters?
 - Have you attended/received any further follow-up events since attending the DAFNE course; what are your views about this?
 - What support do you feel would be of benefit to you at this point in time and in the near future? (*Exploring unmet needs*). What might have helped earlier?
-

Summary questions

- How, if at all, do you see your disease impacting upon your current health and your health in the future?
 - Looking back six months to the time when you attended the DAFNE course, is there anything that might have been done differently 1) on the course itself or looking at how it was structured, 2) by yourself following the course?
 - What would you like to happen next? Preferences for future treatment (pumps Vs MDIs)
 - What's it been like taking part in the trial so far?
 - Views about randomisation outcome
 - Willingness to complete questionnaires etc.
 - Anything else you would like to add?
-

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DAFNE Pump study (REPOSE) Interview sub-study

Interview Topic Guide for DAFNE Educators

Note: the contents of the topic guide might be revised in light of issues identified during an on-going analysis of interview data. This is standard procedure in a qualitative study employing an emergent design.

Background and involvement in DAFNE

- To get some background, can you tell me a bit about your career to date?
 - How, and why, did you first get involved in working with patients with type 1 diabetes?
- When and why did you decide to train as a DAFNE educator?
 - Tell me about your training and what it consisted of?
 - How much experience do you have of working on DAFNE courses?
 - What do you think you personally bring to the course?
 - What previous experiences do you have of moving patients onto pumps?
- What do you think are the biggest and / or most typical challenges T1DM patients encounter in managing their disease?

Background and involvement in the trial

- Can you tell me a bit about how, and why, you come to be involved in the pump trial?
- Were you involved in recruiting patients onto the trial?
 - What were patients' responses to being approached to take part?
 - Was there any sense that patients had a preference for one type of course (pump course vs standard DAFNE) rather than another?
 - Did any patients decline to take part in the trial? Why?

Experiences of delivering DAFNE pump courses

- How does your experience of delivering the pump course compare with your experiences of delivering standard DAFNE courses? Were there any differences in delivery?
 - Has the pump course and your delivery of it panned out in the ways that you had had initially expected?
 - Did any issues arise delivering the pump course which you had not expected, what were these; how did you deal with these?
 - What do you think about the way in which the curriculum has been adapted for pump course? Do you think that further refinements and adaptations are needed? What are these?
-

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Views about course dynamics

- Do you think there are any obvious differences in how patients interact and support one another on pump courses compared with the standard DAFNE course?
- Do you think there are any differences in the kinds of insulin adjustments (to background, quick acting doses and ratios) made and in how these are considered by patients?
- Do you think the adjustments are more or less conservative on pump course compared to a standard DAFNE course? Why?
- Do you perceive any other obvious differences and/or similarities between how patients have received and responded to the two types of course?

The DAFNE course: attributes of success / failure

- Drawing on examples from a the most recent pump course you have delivered, which elements did you think patients found the most beneficial? Why do you think this? Do you think there were any differences in benefits received on pump course compared to a standard DAFNE course?
- Which features of the course do you think patients find the most difficult to implement? Why do you think this is? (*Draw on specific examples, e.g. CHO counting SMBG, occurrences of hypos*) Did this differ from your experience of difficulties surrounding a standard DAFNE course?

Patients experiences of managing the diabetes on a pump

- What sorts of patients, in your opinion would benefit from being moved onto a pump?
- Based on your experiences to date, what do you think the main issues and challenges patients confront managing their diabetes after moving onto a pump?
- Do you think some patients adapt better to pumps than others? Why?
- What kinds of input and support do you think patients need to manage their diabetes using a pump over time?
- Based on your experience, why do you think some patients discontinue using pumps?

Future courses/other points

- Do you have any suggestions for ways in which this method of delivering a DAFNE pump course might be improved? (*e.g. content of curriculum, timing of courses*).
- Do you anticipate there being any differences in outcomes between patients attending the standard DAFNE courses and patients attending a pump course? (*Explore differences in clinical / psychological outcomes*) Why?
- Do you have anything else you would like to add that I haven't covered?

Appendix 10 Summary of amendments

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
Substantial amendment 1	13 June 2011	To allow ethical review of the consent forms, patient information sheets and interview topic guides for the qualitative substudy/component of the REPOSE Trial	None	20 June 2011
Substantial amendment 2	6 July 2011	<p>Protocol:</p> <ol style="list-style-type: none"> 1. General information: PI and centre details 2. Protocol amendment summary details 3. Trial introductory paragraph, p. 11: to make text agree with Figure 1 4. Urine samples and ACR: clarified that this test will be taken during the trial 5. Inclusion and exclusion criteria: one inclusion and one exclusion criteria added: <ul style="list-style-type: none"> ○ 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 6. DAFNE pre-course pump session: clarified when pump use on saline would be taking place 7. Appendices A–X removed and considered as stand-alone documents from now on 8. Typographical errors corrected (e.g. clarification of the cut-off points for the HbA_{1c} categories) <p>Patient information sheet:</p> <ol style="list-style-type: none"> 1. Geographical areas for the trial have been amended according to centre removal and additions, p. 2: sentence inserted to clarify that ACR will be measured by urine sample 2. Sentence amended to clarify process of continuation of pump therapy in England and Scotland <p>Northwest 3 REC-Liverpool East listed as ethics committee for which approval has been granted</p>	<p>Protocol to v3, 28 June 2011</p> <p>Patient information sheet to v3, 28 June 2011</p>	20 July 2011

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
		<p>REPOSE leaflet:</p> <ol style="list-style-type: none"> Addition to clarify that urine samples will be taken in addition to blood samples at baseline, 6, 12 and 24 months <ul style="list-style-type: none"> Minor amendments included as notification: consent form – version and date of the appropriate patient information sheet has been amended <p>CTA:</p> <ol style="list-style-type: none"> Centres amended Inclusion/exclusion criteria added Contact details, typographical errors and updated details (ethics approval details, ISRCTN number) added <p>No changes made to the following documents, but omitted from original application to ethics:</p> <ul style="list-style-type: none"> follow-up instructions for filling in your diary, v1, 7 January 2011 DTSQc (validated questionnaire) 	<p>REPOSE leaflet, to v3, 28 June 2011; participant consent form, to v3, 28 June 2011; baseline hypoglycaemic recall forms: 1 × severe, 2 × moderate, to v2, 28 June 2011; follow-up hypoglycaemic recall forms: 1 × severe, 2 × moderate, to v2, 28 June 2011</p> <p>CTA</p>	
Substantial amendment 3	8 August 2011	<p>To allow ethical review of a consent form, patient information sheet and interview topic guide for interviews undertaken with two to three participants who were involved in a pump pilot study (a smaller-scale version of the REPOSE Trial)</p> <p>The aim was to create a short video clip to show to potential participants for the REPOSE Trial at local information meetings for the trial</p> <p>The aim of the video clips is to give potential participants an understanding of what it is like to take part in a clinical trial and be on pump therapy to control their diabetes, from the perspective of someone who has taken part in a similar trial (i.e. the pump pilot)</p> <p>In addition, the video clip is introduced and ended by short foreword and ending by the chief investigator</p>	<p>No documents changed but the following documents were reviewed:</p> <ul style="list-style-type: none"> informed consent form for REPOSE video clip, v1, 2 August 2011 patient information sheet for REPOSE video clip, v1, 2 August 2011 interview topic guide for REPOSE video clip, v1, 2 August 2011 other REPOSE video elements: foreword and closing statement from chief investigator, v1, 2 August 2011 	22 August 2011
Substantial amendment 4	6 September 2011	<ol style="list-style-type: none"> To add and remove centres: <ul style="list-style-type: none"> addition of Royal Infirmary of Edinburgh (PI: Dr Alan Jaap) removal of University of Edinburgh (Dr Julia Lawton) and Monklands Hospital (Dr Thekkepat Sandeep) Notification that Harrogate and District NHS Foundation Trust (PI: Dr Peter Hammond) are delivering part of the trial intervention using 	N/A	7 September 2011

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
Substantial amendment 5	12 September 2011	<p>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</p> <p>Protocol:</p> <ol style="list-style-type: none"> 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 v3 to v4 3. Trial summary, p. 7: list of centres amended to correspond with removal/addition of centre 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 1 month to 6 weeks 6. Table 1: Documents for Data collection, pp. 26–30 – details of severe and moderate hypoglycaemic episodes recording process amended in table 7. Typographical errors and formatting: references to appendices removed from protocol; formatting of figures undertaken <p>Participant consent form</p> <p>REPOSE participant information sheet</p> <p>SAE contact card</p> <p>Psychosocial questionnaire</p> <p>Follow-up instructions for filling in your diary</p> <p>Minor amendments included for notification:</p> <ul style="list-style-type: none"> • REPOSE invitation letter to be sent with patient information sheet • Consent for qualitative study 	<ul style="list-style-type: none"> • Protocol to v4, 1 September 2011 • Participant consent form, v4, 1 September, 2011 • REPOSE invitation letter to be sent with patient information sheet, v2, 1 September 2011 • REPOSE participant information sheet, v4, 1 September 2011 • SAE contact card, v2, 1 September 2011 • Psychosocial questionnaire, v2, 1 September 2011 • Follow-up instructions for filling in your diary, v2, 1 September 2011 • Consent for qualitative study, v2, 1 September 2011 	NRES, 19 September 2011

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
		<p>New documents:</p> <ol style="list-style-type: none"> 1. Non-participation form, v1, 1 September 2011 (replaces non-participation details in REPOSE invitation letter to be sent with patient information sheet, v1, 7 January 2011) 2. Instructions for recording hypoglycaemic episodes, v1, 1 September 2011 (replaces baseline instructions for filling in your diary, v1, 7 January 2011) <p>Severe hypoglycaemic episodes log, v1, 1 September 2011, and moderate hypoglycaemic episodes form, v1, 1 September 2011 (replaces baseline hypoglycaemic recall forms: 1 x severe, 2 x moderate, v2, 28 June 2011)</p> <p>CTA</p>	<ul style="list-style-type: none"> • Non-participation form, v1, 1 September 2011 • Instructions for recording hypoglycaemic episodes, v1, 1 September 2011 • Severe hypoglycaemic episodes log, v1, 1 September 2011 • Moderate hypoglycaemic episodes form, v1, 1 September 2011 <ul style="list-style-type: none"> • CTA 	
Minor amendment 1	24 October 2011	<ol style="list-style-type: none"> 1. Reformatting or minor changes to the following documents: <ul style="list-style-type: none"> REPOSE leaflet, v3, 7 October 2011 (previously v2, 28 June 2011) REPOSE poster, v2, 7 October 2011 (previously v1, 7 January 2011) SAE contact card, v3, 7 October 2011 2. Name changes of centres: <p>The names of some centres on the CTA are listed slightly incorrectly (e.g. Cambridge centre is listed as Cambridge University rather than Cambridge University Hospitals NHS Foundation Trust)</p> 	<ul style="list-style-type: none"> REPOSE leaflet, v3, 7 October 2011 REPOSE poster, v2, 7 October 2011 SAE contact card, v3, 7 October 2011 	NRES approval: N/A; notified in substantial amendment 6
Minor amendment 2	3 November 2011	Consent, v6, 3 November 2011: revised so the participant ID is now the participant's DAFNE number	Consent, v6, 3 November 2011	NRES approval: N/A; notified in substantial amendment 6
Minor amendment 3	9 January 2012	REPOSE invite letter, v3, 6 January 2012: addition of an optional sentence to inform potential participants the date of local recruitment evenings/afternoons.	REPOSE invitation letter, v3, 6 January 2012	NRES approval: N/A; notified in substantial amendment 6
Minor amendment 4	12 January 2012	REPOSE GP letters – MDI and pump: minor amendments so the trial name listed is REPOSE not the pump pilot study	<ul style="list-style-type: none"> REPOSE GP letter: MDI, v2, 9 January 2012 REPOSE GP letter: Pump, v2, 9 January 2012 	NRES approval: N/A; notified in substantial amendment 6
Minor amendment 5	18 January 2012	<p>Agreed in risk assessment meeting with Sponsor on 9 January 2012 – amendments to the REPOSE protocol:</p> <ol style="list-style-type: none"> (a) Clarification of the IMP management during the trial, including tracking, accountability and labelling (b) Clarification to one of the exclusion criteria – that only patients with a 		NRES approval: N/A; notified in substantial amendment 6

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
		<p>strong need for a pump will be excluded from taking part in the trial</p> <p>(c) Clarification as to what constitutes the AE 'Unexplained constantly high blood glucose readings', which is defined as three consecutive readings > 20 mmol and over 12 hours</p> <p>(d) Change to the SAE reporting process. SAE forms are to be faxed to the Sheffield CTRU instead of the sponsor (as delegated by the sponsor)</p> <p>(e) Addition of pump site infection as an AE</p> <p>(f) At present there are two outcomes listed as primary outcomes. It was discussed at our TSC that there should only be one primary outcome. Therefore, we have downgraded 'The proportion of participants reaching the NICE target of a HbA_{1c} level of 7.5% (58 mmol/mol) or less' to a secondary outcome</p> <p>(g) In addition, minor typographical corrections and formatting have been undertaken</p>		
Substantial amendment 6	17 January 2012	<p>1. Questionnaire: amendment to question listing qualifications and educational attainment so applicable to both England and Scotland</p> <p>2. Time allocation revealed to patients: from 2 weeks before their DAFNE course to 4 weeks before their course, to allow the participant a greater amount of time to know their allocation to a pump or MDI. In addition, this change will allow pump participants more time to organise attendance of a family member or friend for support at their first appointment when the participant switches to pump therapy (this often happens in standard clinical care)</p> <p>Notification of minor amendments 1–5</p>	Psychosocial questionnaire, v3, 16 January 2012; protocol, v5, 4 January 2012	6 February 2012
Minor amendment 6	18 January 2012	The lost to follow-up definition (p. 33) has been amended to clarify that lost to follow-up participants are those who fail to attend more than two follow-up visits, <i>including the 24-month follow-up appointment</i> (previous definition was participants who failed to attend more than two follow-up visits)	REPOSE protocol, v6, 16 January 2012	NRES approval: N/A; notified in substantial amendment 7
Substantial amendment 7	17 January 2012	<p>1. Blinded review of HbA_{1c} (measure of the level of blood glucose control):</p> <p>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 HbA_{1c} category (i.e. $\geq 7.5\%$)</p>	REPOSE protocol, v6, 16 January 2012	6 February 2012

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
		<p>or < 7.5%). The trial statistician will look at the proportions in each HbA_{1c} category, and numbers of participants with a HbA_{1c} of \geq 7.5% threatens the ability of the trial to detect a difference in primary outcome (i.e. there are substantially more subjects recruited with a HbA_{1c} of < 7.5% than anticipated), then an additional inclusion criteria will be added to limit recruitment only to participants with a HbA_{1c} of \geq 7.5% in order to ensure that the trial can detect a difference in the primary outcome</p> <p>2. Withdrawal from the pump criteria:</p> <p>Removal of 'Participant becomes pregnant' as a reason for withdrawal from the pump. Amended so that the decision whether or not 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)</p> <p>3. Consent process: Amended to allow the witnessing of the consent by the educator can take place when the consent form (signed by the participant) is received in the post (instead of at the baseline appointment)</p> <p>Notification of minor amendment 6</p>		
Substantial amendment 8	23 January 2012	Amendment to the psychosocial questionnaire so that the HFS and DSQOL are exact copies of the validated versions	Psychosocial questionnaire, v4, 20 January 2012	6 February 2012
Minor amendment 7	7 February 2012	<p>1. Qualitative substudy consent form – amended so that the participant ID is now the DAFNE number (as for the main trial consent form: minor amendment 2): v3, 7 February 2012</p> <p>2. REPOSE pump diary, v2, December 2011. The REPOSE participants complete a blood glucose diary and are taught this during their normal DAFNE course. The blood glucose diary for the MDI participants is the standard version that is used during non-trial DAFNE courses. For the pump participants, this diary has been slightly modified so that it is applicable to pump participants</p> <p>(Please note that no other versions of the pump diary have been used. The v2 pump diary reflects internal editing at DAFNE, who modified the MDI diary)</p>	Qualitative substudy consent form, v3, 7 February 2012	Submitted with substantial amendment 9 to REC

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
Minor amendment 8	13 April 2012	<p>Clarification of the exclusion criteria of having used pump therapy in the last 3 years</p> <p>Clarified that this must be 'significant use', which is defined as no more than 2 weeks use of the pump in the last 3 years</p> <p>Discussed and agreed this definition with the TMG today</p>	REPOSE protocol, v7, 3 April 2012	Submitted with substantial amendment 9 to REC
Substantial amendment 9	16 April 2012	<p>Creation of a new participant letter to be sent with the follow-up psychosocial questionnaire</p> <p>Addition of Nottingham as a research centre</p> <p>Notification to REC of minor amendments 7 and 8</p>	Psychosocial questionnaire letter, v1, 11 April 2012	1 May 2012
Minor amendment 9	24 May 2012	Change of sponsor/lead NHS R&D details from Jim Lithgow to Erica Wallis	None	Ethics approved on 24 May 2012
Substantial amendment 10	29 May 2012	Change of PI at KCH centre from Professor Stephanie Amiel to Dr Pratik Choudary	None	27 June 2012
Minor amendment 10	12 June 2012	<p>Increased number of centres where qualitative research will take place from 3–4 to 7</p> <p>Altered time the educators find out about treatment allocation from 6 weeks to 4–6 weeks</p> <p>Clarified inclusion criteria regarding having a 12-month history of diabetes: participants must have had a 12-month history of diabetes by the time of baseline/DAFNE course</p>	REPOSE protocol, v7.1, 12 June 2012	Submitted with substantial amendment 10 to REC
Minor amendment 11	6 July 2012	<p>Clarification that the review of baseline HbA_{1c} is not blinded, as it does not need to be</p> <p>Clarification of severe needle phobia exclusion criteria: clarification that the severity of phobia assessed considering if the phobia might preclude full participation in either treatment arm or influence the participant's preference for pump therapy</p> <p>Clarification of unstable psychological problems: clarification that such conditions are active enough to preclude the participant safely taking part in the trial (based on investigatory judgement)</p> <p>KCH course 3 and 4: change of venue for DAFNE course, Springfield Medical Centre</p>	REPOSE protocol, v7.2, 9 July 2012	Submitted with substantial amendment 11 to REC

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
Substantial amendment 11	7 August 2012	Creation of a participant newsletter to be issued just before each of the scheduled follow-up appointments, (i.e. 6, 12 and 24 months post baseline)	6-month follow-up participant newsletter, v1, 24 July 2012	Ethics approval: 21 August 2012
Substantial amendment 12	24 August 2012	To increase the number recruited to the study. Dropouts 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.	REPOSE protocol, v8, 20 August 2012	Ethics approval: 12 September 2012
Minor amendment 12	24 August 2012	<p>Psychosocial questionnaire, v4.1, 28 June 2012:</p> <ul style="list-style-type: none"> Minor formatting to make some text bold to highlight that participants choose one option only for qualifications and employment questions <p>REPOSE protocol v8:</p> <ul style="list-style-type: none"> The time for follow-up questionnaires to be sent prior to a follow-up appointment has been changed from 4 weeks to two to 6 weeks to allow for holiday periods 	<p>Psychosocial questionnaire, v4.1, 28 June 2012</p> <p>REPOSE protocol, v8, 20 August 2012</p>	Submitted with substantial amendment number 12 to REC
Minor amendment 13	12 November 2012	To amend the patient information sheet to include the new research centre (Nottingham); the consent form references the patient information sheet and it is therefore necessary to amend this	<p>Patient information sheet, v5.1, 4 September 2012</p> <p>Informed consent form, v6.1, 4 September 2012</p>	Submitted with substantial amendment 13 to REC
Substantial amendment 13	9 November 2012	Change of PI at KCH centre, back to Professor Stephanie Amiel from Dr Pratik Choudhary	None	Ethics approval: 12 November 2012
Substantial amendment 14	12 January 2013	Creation of a participant newsletter to be issued just before the 12-month follow-up appointment	12-month follow-up participant newsletter, v1, 7 January 2013	Ethics approval: 13 February 2013
Substantial amendment 15	20 May 2013	<p>REPOSE protocol v9:</p> <ul style="list-style-type: none"> Data collection procedure: added letters as a method of reminding participants of appointments and removed specified time frame for reminders Participant retention and return of data: in cases when it has not been possible for a participant to attend their follow-up visit, attempts will be made by the educator to collect appropriate data from the participant over the telephone, and/or to obtain the relevant data from the participant's medical records A second questionnaire will be posted to the participant with a pre-paid reply envelope when the participant-completed psychosocial questionnaire has not been returned 	REPOSE protocol, v9, 9 May 2013	Ethics approval: 10 June 2013

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
		<ul style="list-style-type: none"> Participant identification centres will be used at some centres to assist in the identification of suitable participants Amendment to KCH PI 		
Substantial amendment 16	26 July 2013	Creation of a letter and supporting documentation to send to all REPOSE participants reminding them of how to deal with illness and other problems that may occur	<p>REPOSE Ketone Management Reminder 2013 – CSII – v1, 28 June 2013</p> <p>REPOSE Ketone Management Reminder 2013 – MDI – v1, 28 June 2013</p> <p>REPOSE Ketone Management Reminder Letter – CSII v1, 28 June 2013</p> <p>REPOSE Ketone Management Reminder Letter – MDI v1, 28 June 2013</p>	Ethics approval: 5 August 2013
Substantial amendment 17	23 September 2013	Creation of a participant newsletter to be issued 18 months post course	18-month follow-up participant newsletter, v1, 15 August 2013	Ethics approval: 3 October 2013
Substantial amendment 18	24 December 2013	<p>Three additional questionnaires to be added to the psychosocial questionnaire pack at the 24-month time point only:</p> <ul style="list-style-type: none"> DAFNE principles questionnaire use of bolus calculators questionnaire pump use questionnaire <p>Creation of a new participant letter to be sent with the follow-up psychosocial questionnaire prior to the 24-month follow-up appointment incorporating information regarding:</p> <ul style="list-style-type: none"> reporting severe hypoglycaemic episodes enclosure of a £10 gift voucher <p>REPOSE protocol v10:</p> <ul style="list-style-type: none"> Inserted details regarding the three additional questionnaires: adherence to DAFNE principles, use of bolus calculators, use of pump features <p>Amended <i>Table 1</i> – documents for data collection to include a separate post psychosocial questionnaire pack for the 2-year follow-up visit</p>	<p>DAFNE principles questionnaire, v1, 12 December 2013</p> <p>Use of bolus calculators questionnaire, v1, 12 December 2013</p> <p>Pump use questionnaire, v1, 12 December 2013</p> <p>24-month psychosocial questionnaire letter, v2, 22 January 2014</p> <p>REPOSE protocol, v10, 11 December 2013</p>	Ethics approval: 3 February 2014

Amendment number and type	Date submitted	Summary of amendment	Documents changed	Date approved
Substantial amendment 19	24 December 2013	Creation of a participant newsletter to be issued 24 months post course	24-month follow-up participant newsletter, v1, 3 December 2013	Ethics approval: 13 January 2014
		Creation of a letter to send to all REPOSE participants reminding them of how to use their bolus calculator	Bolus Calculator Intervention Letter, v1, 11 December 2013	
Substantial amendment 20	5 March 2014	REPOSE Protocol v11.1: <ul style="list-style-type: none"> • 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 and that they are exempt from immediate reporting • Participant retention and return of data: when it is difficult for the participant to attend the hospital, appropriate research staff may offer the participant the opportunity to visit them in their home or at an alternative NHS location to carry out data collection 	REPOSE protocol, v11.1, 31 March 2014	Ethics approval: 4 April 2014
Minor amendment 14	23 March 2015	REPOSE protocol v11.2: <ul style="list-style-type: none"> • Further details will be collected from patient notes on episodes of DKA, when such data have not been recorded on the SAE. Additional data will be collected on cause; whether or not sick day rules were implemented; bicarbonate on admission; pH on admission; most recent HbA_{1c} prior to admission; if on pump, whether or not there was a malfunction; whether or not the patient was at home or away; and, number of previous episodes of DKA 	REPOSE protocol, v11.2, 24 March 2015	Acknowledgement received from REC: 8 April 2015

CTA, Clinical Trials Authorisation; FU, follow-up; KCH, King's College Hospital; N/A, not applicable; NRES, National Research Ethics Service.

Appendix 11 Diabetic ketoacidosis/illness letter and troubleshooting documents issued to participants

DKA letter issued to pump participants



[TRUST LOGO HERE]

Dear REPOSE Participant,

Recruitment and delivery of all the trial courses has now been completed, and many of you are already well over 12 months into the study.

One of the crucial things we need to collect in order to carry out the economic evaluations of the trial is the contact you have with health professionals regarding your diabetes control / treatment up until you complete the study at 2 years (after your course).

Therefore please remember to contact your local REPOSE team about any of the following:

- Advice regarding your diabetes
- Changes to your diabetes treatment
- Bad / severe hypos (needing help from another person)
- An increase in the number of hypos you are having
- Unexplained high blood glucose readings (over 20mmol/l for more than 12 hours)
- Any blood glucose reading above 30mmol/l
- Hospital admissions - for any reason
- Pregnancy
- Pump malfunctions (after first notifying Medtronic)
- Infusion site infection

We hope that you continue to find your course workbook a helpful source of information, however we have attached some additional advice about managing high blood glucose levels and illness / ketones.

Yours, etc.....

[insert name of local PI/educator and contact details]

V1, 28Jun2013

DKA troubleshooting document issued to pump participants



TROUBLESHOOTING PROBLEMS AND MANAGING ILLNESS WITH YOUR INSULIN PUMP

If your blood glucose levels are running high, do not panic, but ask yourself some simple questions:

Are you taking enough insulin?

- Have you given the correct bolus according to the carbohydrate content of your meal?
- Did you forget to bolus before the meal? HINT: look at your bolus history on the pump*
- Did you overeat when treating a hypo?
- Is your basal rate too low? This may be true when you have just started on a pump.
- Is the pump 'suspended'? – restart it.

* If you have forgotten your meal bolus and remembered 2 hours later, EITHER give the bolus to match your carbohydrate intake of that meal, OR give a correction dose based on your present blood glucose level (not both).

Have your insulin requirements increased for any reason?

- Are you ill?
- Has your activity altered in any way?
- Are you feeling more stressed than normal?
- If female, at what stage of the menstrual cycle are you? 2-7 days prior to your period there is an increase in the circulation of progesterone causing a rise in blood glucose levels.
- Are you taking any medications, which may cause high blood sugar? (Ask your pharmacist.)
- Are you dehydrated, which may reduce the flow of insulin into the tissues?
- Has the temperature dropped? – insulin absorption is reduced in cool temperatures.
- Is the site of your infusion set inflamed? Does it need to be changed?

Are you having any difficulties with the insulin pump itself?

- Is there an air bubble in the infusion set?
- Is the infusion set inserted correctly or still in place on the skin?
- Are the infusion set and adapter connected properly?
- Did you fully prime the infusion set when you changed the set?
- Has the infusion set been placed in an area of hard/lumpy skin?
- Has the insulin itself been exposed to extreme temperatures?
- Is there any blood in the infusion set?
- Has the needle/cannula been in for more than 72 hours?
- Has the insulin expired? Check the insulin bottle in use.
- Is the pump alarming? eg low reservoir, low battery, occlusion (blocked tube).

If any of the above answers are YES, you should immediately change the full infusion set and reservoir and consider using insulin from a new vial/cartridge if possible.

Carry out a self-test to check that the pump is functioning properly (found in utilities menu). If you are concerned that the pump may not be working, please ring Medtronic's help line immediately (01923 205167 option 1).

V1, 28Jun2013



Reduce the risks of hyperglycaemia by:

1. Checking blood glucose levels 4–6 times daily (additional tests will be needed when unwell, exercising or pregnant).
2. Using a correction bolus when appropriate.
3. Changing infusion set every 2–3 days.
4. Checking the infusion set and site regularly.

Hyperglycaemia management:

If your blood glucose is over 13mmol/l (for no apparent reason):

1. Take a correction bolus **via your pump**.
2. Re-check blood glucose in 2 hours.

If there has been no change or if your blood glucose has risen further:

1. Take a correction injection **using a syringe or pen**.
2. Check for KETONES – if present, follow ketone management (sick day rules).
3. Change your infusion set, site and reservoir (especially in hot weather).
4. Consider using a new insulin vial.
5. Check the pump by performing a self-test (found in utilities menu).
6. Re-check blood glucose in 2 hours.

If ketones remain negative:

1. Continue to take correction boluses via your pump every 4–6 hours (see 'Minor Illness' guidelines overleaf)
2. Remember to keep checking for ketones if blood glucose is still high
3. Think about why they may be high:
 - Are you becoming unwell?
 - Have you changed your pump settings and made a mistake?

Ketone management: (see guidelines overleaf from your course workbook)

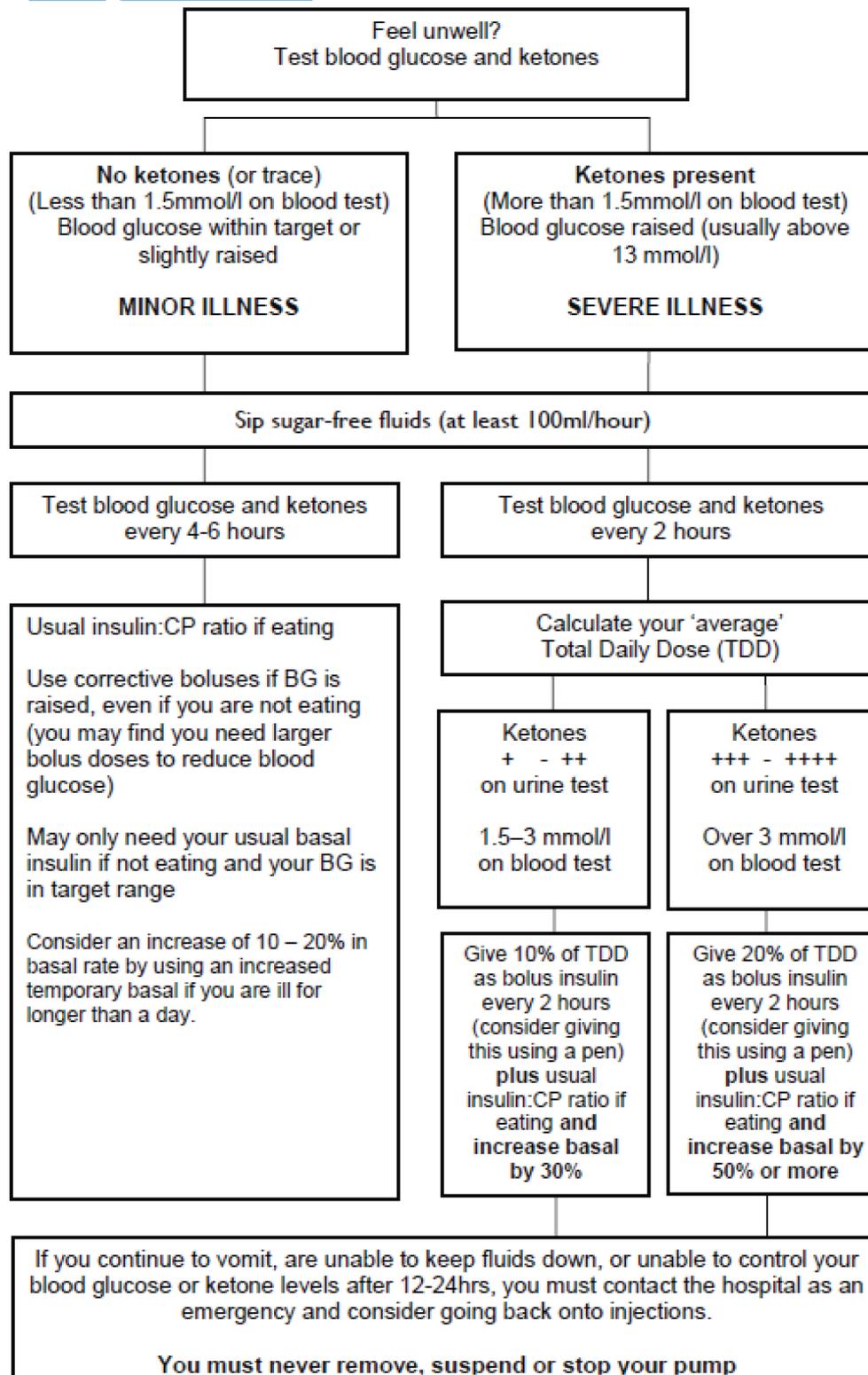
If ketones are present (i.e. small, moderate or large on urine test / over 1.5mmol/l on blood test), remember:

1. Carry out your usual pump check procedures:
 - Take a correction injection using a syringe or pen.
 - Change your infusion set, site and reservoir (especially in hot weather).
 - Consider using a new insulin vial.
 - Check the pump by performing a self-test (found in utilities menu).
2. Drink at least 100ml of sugar free fluid per hour.
3. Use a temporary increased basal rate of 130% - 150%, according to ketone level.
4. Re-check your blood glucose and ketone levels every 2 hours.
5. Use 2 hourly boluses of 10% or 20% of your total daily dose (TDD), according to ketone level – **remember, you need to override the Bolus Wizard!**
6. Have some carbohydrate with usual bolus ratio (e.g. 3 CPs every 6–8 hours).

If the ketones do not clear within 8–12 hours:

1. Try a temporary increased basal rate of 175%.
2. Take 20% TDD doses **using a syringe or pen** every 2 hours.

V1, 28Jun2013



V1, 28Jun2013



Contact numbers for URGENT medical support:

Diabetes team (during office hours):

Diabetes team (out of hours):

GP:

Local on-call/out of hours GP services:

Emergency Department:

Call 999

PUMP TECHNICAL PROBLEMS

If you think your pump is not working properly / broken, please contact the Medtronic Helpline immediately. Please let your DAFNE / Pump team know you have had a problem with your pump.

MEDTRONIC HELPLINE

24hr Product Support Line:

████████████████████

Please note that the pump companies may not give medical advice and can only offer technical support if you are having problems with the pump. Please contact the Diabetes Team if you need advice regarding your diabetes.

If you cannot reach your Diabetes team for clinical support, return to your regular insulin injections and doses and contact the Diabetes team at the earliest opportunity.

V1, 28Jun2013

DKA letter issued to MDI participants



[TRUST LOGO HERE]

Dear REPOSE Participant,

Recruitment and delivery of all the trial courses has now been completed, and many of you are already well over 12 months into the study.

One of the crucial things we need to collect in order to carry out the economic evaluations of the trial is the contact you have with health professionals regarding your diabetes control / treatment up until you complete the study at 2 years (after your course).

Therefore please remember to contact your local REPOSE team about any of the following:

- Advice regarding your diabetes
- Changes to your diabetes treatment
- Bad / severe hypos (needing help from another person)
- An increase in the number of hypos you are having
- Unexplained high blood glucose readings (over 20mmol/l for more than 12 hours)
- Any blood glucose reading above 30mmol/l
- Hospital admissions - for any reason
- Pregnancy

We hope that you continue to find your course workbook a helpful source of information, however we have attached some additional advice about managing high blood glucose levels and illness / ketones.

Yours, etc.....

[insert name of local PI/educator and contact details]

V1, 28Jun2013

DKA troubleshooting document issued to MDI participants



TROUBLESHOOTING PROBLEMS AND MANAGING ILLNESS

If your blood glucose levels are running high, do not panic, but ask yourself some simple questions:

Are you taking enough insulin?

- Have you given the correct dose of QA insulin according to the carbohydrate content of your meal?
- Did you forget to take your QA insulin before the meal?
- Did you overeat when treating a hypo?
- Are your BI doses too low?
- Did you forget a dose of BI?

* If you have forgotten your meal QA and remembered 2 hours later, EITHER give the dose to match your carbohydrate intake of that meal, OR give a correction dose based on your present blood glucose level (not both).

Have your insulin requirements increased for any reason?

- Are you ill?
- Has your activity altered in any way?
- Are you feeling more stressed than normal?
- If female, at what stage of the menstrual cycle are you? 2-7 days prior to your period there is an increase in the circulation of progesterone causing a rise in blood glucose levels.
- Are you taking any medications, which may cause high blood sugar? (Ask your pharmacist.)
- Are you dehydrated, which may reduce the flow of insulin into the tissues?
- Has the temperature dropped? – insulin absorption is reduced in cool temperatures.

Are you having any difficulties with the insulin itself?

- Is there an air bubble in your cartridge? Clear this by doing a test / air shot, or change the cartridge
- Have you changed and attached a new needle correctly? Remove it and attach another needle
- Did you carry out a test / air shot when you changed the needle?
- Have you injected in an area of hard/lumpy skin (Lipo)? Change your injection site
- Has the insulin itself been exposed to extreme temperatures? If in doubt, use a new cartridge / batch
- Has the insulin expired? Check the insulin cartridges in use and change if necessary.

V1, 28Jun2013



Reduce the risks of hyperglycaemia by:

1. Checking blood glucose levels 4–6 times daily (additional tests will be needed when unwell, exercising or pregnant).
2. Using a correction dose of QA when appropriate.
3. Checking injection sites regularly.

Hyperglycaemia management:

If your blood glucose is over 13mmol/l (for no apparent reason):

1. Take a correction dose of QA.
2. Re-check blood glucose in 4 hours.

If there has been no change or if your blood glucose has risen further:

1. Take a further correction dose of QA.
2. Check for KETONES – if present, follow ketone management (sick day rules).
3. Consider using a new insulin cartridge.
4. Re-check blood glucose in 4 hours.

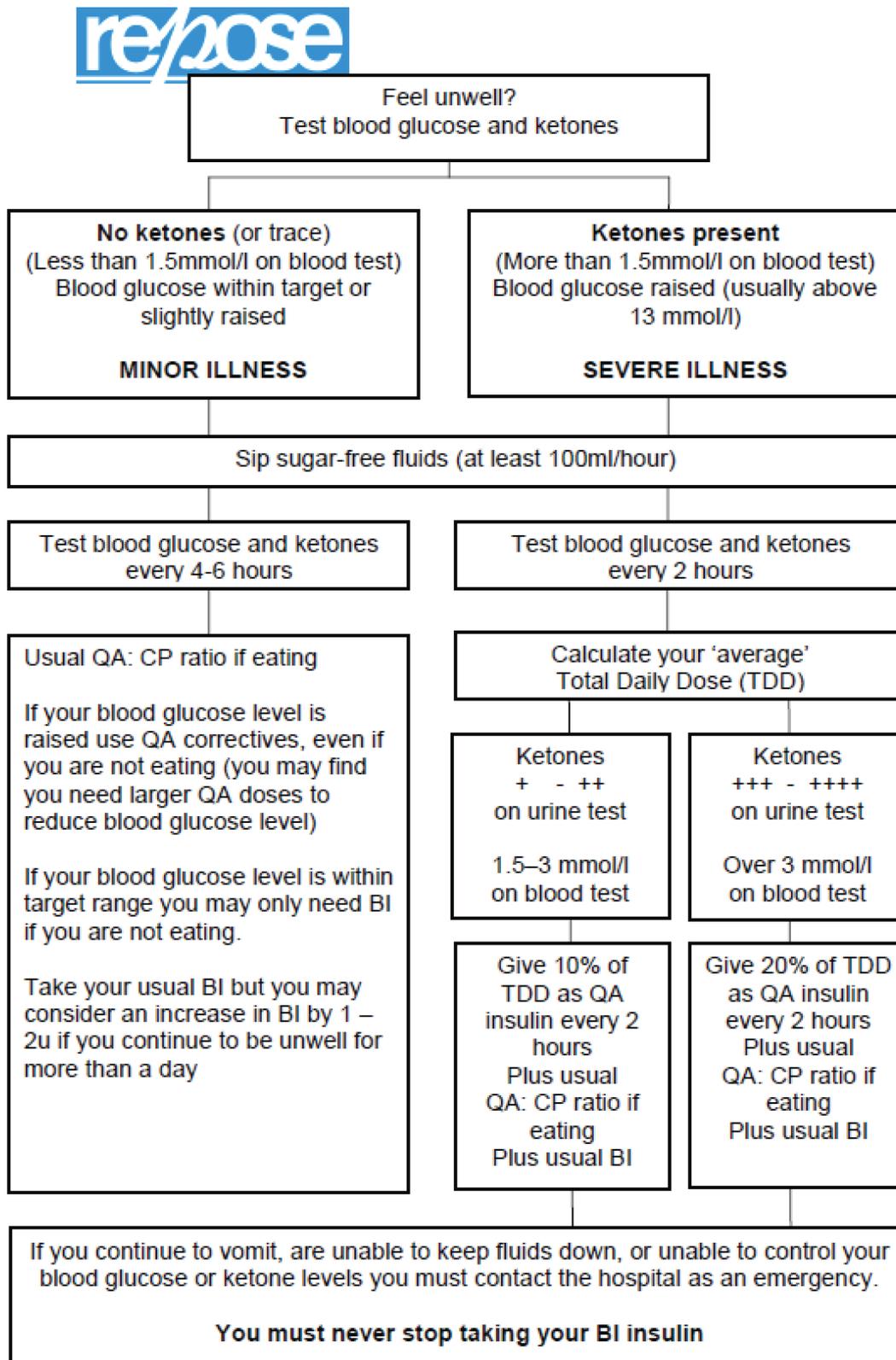
If ketones remain negative:

1. Continue to take correction doses of QA every 4-6 hours (see 'Minor Illness' guidelines overleaf)
2. Remember to keep checking for ketones if blood glucose is still high
3. Think about why they may be high:
 - Are you becoming unwell?
 - Have you missed a dose of (BI) insulin?

Ketone management: (see guidelines overleaf from your course workbook)

If ketones are present (i.e. small, moderate or large on urine test / over 1.5mmol/l on blood test), remember:

1. Drink at least 100ml of sugar free fluid per hour.
2. Re-check your blood glucose and ketone levels every 2 hours.
3. Use 2 hourly QA doses of 10% or 20% of your total daily dose (TDD), according to ketone level – **remember, you need to override the Bolus Adviser!**
4. Have some carbohydrate with usual QA:CP ratio (e.g. 3 CPs every 6-8 hours).



V1, 28Jun2013



Contact numbers for URGENT medical support:

Diabetes team (during office hours):

Diabetes team (out of hours):

GP:

Local on-call/out of hours GP services:

Emergency Department:

Call 999

V1, 28Jun2013

Appendix 12 Twenty-four month letter incorporating information about severe hypoglycaemia reporting



[insert date and address]

Dear [insert name]

Thank you for your contribution to the REPOSE study, we very much appreciate your help.

It is now 2 years since you attended your REPOSE DAFNE course. At this point we ask our study participants to complete the enclosed questionnaire. You may have filled in a similar questionnaire around the time of your last REPOSE follow-up visit.

We would be very grateful if you could complete this and bring it with you to your follow-up appointment at [insert site] which is due to take place in [insert time period e.g. X weeks time/a few weeks time/ around one month's time]. *[delete as appropriate]* Even if you have changed your treatment since starting the study or have missed any earlier appointments, we would still like you to complete the questionnaire.

Please answer all the questions as fully as you can. Although some questions may appear similar, it is still important that you answer every one. Your information is very important to us.

One important piece of information that we hope you will provide at your final visit is the number of hypos you have experienced (both severe and non-severe). We want to reassure you that all the information you provide as part of the REPOSE trial is kept completely anonymous and would not be sent to any organisation where participants could be identified.

[If envelope enclosed, insert the following:] If you prefer/If you are unable to attend your follow-up appointment *[delete as appropriate]*, please return your questionnaire in the pre-paid envelope provided.

We are well aware of the considerable effort we have asked of people who have taken part in REPOSE. As a small token of our appreciation of your help in assisting us complete this Trial successfully, we are enclosing a £10 voucher.

V2, 22Jan2014

Best wishes,

The REPOSE team

V2, 22Jan2014

DAFNE number:

			/				
--	--	--	---	--	--	--	--

PERMISSION FOR FUTURE CONTACT

Would you be willing to be contacted in the future by a member of the REPOSE study team to talk about your diabetes and experiences of taking part in the REPOSE study?

Your contact details will be stored securely and only used by members of the REPOSE study team.

If you wish to be contacted then please complete the details below and return in the pre-paid envelope.

Print name.....

Signature.....

Date.....

V2, 22Jan2014

Appendix 13 Bolus calculator letter issued to participants



[TRUST LOGO HERE]

Dear REPOSE Participant,

Many thanks for your continued participation in the REPOSE trial. This letter is being sent to all participants in the trial. If you have already discussed the following issues with your local diabetes team then please ignore this letter.

You were given a Bolus Advisor (multiple daily injections patients) or Bolus Wizard (in the insulin pump) at the start of the trial and given the option of using this to assist you in the management of your diabetes. I know that some of you are using the device and some are not. However, we have recently discovered that some people may not be using these devices as they were intended. We have decided that it would be a good idea to send a reminder as to how we think they should be used.

If you are currently using the device, I'd like to clarify a couple of important things, to ensure you are using it most effectively:

- 1) Your carbohydrate to insulin ratio and / or your insulin sensitivity may change over time, therefore you cannot assume that the values that were programmed into your device at the end of the course are the same ones as you need now. If your blood glucose readings are not regularly within target your ratios and / or insulin sensitivity may need changing. If you are unsure how to do this please contact your local DAFNE educator.
- 2) The bolus advisor / bolus wizard cannot detect patterns in blood glucose readings and therefore is not a replacement for a diary. Prior to changing any settings you should carefully reflect on your diary. If you are not using a diary regularly, try for a few days, to keep a record of your blood glucose values before meals, your carbohydrate intake and your insulin doses. Then look at the diary or your records to try to detect patterns. Before making any changes to ratios / insulin sensitivities we would advise that you check your background / basal insulin by having carb free meals – please refer to your handbook or contact your local DAFNE educator if you would like any advice about this.

v1, 11Dec2013

[TRUST LOGO HERE]

If at any stage you require further advice then please don't hesitate in getting in touch, using the contact details below.

Yours sincerely,

[INSERT NAME OF LOCAL PI/EDUCATOR AND CONTACT DETAILS]

v1, 11Dec2013

Appendix 14 Results of the Gompertz, log-logistic and log-normal parametric survival models used to predict treatment switching

TABLE 74 The results of the Gompertz, log-logistic and log-normal parametric survival models fitted to individuals in the CSII arm of the REPOSE Trial

Parameter	Coefficient	Robust SE	95% CI
Gompertz model			
HbA _{1c}	0.220	0.236	-0.243 to 0.684
Number of DKAs	-0.983	0.468	-1.901 to -0.065
Number of severe hypoglycaemic events	0.407	0.090	0.230 to 0.584
Constant	-4.307	2.232	-8.682 to 0.068
Gamma parameter	-0.316	0.479	-1.256 to 0.624
Log-logistic model			
HbA _{1c}	-0.294	0.286	-0.855 to 0.267
Number of DKAs	1.406	0.676	0.081 to 2.730
Number of severe hypoglycaemic events	-0.554	0.170	-0.887 to -0.220
Constant	5.637	2.510	0.718 to 10.557
ln gamma parameter	0.215	0.230	-0.235 to 0.665
Log-normal model			
HbA _{1c}	-0.307	0.292	-0.879 to 0.264
Number of DKAs	1.867	0.755	0.387 to 3.347
Number of severe hypoglycaemic events	-0.656	0.180	-1.009 to -0.304
Constant	6.406	2.520	1.466 to 11.346
ln sigma parameter	1.002	0.206	0.598 to 1.405

TABLE 75 The results of the Gompertz, log-logistic and log-normal parametric survival models fitted to individuals in the MDIs arm of the REPOSE Trial

Parameter	Coefficient	Robust SE	95% CI
<i>Gompertz model</i>			
HbA _{1c}	0.350	0.170	0.016 to 0.683
Number of DKAs	-6.009	0.562	-7.110 to -4.908
Number of severe hypoglycaemic events	0.512	0.094	0.329 to 0.696
Constant	-8.080	1.471	-10.963 to -5.197
Gamma parameter	1.055	0.669	-0.256 to 2.366
<i>Log-logistic model</i>			
HbA _{1c}	-0.181	0.121	-0.418 to 0.055
Number of DKAs	2.609	0.799	1.044 to 4.175
Number of severe hypoglycaemic events	-0.232	0.070	-0.368 to -0.095
Constant	3.676	1.317	1.094 to 6.258
In gamma parameter	-0.780	0.317	-1.401 to -0.160
<i>Log-normal model</i>			
HbA _{1c}	-0.190	0.107	-0.400 to 0.021
Number of DKAs	1.617	0.517	0.603 to 2.630
Number of severe hypoglycaemic events	-0.283	0.101	-0.481 to -0.086
Constant	4.117	1.291	1.587 to 6.647
In sigma parameter	0.066	0.338	-0.596 to 0.728
In, natural logarithm.			

Appendix 15 End of trial for pump participants: standard operating procedure



REPOSE SOP Number 16: End of trial for pump participants

1) Purpose

This guideline describes the process for managing pump participants at the end of the REPOSE trial.

2) Background

The insulin pumps being used by REPOSE participants have been provided free of charge by Medtronic and were supplied with a two year warranty. The pump consumables are being paid for by DoH/CSO/PCT and funding of these is also limited to the 2 year duration of the trial

3) Procedure

3.1 Decision whether to continue on the pump

Local staff will make a clinical decision with the participant as to whether they would benefit from continued use of a pump. Such discussions and any final decision **should not be taken until the participant has completed data collection for the trial** (i.e. after the 24 month follow up data collection). This is to ensure that any decision does not impact on a participant's behaviour during the trial which could affect REPOSE outcomes. In cases where continued use of a pump is considered appropriate, funding will need to be sought locally.

3.2 Timing of the 24 month follow-up visit and the use of pumps to trial completion

All REPOSE participants' 24 month visits should be booked in the first half of the data collection window if possible, regardless of which arm they are in (i.e. up to 6 weeks prior to the exact 24 month date).

Medtronic have agreed a 2 month extension of the pump warranties. This will allow participants who have to attend the 24 month follow-up in the second half of the 12 week data collection window to continue using the pump until the end of their participation in the trial. The agreements for the funding of pump consumables are for a fixed amount and cannot be changed. Therefore any continued use of pump consumables during this time may need to be funded locally. In practice however, we do not expect this to be required, as those participants who complete the trial early should offset any who are followed up late.

3.3 Post-trial arrangements

It will be up to local diabetes teams to determine how the transition between trial completion and continued pump use is managed. The ordering systems used for REPOSE are trial specific and will not be valid for non-REPOSE participants, normal local procedures should be used.

If the decision is that the patient is continuing on pump therapy, Medtronic can accommodate one of the following two options:

1. A new pump with 4 year warranty can be purchased for the patient with access to full training and resources.
2. An extension to the warranty of 1 year 10 months resulting in cumulative 4 year warranty for the existing pump can be purchased (this option should be discussed and agreed in advance of the 2 year 2 month warranty period ending).

Where no longer required, pumps should be disposed of at site or returned to Medtronic clearly marked as a REPOSE study pump.

Version 1, 06Jan2014

Appendix 16 Closeout qualitative substudy: staff topic guide

Demographic

- Role/occupation.
- Years of diabetes/DAFNE experience.
- Years of experience of working with insulin pumps prior to the trial.

Clinical use of pumps in site

- How are pumps usually funded in your centre?
- What clinical and other criteria are used to determine who is referred for a pump?
 - Prompt NICE/SIGN: how are NICE guidelines on pumps interpreted at your centre/by you? Why interpreted in this way?

REPOSE

- Tell me about your work on REPOSE – how were you involved (recruitment, training, delivery, contact with patients during the trial, closeout)?
 - Was recruitment difficult in your centre? How did it end up regarding pumps and MDI?
- Why do you think the patients recruited from your centre agreed to take part in the trial? (Probe patients' preferences: what did you think about this and how did you manage this?)
 - Do you think more patients really wanted pumps even if they did not' fess up at the time?
- What do you think about the inclusion/exclusion criteria used in REPOSE and the fact that the trial's criteria were different to NICE criteria?
- What do you think about these differences? How did these make you feel about dealing with these patients?
- Any problems and difficulties encountered during the trial (e.g. patient complaints, withdrawals)? How did you address these?
- Impact of trial on clinical practice? CLOSEOUT
- What do you think about the information given at recruitment about closeout (probe around information about potential withdrawal of pump at end of trial)?
- How did patients recruited react to this at the time?
- What expectations did you have about closeout? WHY?
 - What did you think closeout would be like? WHY?
 - What problems or challenges did you think might arise at closeout? WHY? When did these change?
 - What expectations did patients in your site have about closeout do you think?

So what happened in the end? Can you talk me through your experiences of closeout?

- What happened in your site?
- Did you have a SOP/protocol for closeout? How did this differ from trial protocol? Why?
- What decisions were made about whether to continue or discontinue pump treatment in your site? To what extent were NICE guidelines used/followed?
 - How were they made? Who made them? Why?
- Were these decisions about closeout made in general or on a case to case basis – WHY?
- How did patients react to closeout decisions?
 - How did you manage their reactions?
- In hindsight, what would you have done differently at closeout? Why?

General topics

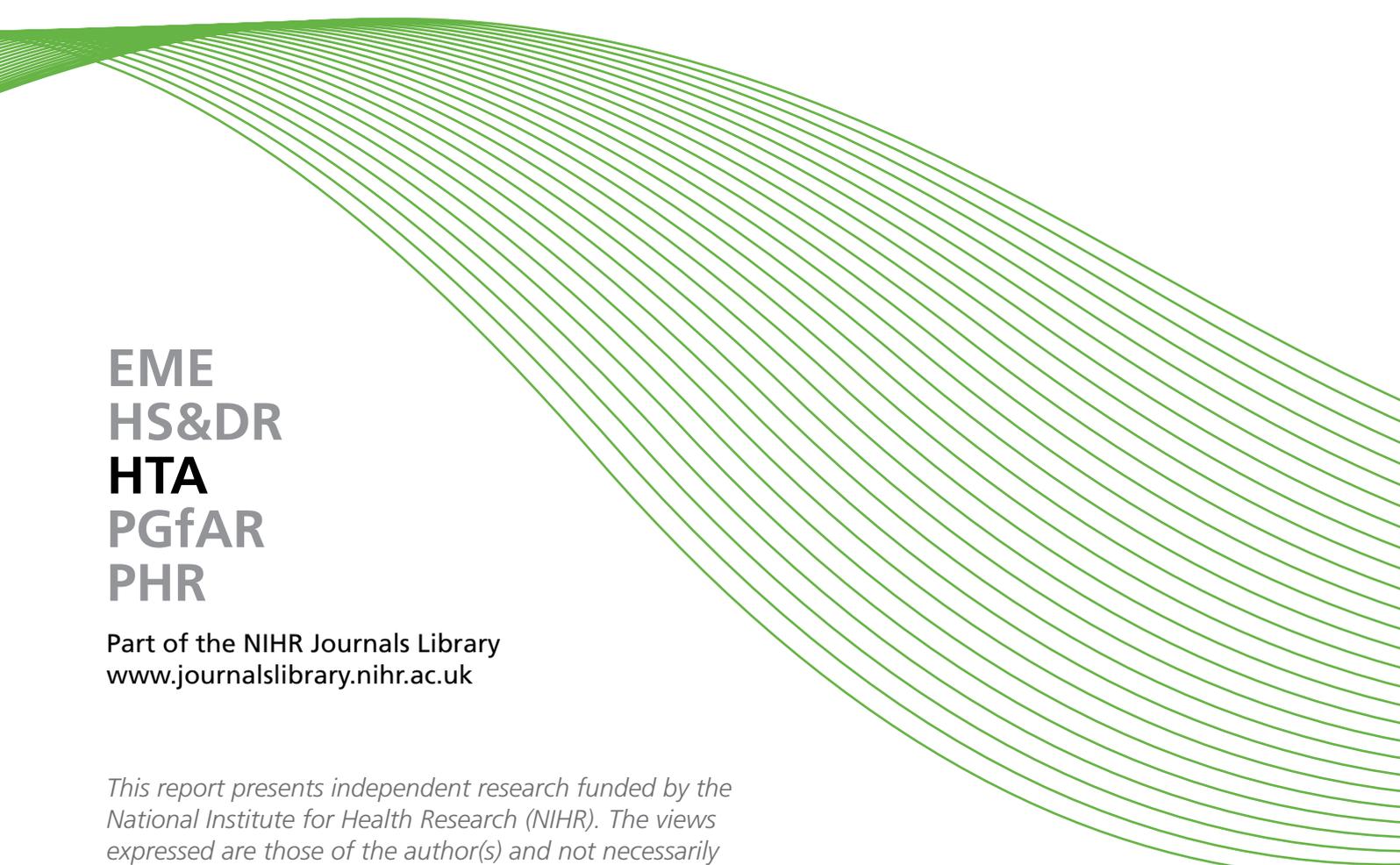
- What did you think of the trial? (Design, rationale.)
- Do you think the trial will work? Why?
- How did people do in the MDI arm?
- Do you think there will be a difference between pump and MDI arms?
- If you think there are benefits in clinical outcomes, why do you think they have occurred?

Generic experiences and needs

- What information and support did you receive when closing out REPOSE? Where/from whom did it come? (CTU, local PI.)
- What unmet needs for support did you have and how could these be addressed in future trials? (Prompt debriefing – pre-empting? Who should provide?)
- Experiences of working on and closing out other trials before or since to REPOSE? Issues or problems that have arisen on the closeout of earlier trials. How did REPOSE differ and why?
- Anything missed out?
- Anything to add?

Appendix 17 Closeout qualitative substudy: participants

Variable	<i>n</i>	%
REPOSE centres		
Number of centres	7	
Interviewees per centre range	1–5	
Interviewees per centre mode	3	
Role		
Diabetes consultants	7	33
DAFNE educators	14	66
Diabetes specialist nurses-to-dietitians	8 : 6	38 : 29
DAFNE experience, years		
5–10	14	66
10–15	4	21
> 15	3	14
Pump therapy experience, years		
< 5	5	24
5–10	9	42
10–15	5	24
> 15	2	10

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

**EME
HS&DR
HTA
PGfAR
PHR**

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