The University Of Sheffield.

The REPOSE (Relative Effectiveness of Pumps over MDI and Structured Education) Trial

REPOSE

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Sponsor:

Sheffield Clinical Trials Research Unit (CTRU)

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This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients.

Contents

Abbreviations

Definition of terms

RCT	Randomised Controlled Trial
DAFN	Dose Adjustment for Normal Eating
CSII	Continuous Subcutaneous Insulin Infusion
SC	Subcutaneous/Under the skin
MDI	Multiple Daily Injections
SMBG	Self-Monitoring of Blood Glucose
TIDM	Type 1 Diabetes Mellitus
HbA1c	Glycosylated Haemoglobin (measure of glycaemic control)
QoL	Quality of Life
QALY	Quality adjusted life years
Hypoglycaemia	Blood glucose below the normal range
Hyperglycaemia	Raised blood glucose
Ketoacidosis	A diabetic emergency that results from inadequate insulin
Insulin Analogues	Insulin that has been modified from human insulin to improve its rate of absorption from the injection site
Glargine	A long acting insulin
NPH	Neutral Protamine Hagedorm insulin: intermediate lasting human insulin

General information

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Protocol amendments from Version 01 to 02

Change to Table 1 in order to more clearly define which questionnaires are in the psychosocial questionnaire pack across the time periods.

p.33: section on Site & Trial Closure Procedures – addition of couple sentences defining end of trial.

Protocol amendments from Version 02 to 03

Change to general information: details of principal investigators.
p.11: change to Trial Design introductory paragraph so in agreement with process described in Figure 1.
p. 13, **p.27-29** (Table 1) and **p.31** clarification that urine samples will be taken to measure albumin-creatinine ratio.
p.18: one inclusion and one exclusion criteria added.
p.23: sentence inserted to clarify saline use in pump will begin from at the pre-course session (i.e. not DAFNE course).
Appendices A to X removed and considered from this point forward as standalone documents.
Typographical errors corrected e.g. clarification that HbA1c categories are ≥7.5% and <7.5%.

Protocol amendments from Version 03 to 04

Change to general information: details of principal investigators, sponsor contact.
p.7: List of sites amended in the Trial summary.
p.14: removal of religion as part of demographic analyses.
p.23: Time at which REPOSE educator find out which treatment arm participants has been allocated to altered from one month to six weeks.
Table 1: Documents for Data collection: **p.26-30:** Severe and moderate hypos recording process amended.
Typographical errors and formatting: References to appendices removed from protocol.

Protocol amendments from Version 04 to 05

p.4-5: Amendments to site addresses.

p.13: The proportion of participants reaching the NICE target of an HbA1c level of 7.5% (58mmol/mol) or less removed from the 'Primary Endpoints' heading and inserted in the Secondary Endpoints' heading.

p.20: The exclusion criteria number 14 clarified that it is only patients with a **strong** need for a pump that are excluded from taking part in the trial.

p.23 The participant will find out which course they are allocated to four weeks prior to the DAFNE course.

p.36: Clarification that 'Unexplained constantly raised blood glucose readings' is defined as 3 consecutive readings >20mmol and over 12 hours.

p.36: Pump site infection added as an adverse event.

p.37-8 and Figure 6: Clarified that SAE forms are form faxed to the Sheffield Clinical Trials Research Unit (as delegated by the Sponsor).

p.39: IMP Management and Labelling process clarified.

p.44. Inserted:

40.MRC/DH/MHRA. Risk-adapted approaches to the Management of Clinical Trials of Investigational Medicinal Products. 2011. Available at: http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf

41. Brosteanu et al. Risk analysis and risk adapted on-site monitoring in non-commercial clinical trials. Clinical Trials 2009: 585-596.

Protocol amendments from Version 05 to 06

p.21: Participant becomes pregnant removed as a withdrawal from the pump criteria

p.22: Modification to the consent process to allow witness of consent at the time the consent form is posted back (instead of at the time of the baseline appointment).

p.33: Lost to follow-up definition clarified (failure to attend teo follow-up visits including the 24 month follow-up)

p.40: Description of a blinded review process after Course 2, 4 and 5 to monitor the numbers of participants with an HbA1c of ≥7.5% in order that the primary outcome is remains powered.

Protocol amendments from Version 06 to 07

p.21: Clarified exclusion criteria number 3: 'Has used CSII within the last 3 years to define CSII use as more than 2 weeks use in the last 3 years

Protocol amendments from Version 07 to 07.1

p.4: Amendment to KCH Principal Investigator

p.8, p25: Time at which REPOSE educator find out which treatment arm participants has been allocated to altered from six weeks to 4 to 6 weeks.

p.21: Clarified the inclusion criteria: Have had type-1 diabetes for at least 12 months to state that this at the time of the DAFNE course timepoint.

p.35: Change of number of Trusts to be involved in qualitative research from 3 to 4 Trusts to all 7 Trusts.

Protocol amendments from Version 07.1 to 07.2
p.4: Amendment to Sponsor contact

p.21: Clarification to two exclusion criteria: severity of needle phobia and unstable psychological conditions.

p.41: Clarification that the HbA1c baseline review is not blinded

Protocol amendments from Version 07.2 to 8

Pages 9, 14, 20, 23, 26 amended number of research sites from 7 to 8

p. 9: inserted Nottingham University Hospitals

p. 28 & 33: amended length of time the psychosocial questionnaire will be issued to participant at follow up appointments from 4 weeks to approximately 2-6 weeks

p. 42-43: inserted **Review of Sample Size in August 2012**

Protocol amendments from Version 8 to 9

p. 4 amendment to KCH Principal Investigator

p. 23 inserted: 4. PIC sites will be used at some centres to assist in the identification of suitable participants

p. 28 added letters as a method of reminding participants of appointments and removed timeframe of reminders

p. 35 inserted: 4. Where 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 phone, and/or to obtain the relevant data from the participant's medical records.

p. 35 inserted 5. Where the participant completed psychosocial questionnaire has not been returned, a second questionnaire will be posted to the participant with a pre-paid reply envelope.

Protocol amendments from Version 9 to 10

p. 15 inserted: e) Adherence to DAFNE principles, f) Use of bolus calculators, g) Use of pump features

p. 19 inserted the following paragraphs:
Adherence to DAFNE principles
Use of bolus calculators
Use of pump features

p. 33-34 amended Table 1: Documents for data collection to include a separate post psychosocial questionnaire pack for the 2 year follow up visit

Protocol amendments from Version 10 to 11

p.23 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
p.38-39 clarified that pregnancies will be recorded as serious adverse events and that they are exempt from immediate reporting
p.36 inserted 6. Where participants do not live locally and/or repeated follow up appointments have been missed, appropriate research staff (e.g. research nurse, educator, PI) may arrange to visit the participant in their home or at an alternative NHS location to carry out data collection

p.39 removed assessment of adverse events for severity. Clarified that AEs will be assessed for relationship to study drug and seriousness

Protocol amendments from Version 11 to 11.1

p.36 amended 6. To make it easier for participants that do not live locally and/or where it is difficult for the participant to attend the hospital, appropriate research staff (e.g. research nurse, educator, PI) may offer the participant the opportunity to visit them in their home or at an alternative NHS location to carry out data collection.

Protocol amendments from Version 11.1 to 11.2

p.17 further details will be collected from the patient notes for episodes of DKA

Trial Summary

For type-1 diabetes, the aim of insulin therapy is to keep blood glucose close to normal while avoiding hypoglycaemia but this is severely limited by the relative crudeness of current insulin delivery in comparison with the physiology of the β-cells which secrete insulin. Insulin is generally administered by multiple injections (MDI) with the dose adjusted according to eating and exercise. Insulin can now also be administered using a pump (CSII), which is a device, roughly the size of a mobile phone and containing sufficient insulin to supply both the needs of basal metabolism throughout the day, and the boluses which have to cover meals. The use of CSII is expensive compared to injections, but there are important potential benefits which include improved glycaemic control, reduced risk of hypoglycaemia (low blood sugar) and a more flexible lifestyle and better quality of life. There have been no trials in adults that have compared CSII treatment with MDI where the same structured training in intensive insulin therapy has been given, so the precise benefit of the pump technology is still unclear. There is a need to establish this, and identify patients who benefit the most so that the Department of Health can calculate the proportion of adults that would benefit from CSII therapy and so ensure that commissioning bodies provide the necessary reimbursement. The aim of the trial is therefore to establish the added benefit of CSII therapy over multiple injections on glycaemic control and hypoglycaemia in individuals with Type 1 diabetes receiving similar high quality structured training in insulin therapy. Additional assessments will include effects on quality of life and cost effectiveness.

The trial is a multi-centre randomised controlled trial whereby between 40 and 49 type-1 diabetic, adult volunteers, aged 18 and above, will be recruited per site from 8 secondary care centres (Sheffield, Kings College Hospital London, Harrogate District Hospital, Addenbrooke's Hospital Cambridge, Nottingham University Hospitals Glasgow Royal Infirmary, Dumfries and Galloway Royal Infirmary and Edinburgh Royal Infirmary). The sites will be required to recruit participants to at least 3 CSII DAFNE (Dose Adjustment for Normal Eating) courses and 3 MDI DAFNE courses. This will mean that in total on the trial, 140 participants are randomised to CSII and 140 to MDI. Participants will be recruited through direct approach if already on the waiting list for a DAFNE course or through advertisement in various clinics.

Randomisation of CSII and MDI courses will be completed on a computer generated system at Sheffield Clinical Trials Research Unit (CTRU). Educators will be blinded to the type of course that they are allocating participants to until four to six weeks before the course commences.

For each participant biochemical (HbA1c, rates of hypoglycaemia, weight, lipids) and quantitative psychosocial measures (QoL, fear of hypoglycaemia, diabetes treatment satisfaction, emotional wellbeing) will be assessed at baseline (before the course), 6 months (after the course has ended), 12 months and 24 months. A qualitative psychosocial analysis (interviews) and health economic analysis will also be undertaken.

1. Introduction

People with Type 1 diabetes (around 250,000 individuals in the UK) have lost the ability to make insulin due to autoimmune destruction of the insulin secreting 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 (sc) injection with the dose adjusted according to eating and other activities such as exercise.

Traditionally, insulin was given twice a day, often as pre-mixed insulin, but such an approach imposes a rigid lifestyle on patients and makes it difficult to maintain glucose 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 before eating, separately from the background insulin needed to control blood glucose in between meals, which is generally given twice daily (1, 2). This often involves a total of 5, even 6 injections a day, frequent checks of blood glucose from finger prick samples using a portable meter and dose adjustment based on the amount of carbohydrate eaten at each meal.

Insulin given subcutaneously cannot reproduce the physiological insulin profiles of non-diabetic individuals due to the limitations of insulin formulations and the site of delivery. The relatively slow rate of insulin absorption leads to post-prandial hyperglycaemia and post-absorptive hypoglycaemia, particularly at night. Short and long acting insulin analogues have slightly more physiological profiles but cannot reproduce those seen in people without diabetes (3). Systematic reviews of clinical trials of insulin analogues involving people with Type 1 diabetes have reported only minor advantages compared to human insulin (4, 5).

Thus, keeping blood glucose close to normal can delay or prevent complications but brings with it, frequent periods of hypoglycaemia. These range from the need to ingest quick acting carbohydrate to correct mild symptoms, to odd behaviour or loss of control while driving due to cerebral dysfunction, through to major episodes of coma and seizure. The inability of intermittent injection therapy to control blood glucose tightly without an attendant risk of hypoglycaemia results in many patients maintaining blood glucose at higher than desirable levels. A high proportion go onto develop serious diabetic complications which reduce both the length and quality of their lives. There is therefore an urgent need for better methods of insulin delivery.

Insulin can now also be administered using an infusion pump (the size of a small mobile phone), which delivers insulin continuously under the skin via a small plastic tube and cannula (Continuous subcutaneous insulin infusion, CSII) (6,7). The devices are filled with reservoirs of quick acting insulin (usually an insulin analogue) and can supply both the insulin needed for both background replacement and cover meals. When infused at low rates in between eating they mimic basal insulin secretion and this is generally delivered more consistently and accurately than is achievable by long acting insulin injections. Rapidly infused insulin boluses, delivered from the pump and controlled by the patient, cover each meal.

The purchase and use of subcutaneous insulin infusion is more expensive than multiple injections, with the pumps costing around £2500 each plus £1500 a year

extra for running costs. The marginal cost per annum over MDI is about £1800. (8).

The potential advantages are a more stable blood glucose, with reduced risk of hypoglycaemia, plus a more flexible lifestyle. Pump treatment may deliver insulin more effectively than multiple injections but doesn't provide a technological cure. Indeed, its successful use requires frequent blood glucose monitoring by the user with careful thought needing to be given to adjustment of both the background rates, particularly during the night and the insulin dose needed at each meal. Thus its use is more likely to be successful in individuals who are actively and effectively self-managing their diabetes rather than those who expect the pump to manage their diabetes for them.

CSII is used by around 20% of adults with Type 1 diabetes in the USA, while in contrast, the proportion in the UK is around 1-2%.(9) 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.(9) NICE have recently extended recommendations for the use of Continuous Subcutaneous Insulin Infusion (CSII) in adults with Type 1 diabetes. The guidance suggests that pump treatment be considered for individuals experiencing problems with hypoglycaemia particularly when this limits the ability to improve glycaemic control. NICE have noted the paucity of evidence for efficacy from randomised controlled trials (10).

There have been two appraisals of CSII by NICE, both supported by technology assessment reports undertaken by some of the present applicants, which reviewed the evidence on clinical and cost-effectiveness. The first report (11) noted that there were no trials of CSII against "best MDI" with long-acting and short-acting analogue insulins; that some trials had unequal amounts of education in the arms (with more in the CSII arms); and that the trials had focused on easily measurable outcomes such as HbA1c, rather than on benefits in terms of flexibility of lifestyle and quality of life. The report recommended trials of CSII against analogue-based MDI. The second report (8) found that few such trials had been done – one on children, not relevant to this bid, and three in adults. However the three in adults were small and short-term. One (12) was only a pilot study in adults with altered hypoglycaemia awareness and debilitating hypoglycaemia. The arms were analogue MDI, CSII, and the third was education and relaxation of glycaemic targets. There were only seven patients in each arm. None had been on analogues before, and some had never tried MDI, and so were not representative of the type of patients in whom NICE recommends CSII. The trial lasted for 24 weeks.

The second trial (13) recruited 39 adults with T1DM who had already been on CSII therapy for at least six months, and who were randomised to stay on CSII or to switch to glargine based MDI. Patients had four months on each form of treatment. The primary endpoint was glucose variability, which was 5-12% less with CSII. Despite this, there was no significant difference in the frequency of hypoglycaemic episodes or HbA1c.

The third (14) recruited 57 (50 in the final analysis) patients with T1DM naive to CSII and glargine in Italy, UK (Newcastle, Bournemouth) and France. Previous treatment was with NPH-based regimens. Follow-up was for 24 weeks. Patients were randomised to CSII or analogue MDI in an equivalence study. The difference in HbA1c at study end was only 0.1%. Costs were three times higher with CSII.

Thus, the evidence base from trials for comparing CSII and "best MDI" remains weak in terms of numbers, with a total of only 103 patients and short follow-up.

Furthermore, the patients in the trials were dissimilar to those considered suitable for CSII by NICE, which expects patients to have tried analogue-based MDI before CSII.

Given the paucity of RCTs, the assessment group looked also at observational studies of adults switching to pumps for clinical indications, largely due to the limitations of intermittent injections. This has the advantage of measuring change in glycaemic control and hypoglycaemia in those who have most to gain and these studies showed improved HbA1c of the order of around 0.5%. Bias in observational studies is more of a problem and results must be treated with caution. Furthermore, of 48 observational studies, only nine reported quality of life. Study numbers were small, with at most 35 patients. Duration was usually short. The longest study noted that initial benefits from CSII might not be sustained.

NICE was therefore again faced with an evidence base with considerable short-comings, too few trials, durations too short, numbers too small, and a need to use observational studies.

A recent meta-analysis by Monami and colleagues (15) 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. Bolli and his colleagues (16) carried out an RCT of CSII versus glargine based MDI and found no difference in HbA1c. However, it should be noted that Bolli et al excluded patients who had had more than two severe hypoglycaemic events in the previous six months, and it may be that such patients have most to gain from CSII. In a UK review of results from a CSII service, Chandrasekara and colleagues (17) reported modest improvements in Hba1c but marked improvements in hypoglycaemia and hypo awareness.

A Canadian economic analysis by St Charles and colleagues (18) noted that lifetime costs were much higher with CSII but concluded that the QALY gain (0.655 QALYs over 60 years, based mainly on HbA1c effects from short-term trial, and estimated long-term complications) might be enough to render CSII cost-effective. Cost per QALY was estimated at $24,000. A similar exercise (19) from a Third-party US payer perspective also concluded that CSII was cost-effective compared to MDI. This study was also funded by Medtronic and one author was from the company. Both these cost-effectiveness studies assumed a difference in Hba1c of 1.2%, which is higher than usually found. This figure has been used in other studies supported by Medtronic. There is a need for an independent cost-effectiveness analysis from a UK perspective.

We hypothesise that much of the benefit of pumps may come from the re-training and education in insulin use given to allow patients to use pumps safely. 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 then decide not to switch to CSII 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. 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, 20, 21) Conversely, a study from Stirling reported that CSII gave additional benefit in already educated

patients, but it had only seven patients (22). Another recent study, so far available in abstract only, also concluded that CSII gave additional benefits to DAFNE (23).

To our knowledge, no trials in adults have compared pump treatment with injections where the same structured training in insulin adjustment has been given, so the added benefit of the pump technology is still unclear. There is an urgent need to establish this, and identify patients who benefit the most. This will enable the Department of Health (DH) via NICE to calculate the proportion of adults with Type 1 diabetes that would benefit from pump therapy to guide the commissioning bodies that are expected to provide funding. A randomised controlled trial is needed to establish these outcomes without bias.

The DAFNE (Dose Adjustment for Normal Eating) course is a 1-week structured course teaching skills in insulin self-adjustment and carbohydrate counting, currently being delivered in over 78 centres across the UK and Ireland (with over 17,500 individuals now trained)(2). We propose a novel study in which adults waiting for a DAFNE course are randomly allocated to undertake either the standard course with injections or DAFNE incorporating use of pump therapy. The investigators involved in this study are already undertaking research into other aspects of DAFNE: measuring cost-effectiveness, identifying which components are crucial, and factors determining which DAFNE patients manage their diabetes more effectively. We have obtained funding to pilot a combined DAFNE and pump course and we will use this work to refine the curriculum, ensure that the measurements we want to make are feasible and estimate likely recruitment rates. The applicants have expertise in structured Type 1 diabetes education, pump therapy (having trained in total over 500 pump patients) and in health economic assessment of diabetes interventions.

The aim of our trial will be to establish for patients, professionals and those funding the service, the added benefit of using a pump during intensive insulin therapy. The applicants have been involved in the NICE appraisal of insulin pumps, been members of NICE appraisal committees and have a good understanding of what evidence NICE needs. Our aim is to inform the next NICE reviews of insulin pumps and structured education.

We will conduct this trial in compliance with the protocol, GCP and regulatory requirements.

2. Aims and objectives

The aim of the study is to conduct an RCT comparing optimised MDI therapy (using rapid and twice daily long-acting insulin analogues) with CSII in adult type-1 diabetic patients provided with high quality structured education (Dose Adjustment for Normal Eating-DAFNE).

1) During the RCT the following measures will be assessed over 2 years:
   a) biomedical outcomes (HbA1c, rates of hypoglycaemia, insulin dose, body weight, albumin-creatinine ratio),
   b) quantitative and qualitative psychosocial outcomes (quality of life (generic and diabetes specific), treatment satisfaction, fear of hypoglycaemia, hypoglycaemia unawareness, self-efficacy, social support, adherence to treatment, emotional well-being, acceptability of technology),
   c) adverse events (severe hypoglycaemia. hospital admissions with hypoglycaemia, diabetic ketoacidosis)

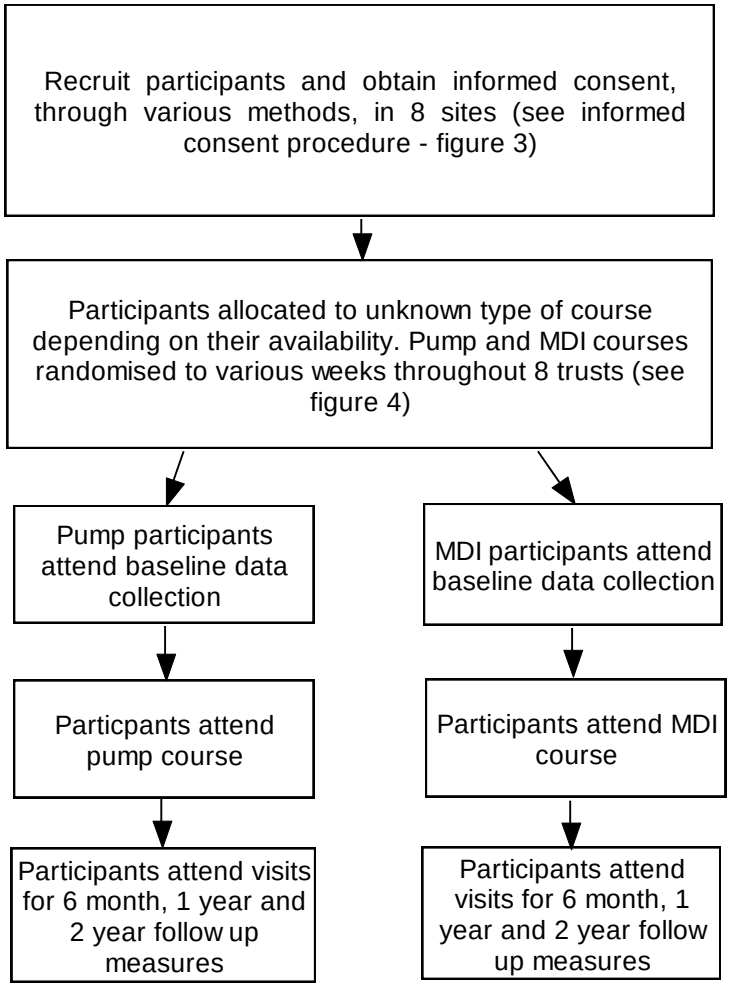
2) Through a combined analysis of the quantitative and qualitative measures we will identify factors which predict and/or help explain outcomes on CSII.

3) A cost effectiveness analysis will be undertaken to determine whether the marginal benefits of CSII over optimised MDI (if demonstrated) are commensurate with the marginal costs, as reflected in a cost per QALY acceptable to NICE.

3. Trial Design

REPOSE is a multi-centre parallel group, cluster randomised controlled trial, in which 280 adults with type-1 diabetes will be recruited from 7 trusts/Health Boards across the UK. The participants will be male or female above the age of 18 yrs. The participants will be allocated a place on a week-long DAFNE course depending on their availability. Prior to the course starting, the courses will be randomly allocated to be either CSII or MDI treatment. Participants will be requested to attend visits in order to obtain biochemical, psychosocial and health economic follow-up measures at baseline (i.e. after course allocation), 6 months, 1 year and 2 years after they have completed the DAFNE course. The diagram below gives an overview of the trial design.

Figure 1. Model of Trial Design



Primary Endpoints

HbA1c is a measurement of glycosylated haemoglobin which reflects overall blood glucose values over the previous 6-8 weeks(24). This is regarded as the gold standard measure of glycaemic control. There is a strong relationship between HbA1c and the risk of developing long term diabetic complications and it is accepted as a surrogate for long term outcomes in individuals with diabetes(25). With this in mind, the primary endpoints for the trial will be:-

- The change in HbA1c after 2 years in those participants whose baseline HbA1c was at or above 7.5% (58mmol/mol).

Since HbA1c can be measured by different techniques we will ensure standardisation by measuring HbA1c in blood samples at a central laboratory.

Secondary Endpoints

The secondary endpoints include the following:

Demographic measures

Biomedical Endpoints

a) The proportion of participants reaching the NICE target of an HbA1c level of 7.5% (58mmol/mol) or less
b) Hypoglycaemia (severe & moderate)
c) Insulin dose
d) Body weight
e) Blood lipids & proteinuria
f) Diabetic Ketoacidosis

Ancillary Study Endpoints

Quantitative

a) Quality of life (DSQOL, WHOQOLBREF, SF12, EQ5D)
b) Fear of hypoglycaemia
c) Diabetes Treatment Satisfaction
d) Emotional Wellbeing
e) Adherence to DAFNE principles
f) Use of bolus calculators
g) Use of pump features

Qualitative

a) Participant views regarding the pump/multiple injection course & treatment
b) Educator views regarding the pump/multiple injection course & treatment

Health Economic

a) Incremental cost-effectiveness ratio
b) Sensitivity analyses

Demographic Measures
We will collect demographic measures from participants so that we are able to check the sex, age, ethnicity and socioeconomic status of the trial population and assess whether we have recruited a representative sample.

Biomedical Endpoints

Hypoglycaemia
Hypoglycaemia is a major side effect of insulin treatment, which prevents many patients from achieving target glucose levels. CSII has been shown to reduce hypoglycaemia in some studies but since DAFNE and similar educational interventions are also associated with reduction in severe episodes we may have insufficient power to detect a difference in the rate of severe episodes between the two groups. During the last NICE appraisal of CSII, the question of the impact of moderate hypoglycaemia was raised. The point was made that moderate hypos, sufficient to interrupt activities of daily living, might because of greater frequency, have more cumulative effect on quality of life than severe hypos. Furthermore, moderate episodes are likely to be more frequent than severe events. We will therefore record both severe and moderate episodes of hypoglycaemia in participants. This should increase power and identify the ability of CSII to reduce rates of hypoglycaemia. It will also be possible to assess the effects of both, by comparing quality of life measures in those with only moderate hypos, versus those with moderate and severe.

Severe hypoglycaemia – any episode leading to cognitive impairment sufficient to cause either coma or requiring the assistance of another person to recover (27).

Moderate hypoglycaemia – 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.

Insulin dose
Some studies have indicated that CSII results in the use of less insulin. We will therefore record participants' self-reported insulin dose at each time point and calculate units/kg body weight.

Body Weight
If CSII treatment results in the use of less insulin, it may have a favourable effect on weight since with less insulin there is a propensity for the body to store fewer nutrients. We will therefore record weight at each time point of the trial.

Lipids and proteinuria
A recent study (26) reported little difference in HbA1c for CSII compared to MDI but found less progression to microalbuminuria in the CSII group, and also lower cholesterol and lower insulin dose.

Blood samples will be taken using local labs and lipids (including HDL cholesterol). Albumin-creatinine ratio (a sensitive measure of proteinuria) will be measured from urine samples.

Diabetic-Ketoacidosis
This outcome will be measured through the assessment of any SAE's and AEs. Where available, further details will be collected from patient notes, when such data have not been recorded on the SAE. Additional data will be collected on: cause; whether sick day rules were implemented; bicarb on admission; pH on admission; most recent HbA1c prior to admission; if on pump, whether there was a malfunction; whether the patient was at home

or away; and, number of previous episodes of DKA.

4. Ancillary sub-studies

Psychosocial Study

Relatively little research has examined patients understandings and experiences of CSII over the longer term. Most has relied on cross-sectional designs,(28) focused upon the impact of CSII on children/adolescents and their parents, or is biased towards motivated and successful (adult) pump users who are uncritically enthusiastic for the technology.(11) Little is known in adults about the psychosocial impact of moving to CSII. The RCT will therefore integrate a prospective psychosocial research component in which the experiences, perceptions and views of patients in the two arms of the trial are analysed and compared. The psychosocial component will employ a longitudinal, prospective design where the factors influencing psychosocial issues can be identified, both positive and negative.

Drawing upon psychological and sociological expertise, this will employ a mixed methods quantitative (questionnaires) and qualitative (interviews) approach in order to: (1) establish whether, and why, there are differences in QoL and other psychological outcomes between patients using CSII and MDI regimens; (2) examine whether, and why, QoL and other outcomes change over time; (3) understand and explore the added benefit (if any) of CSII technology over MDI from patients' and educators' perspectives; (4) look at why some patients may do better than others using CSII; (5) explore acceptability of, and reasons for, discontinuing (pump) treatment; (6) enhance understanding, and assist in the interpretation, of trial outcomes (e.g. differences in HbA1c between the two arms).

Quantitative component of the Psychosocial Study

Introduction

The quantitative questionnaire component of the trial will address generic and health-specific quality of life, treatment satisfaction, fear of hypoglycaemia, and emotional well-being. There has been limited examination of the impact of CSII on these areas particularly in longitudinal studies, how and why these may change over time and why patients are able or unable to use pump therapy to improve glycaemic control. This information will help us to interpret the findings of the proposed trial but also inform future decisions and guidelines for the introduction of CSII therapy in adults with type-1 diabetes.

Study Design

All participants that have been randomised to both MDI and CSII arms will be invited to take part in the psychosocial element of the trial. A repeated measures longitudinal questionnaire study will explore both differences in outcomes between the two trial arms and the short and long-term predictors and mediators of outcomes. Outcomes will be assessed at baseline, 6, 12 and 24 months after randomisation. The time-points for follow-up have been selected to capture both short and long-term post-treatment changes in psychosocial outcomes. By six months participants should have become settled on their new therapy. At 12 and 24 months, questionnaires will identify whether any changes in psychosocial outcomes have been sustained into the medium and longer term.

Secondary Endpoints/Outcome measures

Quality of life

DSQOL

Diabetes-specific quality of life (QoL) will be assessed using the scale DSQOL, a reliable and valid measure (29) specifically designed for the German study on which UK DAFNE is based, it is included to allow important comparisons to be made between the UK and German studies.

In addition, generic measures of QoL, the World Health Organisation QoL Abbreviated Questionnaire (WHOQOLBREF), the Short Form Health Survey (SF-12)(30) and EuroQoL (EQ5D)(31) will be included.

WHOQOLBREF

The WHOQOLBREF provides a broad and comprehensive assessment of generic QoL, covering the areas of physical and psychological health, social relationships and environment. It has also previously been used in diabetes research.

SF-12

The SF-12 is a short form health survey containing 12 questions on functional health and well-being and mental health. It has proven useful in surveys of general and specific populations, comparing the relative burden of diseases and differentiating the health benefits produced by a wide range of different treatments. The SF-12 will therefore allow comparison of CSII and MDI participants to each other, and in relation to the general population using data from available literature.

EQ5D

The EQ5D is a standardised instrument for use when measuring health in terms of quality adjusted life years (QALYs). It is used to build a composite picture of the participants health status through a combination of assessment in general health outcomes and state of health on that day.

The SF-12 and EQ5D will also be used by the health economists to derive health economic data.

Fear of hypoglycaemia

The Hypoglycaemia Fear Scale (HFS) (32) is a well validated psychometric tool assessing participants fear of hypoglycaemia both overall and in terms of behaviour and worry. It has been used to assess the impacts of different hypoglycaemic events such as severe, moderate and mild hypoglycaemic episodes on fear of hypoglycaemia (33). A specific benefit to the HFS 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.

Diabetes Treatment Satisfaction

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) (34) has proven to be highly sensitive in clinical trials (35, 36). It measures treatment satisfaction which 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.

Emotional Wellbeing
The Hospital Anxiety and Depression Scale (HADS) measures anxiety on one subscale and depression on another through the use of 7 questions for each characteristic. It is important to measure emotional wellbeing in the trial as participants may find it easier to manage their condition after DAFNE education or with one of the treatments. This might have a substantial effect on their emotional wellbeing that the QoL measures are not sensitive enough to pick up.

Adherence to DAFNE Principles
Adherence to DAFNE principles is a new questionnaire intended to gain a better understanding of how participants manage their diabetes after the DAFNE course and to establish the extent to which DAFNE principles are sustained over time.

Use of bolus calculators
Participants in both arms are given access to a bolus calculator for the duration of the trial. With this new questionnaire we seek to understand how effectively these are being used by participants and to determine any barriers to their use.

Use of pump features
This short 5 item questionnaire has been designed to explore the extent to which participants have used some of the more advanced features of their insulin pumps and how they learned to use these features. This information will aid interpretation of the trial findings.

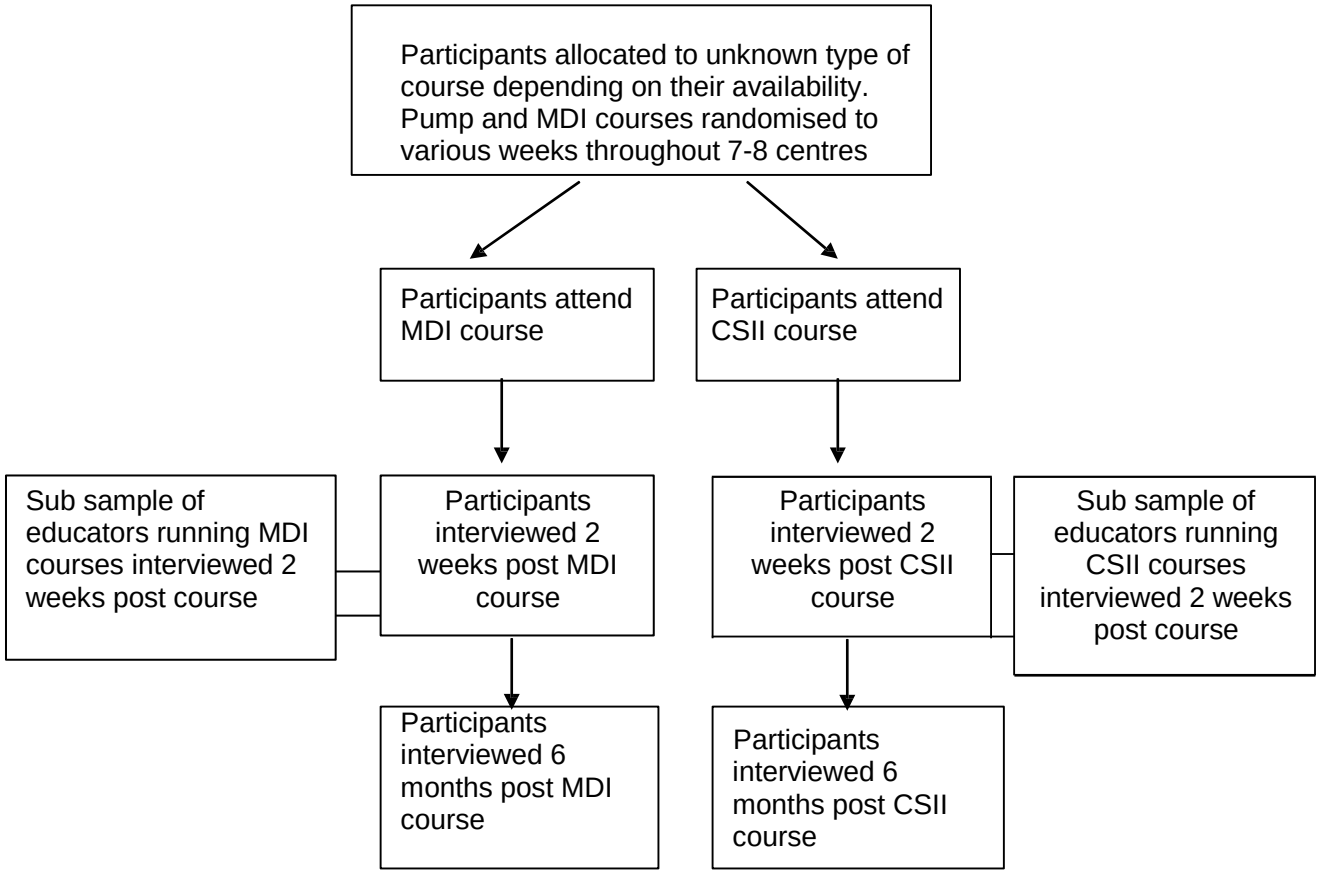
Qualitative Component of the Psychosocial Study

Introduction
Whilst the questionnaire study can establish differences in QoL between CSII and MDI users, qualitative work, drawing directly upon people's own experiences and views (within the context of their everyday lives) is needed to understand why. The qualitative component will focus upon patients experiences of, and views about, participation in the two types of courses which form part of the trial, any changes they have made to their disease self-management in light of course attendance/moving onto a pump (and why). In addition to helping to clarify why there are/are not any differences between the two arms of the study in terms of primary outcomes and QoL, qualitative work may play a role in understanding and explaining retention levels in the trial. Unanticipated issues are common during trials (e.g., high dropout rates; poorer than expected treatment adherence etc.) and prospective qualitative work is crucial in understanding and helping to address such issues.

Study Design
Once the participants have been randomised and are attending the baseline data collection visit, all participants will be asked whether they would like to be contacted by a qualitative researcher to be invited to participate in the qualitative psychosocial element of the trial. From this, a representative sub-sample of around 40 participants, to include 20 from the CSII arm and 20 from the MDI arm of the trial, will be recruited into the qualitative arm of the study. These patients will be interviewed within 2 weeks of completion of their courses and around 6 months later. Patients' educators will also be invited to take part in an interview and these interviews will also take place within about 2 weeks of the course completion.

Data collection has been timed to coincide for the quantitative and qualitative elements at 6 months post DAFNE course. Both teams will work closely together to share ideas and findings and the qualitative work can therefore be used to help in the interpretation of findings arising from the quantitative analysis.

Figure 2. Model of Qualitative Study Design



Secondary Endpoints/Outcome measures

Participant post course interviews
Participants will be interviewed regarding:
a) Understandings of the trial and motivation for participation.
b) Views about outcome of randomisation.
c) Expectations/concerns about trial participation and (if relevant) change to CSII. d) Experience of/views about the course and (if relevant) change to CSII.
e) Changes they have made to diabetes management since the course and short/long terms goals set.
f) Likes/dislikes of CSII or MDI treatment.

Educator post-course interviews
Educators will be interviewed regarding:
a) Insight and experience of what took place on the course.
b) Recommendations for future course development.
c) Recommendations for support that should be offered to patients who move onto pumps.

Participant 6 month follow-up interviews
Participants will be interviewed regarding:
a) Barriers and facilitators to sustaining diabetes management.
b) Reasons for CSII discontinuation and/or treatment non-adherence.
c) Changing perceptions of their disease.
d) Patients views and recommendations regarding support received both prior and subsequent to the course.

Health Economic Evaluation

Introduction
We will complete an economic evaluation as part of the study so that we are able to understand the relative cost-effectiveness of the two treatment strategies. The economic evaluation will follow the guidance set by the National Institute for Health and Clinical Excellence for its Technology Appraisal process (37). As such, it will take an NHS and social service perspective, measure health effects in quality adjusted life years and consider the lifetime horizon of patients.

Study Design
Resource use, mortality and EQ-5D data will be used to form a within trial analysis. This will then be used in conjunction with clinical and demographic variables to estimate lifetime cost-effectiveness using the Sheffield Type-1 Diabetes Policy Model.

Secondary Endpoints/Outcome Measures

Costs and outcomes
Costs and quality adjusted life years will be estimated for each individual recruited to the trial. Mean values for each arm will be calculated.

Incremental cost-effectiveness ratio
Cost-effectiveness will be described using plots of incremental costs and QALYs on the cost-effectiveness plane, together with their associated cost-effectiveness acceptability curves and frontiers. The incremental cost-effectiveness ratio and the probability that CSII will be cost-effective in the range of £20,000-£30,000 per QALY

will be the main focus.

5. Selection and Withdrawal of Participants

Inclusion Criteria

A participant is eligible for the trial if the following criteria are met:

1. Is aged 18 yrs and above.
2. Have had type-1 diabetes for at least 12 months at the time of the DAFNE course (as assessed by date clinically diagnosed).
3. Is fluent in speaking, reading and understanding English.
4. Has no preference to either CSII or MDI arm of the study and is happy to be randomised.
5. Is currently using or willing to switch to Detemir.
6. Is willing to undertake self-monitoring of blood glucose (SMBG), carbohydrate counting and insulin self-adjustment. (Enrolment staff should check that any participant with a baseline HbA1c of above 12% is willing to complete SMBG).
7. Has a need for structured education to optimise diabetes control in the opinion of the investigator.

Exclusion Criteria

A participant is excluded from the trial if any of the following criteria are met:

1. Inability to give informed consent.
2. Is pregnant or planning to become pregnant within the next 2 years.
3. Has used CSII within the last 3 years (defined as more than 2 weeks use in the last 3 years).
4. Has already completed a diabetes education course.
5. Has 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 CSII/pump therapy)
6. Has a current history of alcohol or drug abuse.
7. Has a history of heart disease within the past 3 months.
8. Has hypertension that is not under control with hypertensive medication (diastolic blood pressure >100mmHg and or sustained systolic level >160).
9. Has renal impairment with a chance of needing renal replacement therapy within the next 2 years (Enrolment staff should check that creatinine levels are not above 200 µmol/L).
10. Has recurrent episodes of skin infections.
11. Has 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)
12. Has taken part in any other investigational clinical trial during the 4 months prior to screening.
13. Has any other issue that may preclude the participant from satisfactory participation in the study based on investigatory judgement.
14. Has a strong need for pump therapy in the opinion of the investigator.

Withdrawal Criteria

Withdrawal from the trial

1. Participant wishes to withdraw from the trial

Withdrawal from treatment

1. Participant blood glucose levels remain raised (above 30mmol/L) for a prolonged period, to the extent that the PI perceives the patient's self-management of diabetes to be ineffective and the trial therefore poses a risk to the individual.
2. Participant episodes of hypoglycaemia frequency are increased to the extent that the PI perceives the patient's self-management of diabetes to be ineffective and the trial therefore poses a risk to the individual.
3. Participant withdraws from the CSII DAFNE course.

In the following circumstances, the local PI will decide whether clinically it is better for the participant to remain on or come off the pump according to their level of blood glucose control.

1. Participant becomes pregnant
2. Participant develops the need for renal replacement therapy
3. Participant is found to be abusing alcohol or drugs

Regardless of the fact that participants are withdrawn from treatment, every attempt will be made to follow up the participants unless they specifically request withdrawal from the trial.

6. Randomisation and Enrolment

Enrolment

Figure 3 below explains the recruitment and enrolment process for participants. Recruitment of participants will occur throughout various trusts in England and Scotland and participants will be referred to the 8 trusts running the REPOSE trial.
A number of approaches will be used to inform potential participants about the trial and undertake recruitment. These are:

1. Details of the trial will be advertised through the use of the posters and leaflets in various clinics (diabetes outpatient, dietetic, general GP surgery).
2. Reception staff in diabetes clinics will be informed about the trial and will be provided with leaflets to give to patients who may express interest in the trial.
3. Various clinicians will provide information to patients and refer them to PIs to be screened and enrolled.
4. Participant identification centres (PIC) will be used at some research sites to assist in the identification of suitable participants

The leaflets and posters will provide brief details about the trial and contact numbers of study personnel (educators, PIs and the Trial Manager) for further information.

4. The PIs or educators (diabetes specialists who run the DAFNE courses) will identify participants from a DAFNE waiting list. They will then telephone individuals who are considered fit to participate.

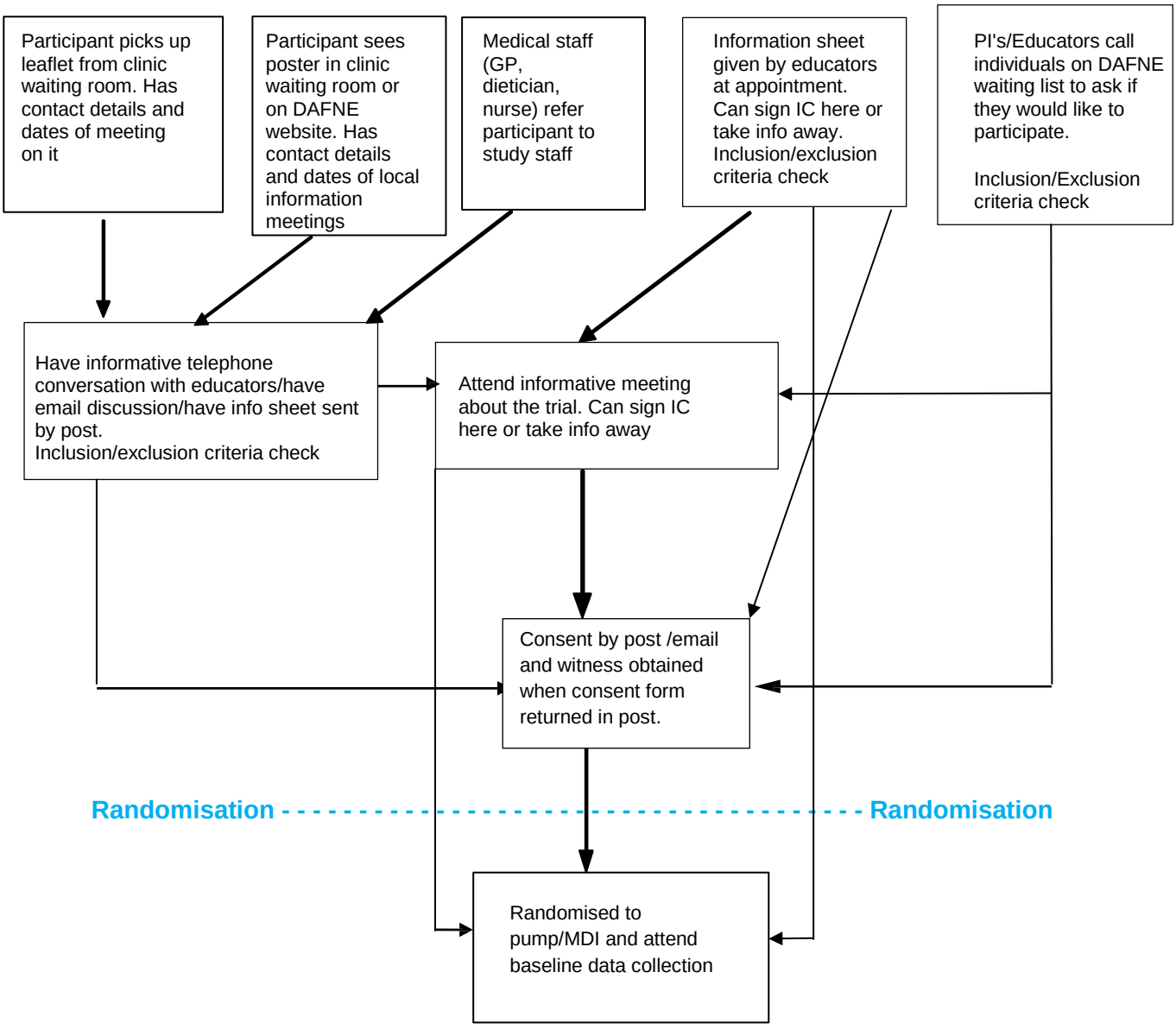
Potential participants who are identified either through the DAFNE waiting list or by patients expressing an interest in the trial will be contacted by a study PI or educator. The PI or educator will give detailed information regarding the trial, and complete a check to assess that the participant fulfills all the inclusion and exclusion criteria listed above, either during a face-to-face or telephone consultation. Potential participants will then be offered a chance to attend a meeting for further information about the trial where informed consent may be obtained.

5. Recruitment may also occur when diabetic patients attend a clinical appointment during treatment of their diabetes, with a trial PI, educator or dietician. The patient will be offered the option of a future or immediate consultation regarding the trial at this point. At this consultation the educator or PI will give detailed information regarding the trial, complete a check to assess that the participant fulfils all the inclusion and none of the exclusion criteria listed above and obtain informed consent immediately or, if the patient requires more time to consider, make a follow-up appointment or advise the patient to attend a local trial information meeting.

All participants who have been approached and who state that they do not wish to participate will be invited to complete a short questionnaire which enquires about the reasons for non-participation.

Trial information meetings will be held during the recruitment period at a number of locations in the study site areas. Community and NHS site venues will be used. The purpose of the meetings will be to provide further information about the trial, to answer questions and to consent those interested into the study. The trial team will be represented by the local PI and/educator and by others such as the CI and the Trial Manager.

Figure 3. Process of Informed Consent



Randomisation

After consent, participants will be allocated to courses depending on their availability in relation to the dates of the courses. A computerised system will be used within Sheffield Clinical Trials Unit in order to randomise 48 DAFNE courses to either MDI or CSII courses across the 8 participating sites. The randomisation for courses will be stratified by site. Within each centre the first four courses will be randomised in pairs (one MDI, one CSII). The remaining courses will be randomised by minimisation. PIs/Educators will attempt to have allocated 7 individuals to each course at least six weeks prior to the course commencing. By this time, the CTRU will inform the centre whether the course has been allocated as a CSII course or as an MDI course and confirm the allocation of a course number. The PIs and educators will have been blinded to the type of course being delivered until four to six weeks before the course commences and staff within the trials unit will be blinded to the identity of those participating. The participant will find out which course they are allocated to four weeks prior to the DAFNE course. Once the course number has been allocated to the course and the type of course is known to the site, further participants will only be allocated to the course in the situation described below.

If for any reason participants are unable to take part in the course at short notice, they will only be able to participate in the same arm of the study as the course they were originally allocated to. The patient will be given possible dates for the next relevant course and will be informed when that course is due to commence as soon as the PI/educator finds out.

In order to maximise recruitment for the courses, the PI's and educators will be able to invite a new participant to take the place of somebody unable at attend. This will occur only where there is a list of reserve participants in place, prior to the time when the course allocation has been revealed to the educators. In this case, the next person on that list would be invited to participate in that arm of the study. The patient will be allocated a screening number at the point at which they have been invited to participate and have had the inclusion/exclusion criteria check. This screening number will be used to assess the next person on the list.

7. Trial Treatment

Insulin

For the purpose of the trial, participants will use insulin analogues (a quick acting insulin analogue and twice daily injections of insulin Detemir). Since insulin is already marketed and licensed for use and the participants will already have been accessing insulin through prescription on a regular basis, there will be no need to change how the insulin is accessed for the trial. Patients will collect insulin from their pharmacist as normal. For this reason, under MHRA legislation there is also no need for an IB (Investigator Brochure) or IMPD (Investigational Medicinal Product Dossier) to be produced for the trial. However, an SmPc (Summary of Product Characteristics) will be produced and kept on file for the types of insulin being used.

DAFNE Course (Standard)

The DAFNE course is designed to teach individuals with diabetes how to live a less restricted life, whilst effectively keeping blood sugar levels under control, therefore minimizing long-term health complications associated with diabetes. Each course takes place over five consecutive days and is delivered to groups of 7 adults. The curriculum uses a progressive modular based structure to improve diabetes management in a variety of social situations. The key topics are nutrition in relation to diabetes, SMBG and ketones, insulin injection and strategies, insulin dose adjustment, hypoglycaemia, exercise, sick day rules and social aspects, contraception & pregnancy. Knowledge and skills are built up throughout the week with active participant involvement and problem solving as key methods of learning. Each meal and snack is used as an opportunity to practise carbohydrate estimation and insulin dose adjustment. In addition to the follow-up time that participants undergo for trial measurements, patients are invited to sessions at 6 weeks post course, at which time aspects of their care are reviewed in group sessions lasting 1-2 hours.

DAFNE Course (Pump)

The 5-day structure of the adult DAFNE course and additional follow-up sessions have been maintained while modifying the course to incorporate the additional skills and learning outcomes of CSII therapy. Thus the principles of insulin dose adjustment taught on the adult course are maintained. The additional components of the course have been modelled informally during existing CSII courses in the participating centres and in a pilot study which has been run in 3 centres. The need to introduce CSII skills requires the addition of a pre-course session, which will be run approximately 2 weeks before the DAFNE course. It is important that any skills for use of CSII are taught entirely separately from the course principles since we need to ensure that CSII participants do not get any extra tuition compared to the MDI participants in order to minimise bias. The participant will learn to use the pump on saline from the point of the pre-course session for CSII skills, and will be asked to switch to insulin on the evening before the DAFNE course. Clinical care would continue for patients as normal after the course. Participants will also be given contact details of the educators, as they would for a standard DAFNE course, in case they wanted to contact a clinician for advice on an ad hoc basis.

Minimisation of Bias

In addition to both courses being run over equal time span, bias will be minimised through:

1. Ensuring that participants in both arms of the study have a bolus calculator to work out the amount of insulin they should be taking.
2. Participants in both arms of the study recording insulin usage/dose through use of a recall question rather than recording directly. This is because a pump would automatically record insulin used, meaning that measurements across the arms are likely to be different methods if we asked participants to record the actual measures.
3. Fidelity testing to ensure that the principles of insulin adjustment are delivered in a similar fashion for both CSII and MDI courses.

Fidelity Testing

Fidelity testing will be carried out to ensure that the courses are delivered according to DAFNE philosophy and principles and that the educators delivering the courses have

the skills to deliver these principles. Since there is already a robust system being used for quality assurance of the MDI courses and these will have already been audited, it is only the CSII courses that will need to be audited in order to check that they run to the same standard.

An experienced DAFNE educator from one of the participating trusts will be employed as an auditor. The auditor will visit each site to observe one of the courses on a Wednesday. Wednesday has been chosen since both the nutrition and diabetes expert that teach on the course will deliver parts of the course on that day. Patients on the course should have settled into the course and be more relaxed by the 3rd day. The auditor will assess that the staff are appropriately trained within the trust and the session delivery. This will be completed through assessment of whether the correct DAFNE content is delivered, whether it is delivered in the correct order and whether the best methods of delivery are used. The educator will be assessed according to certain criterion in a peer support core skills form.

Once the auditor has completed the assessment, feedback will be given in order that the trust and the educators may resolve any problems and the assessment sheets will be kept on file so that any differences in course delivery between the arms of the study may later be identified.

8. Assessments and procedures

Data Collection Procedure

Once participants have been enrolled and allocated a course date, the data collection process starts. Data collection occurs at baseline, course, 6 month, 1 year and 2 year visits. The process includes a post course and 6 month interview for those participants who have consented to and been selected for the qualitative psychosocial element of the study. The participants will be sent data collection documents to fill out approximately 2-6 weeks before the 6 month, 1 year and 2 year visits and are given reminder letters, phone calls or texts prior to the visit. This is so that the patients may bring the completed forms with them to the visit thereby maximizing the return of data. CRFs are filled out by the educator in an interview style at the visit.

Figure 5 and table 1 below outline the data collection process, instruments collected and outcomes of the study covered.

Figure 5. Process for Data Collection

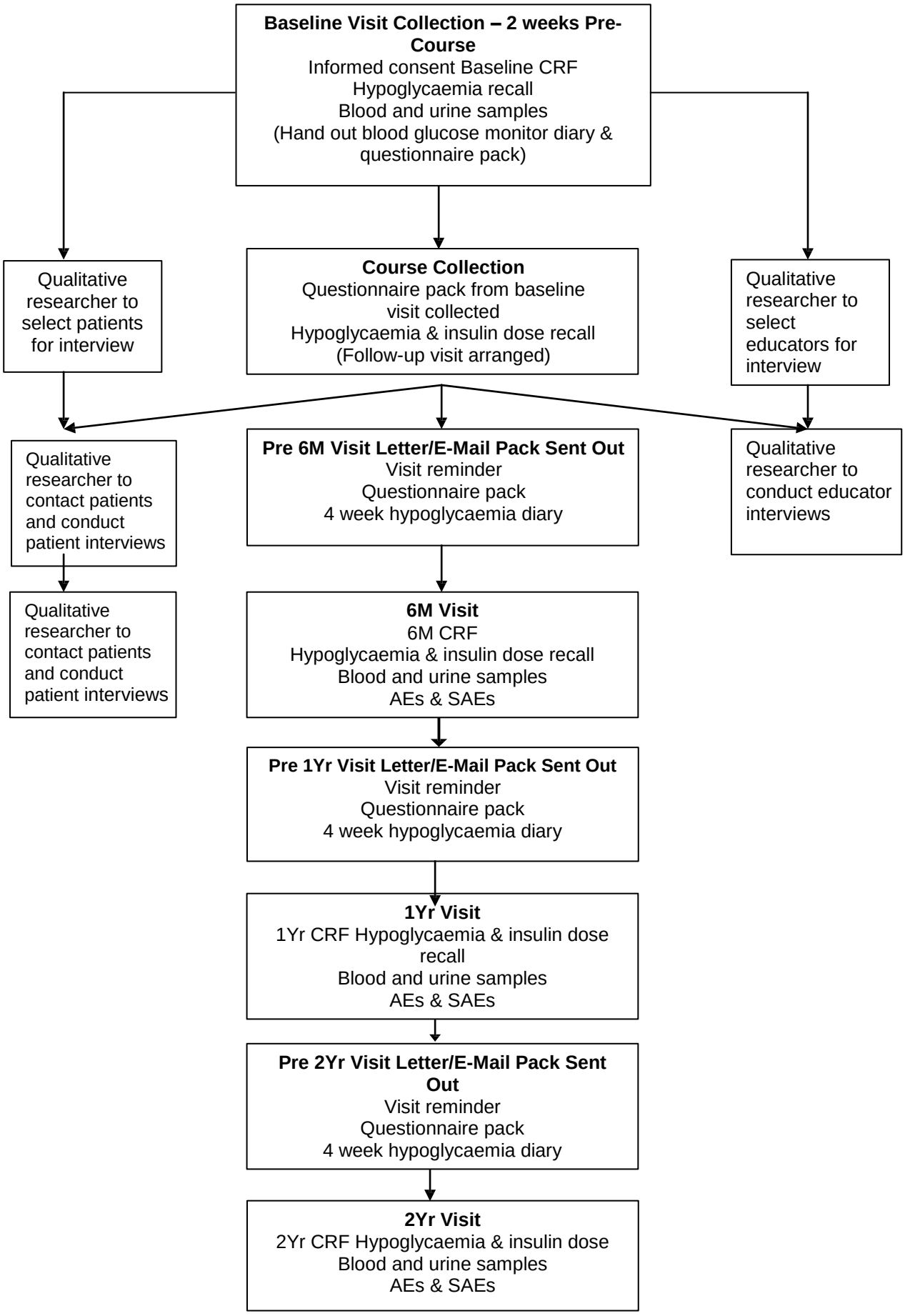


Table 1. Documents for Data Collection

Time Period of Study	Collection Tool	When Sent/Given to Patient	When Collected	Who Collects	Which Element(s) of the Trial Relevant for	What Outcome is Covered
Recruitment	Screening Questionnaire	At time of recruitment conversation (phone or face-to-face)	At time of recruitment conversation (phone or face-to-face)	PIs/Educators approaching patients for recruitment	All	If there are problems with recruitment we can understand why and try to rectify
Recruitment	Inclusion/Exclusion Checklist	At time of recruitment conversation (phone or face-to-face)	At time of recruitment conversation (phone or face-to-face)	PIs/Educators approaching patients for recruitment	All	To ensure correct protocol deviations and violations are avoided
Recruitment	Invitation letter/email with screening & Patient Information Sheet	Sent out at time of recruitment	Returned by participant if willing	PIs/Educators approaching patients for recruitment	All	If there are problems with recruitment we can understand why and try to rectify
Baseline	Informed Consent Sheet - includes full participant contact details	See informed consent process diagram	See informed consent process diagram	PIs/Educators	All	To ensure all participants have consented appropriately
Baseline	Trial CRF	Baseline Visit	Baseline Visit	Educators	Biomedical measures	HbA1c, body weight, lipids & proteinuria, diabetic ketoacidosis, severe hypoglycaemic episodes
Baseline	Baseline Hypo Recall Log	Baseline Visit	Baseline Visit & Course Visit	Educators	Biomedical measures	12 months severe hypo recall & 4 weeks moderate hypo recall
Baseline	Instructions for recording hypos	Baseline Visit	Not collected	Educators	Biomedical Measures	Severe and moderate hypoglycaemic episodes

Time Period of Study	Collection Tool	When Sent/Given to Patient	When Collected	Who Collects	Which Element(s) of the Trial Relevant for	What Outcome is Covered
Baseline	Blood and urine samples	Baseline visit	Baseline visit	Laboratory	Biomedical measures	HbA1c, lipids & proteinuria, albumin-creatinine ratio
Baseline	Demographic questionnaire – (in baseline psychosocial pack)	Baseline visit	Course Visit	Educators	Quantitative psychosocial	Demographics
Baseline	WHOQOL-BREF (in psychosocial questionnaire pack)	Baseline visit	Course Visit	Educators	Quantitative psychosocial	Generic quality of life
Baseline	DSQOL (in psychosocial questionnaire pack)	Baseline visit	Course Visit	Educators	Quantitative psychosocial	Diabetes specific quality of life
Baseline	EQ-5D (in psychosocial questionnaire pack)	Baseline visit	Course Visit	Educators	Quantitative psychosocial, health economics	QALYs
Baseline	SF-12 (in psychosocial questionnaire pack)	Baseline visit	Course Visit	Educators	Quantitative psychosocial, health economics	Functional health and well being and mental health
Baseline	HFS (in psychosocial questionnaire pack)	Baseline visit	Course Visit	Educators	Quantitative psychosocial	Fear of hypoglycaemia

Time Period of Study	Collection Tool	When Sent/Given to Patient	When Collected	Who Collects	Which Element(s) of the Trial Relevant for	What Outcome is Covered
Baseline	Baseline DTSQ (in psychosocial questionnaire pack)	Baseline visit	Course Visit	Educators	Quantitative psychosocial	Treatment satisfaction
Baseline	HADS (in psychosocial questionnaire pack)	Baseline visit	Course Visit	Educators	Quantitative psychosocial	Emotional Wellbeing
Baseline	REPOSE SAE & AE contact card	Baseline visit	Not collected	NA	Biomedical measures	AEs & SAEs
Immediately Post Course	Qualitative Study Patient Information Sheet and Informed Consent (subsample)	Sent within a week of the course	Witnessed & collected on date of interview	Qualitative Researcher	Qualitative psychosocial	Patient qualitative.
2 Weeks Post Course	Participant Interviews (subsample)	Face-to-face	Face-to-face	Qualitative Interviewer	Qualitative psychosocial	See qualitative outcomes section of protocol
Immediately Post Course	Qualitative Study Educator Information Sheet and Informed Consent	Sent within a week of the course	Witnessed & collected on date of interview	Qualitative Researcher	Qualitative psychosocial	Educator qualitative.

Time Period of Study	Collection Tool	When Sent/Given to Patient	When Collected	Who Collects	Which Element(s) of the Trial Relevant for	What Outcome is Covered
2 Weeks Post Course	Educator Interviews (subsample)	Face-to-face	Face-to-face	Qualitative Interviewer	Qualitative psychosocial	See qualitative outcomes section of protocol
Post 6 Months	Participant follow-up interviews	Face-to-face/telephone	Face-to-face/telephone	Qualitative Interviewer	Qualitative psychosocial	See qualitative outcomes section of protocol
Post 6 Months, 1 year, 2 year	6M trial CRF	6 month, 1 year & 2 year visits	6 month, 1 year & 2 year visit	Educators	Biomedical Measures	HbA1c, body weight, lipids & proteinuria, diabetic ketoacidosis, severe hypoglycaemic episodes
Post 6 Months, 1 year, 2 year	Post diary instructions	Sent out 4 weeks prior to 6 month, 1 year & 2 year visits	Not collected	Educators	Biomedical measures	Moderate hypoglycaemic episodes for next 4 week period
Post 6 Months, 1 year, 2 years	Post hypoglycaemia recall log	6 month, 1 year & 2 year visits	6 month, 1 year & 2 year visit	Educators – filled out in conjunction with diary	Biomedical measures.	Moderate hypoglycaemic episodes for preceding 4 week period
Post 6 Months, 1 year, 2 years	Blood and urine samples	6 month, 1 year & 2 year visits	6 month, 1 year & 2 year visit	Laboratory	Biomedical measures	HbA1c & lipids, proteinuria & albumin-creatinine ratio at 1 and 2 years but not 6 months
Post 6 Months, 1 year	Post Psychosocial questionnaire pack (see entries for baseline pack above for separate questionnaires included except for exclusion of baseline demographics and change to DTSQc questionnaire at 1 year)	Sent out approximately 2-6 weeks prior to 6 month & 1 year visits	6 month & 1 year visit	Educators	Quantitative psychosocial, health economics	See entries for baseline pack above for all outcomes covered

Time Period of Study	Collection Tool	When Sent/Given to Patient	When Collected	Who Collects	Which Element(s) of the Trial Relevant for	What Outcome is Covered
Post 2 years	Post Psychosocial questionnaire pack (see entries for baseline pack above for separate questionnaires included) except for the following changes: - Exclusion of baseline demographics - Inclusion of DAFNE principles, use of bolus calculators and use of pump features	Sent out approximately 2-6 weeks prior to 2 year visit	2 year visit	Educators	Quantitative psychosocial, health economics	All outcomes included in the psychosocial questionnaire pack with the addition of: - DAFNE principles - Use of bolus calculators - Use of pump features
Ongoing collection	Severe hypoglycaemia episodes log	Ongoing collection by telephone and CRFs at each visit	Ongoing collection by telephone and CRFs at each visit	Educators – filled out in conjunction with diary	Biomedical measures.	Severe hypoglycaemia episodes throughout duration of the trial
Ongoing collection	AE Identification log	Ongoing collection by telephone and CRFs at each visit	Ongoing collection by telephone and CRFs at each visit	Educators	Biomedical measures	Safety endpoints
Ongoing collection	SAE Identification log	Ongoing collection by telephone and CRFs at each visit	Ongoing collection by telephone and CRFs at each visit	Educators	Biomedical measures	Safety endpoints
Ongoing collection	Contact log	Ongoing collection by telephone and CRFs at each visit	Ongoing collection by telephone and CRFs at each visit	Educators	Health economics	Health economics

At each visit the educators at the trusts will collect data from the participants. The data will then be entered by administrators at each trust into a centralised database. Venous blood samples will be analysed at the trust laboratory for biochemical measures, except for HbA1c, the primary outcome. Two samples for measurement of HbA1c will be taken. One sample will be analysed at the local laboratory while another refrigerated sample will be transported by a courier in a polystyrene transport box to a central laboratory in Newcastle. The data from the central laboratory samples will then be transferred back to the trusts electronically, with only ID numbers to identify the samples, so that the data can be entered by the administrators onto the database. The central laboratory measure will be used as primary measure and the local laboratory measure will be used as backup. We will compare at least one result from each centre and the central lab to allow us to make the necessary adjustment when using HbA1c values measured locally. Urine samples will be analysed at the trust laboratory.

Participant Retention and Return of Data

We will use various resources to ensure that participant retention and data returned is maximised:

1. An automated system will be set up to identify participants that haven't returned for follow-up or haven't returned their questionnaires. Periodic reminders in the form of emails and/or text messages will then be sent both to the participants and to various staff (educators, administrators, study manager, psychosocial researchers) to contact and follow up the patients.
2. The staff will contact the participants using both mobile and landline numbers and will also try calling at various times of the day to ensure that there is chance of reaching the patients when they would not be at work, college or university.
3. Patients will be offered gift vouchers at each stage of the follow up process. These will be given to them at the data collection visit or posted to show appreciation for returning all questionnaires.
4. Where 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 phone, and/or to obtain the relevant data from the participant's medical records.
5. Where the participant completed psychosocial questionnaire has not been returned, a second questionnaire will be posted to the participant with a pre-paid reply envelope.

6.To make it easier for participants that do not live locally and/or where it is difficult for the participant to attend the hospital, appropriate research staff (e.g. research nurse, educator, PI) may offer the participant the opportunity to visit them in their home or at an alternative NHS location to carry out data collection.

Lost to Follow-Up

Participants will be considered lost to follow up if they fail to attend for a baseline visit followed by 2 texts and 2 phone calls or if they fail to attend 2 follow-up visits, including the 24 month visit.

Quantitative Psychosocial Procedures for Data Coding

Once the quantitative data has been input into the database, the quantitative psychosocial researcher will have access to this data directly from the database. The data will be extracted and analysed in SPSS version 17. All questionnaires will be coded according to the validated instructions. Data cleaning will take place (removing

any inadmissible entries such as responses outside the stated range i.e. if the response is a scale of 1-5, then any number above 5 or below 1 will be deleted and treated as missing data) and through checking data entry of 10% of data entered. A quality assurance check will also be completed with identification of any outliers in the data. Outliers will remain in the dataset but will be specifically analysed to determine impact on normal distribution. All data will be subject to a 10% quality assurance data entry check and missing data will be treated at such, with analysis conducted on existing data only.

Qualitative Psychosocial Data Collection & Analysis Procedures

A sub-sample of around 20 patients from each arm of the study will be recruited from the database by the qualitative researcher. The participants will be chosen from all 7 trusts, the exact courses will be selected on the basis of location and timing of courses. A representative sample of the study population will be selected in terms of age, sex, ethnicity, socioeconomic status and duration of diabetes. The patients will be contacted after the baseline data collection visit. Educators (n=12) that have taught the course from which the patients were selected will also be invited to an interview approximately 2 weeks after they have taught the course. The post course interviews will be undertaken face-to-face in a location of patients and educators choosing (e.g. at a DAFNE centre or in the participants home). It is anticipated that each interview will last about one hour. Subject to consent, these interviews will be digitally recorded and transcribed in full to permit in-depth analysis.

At approximately the same time as the 6 month data collection visit, the same participants that were interviewed post course will take part in a 6 month follow-up interview. These interviews will be undertaken on the phone for convenience unless the patient would prefer a face-to-face interview. These interviews will also last approximately 1 hour.

An inductive thematic approach will be used whereby interviews will consist of open ended questions but will be informed by topic guides. This is to ensure the discussion stays relevant to the study aims and objectives, whilst allowing participants to raise and discuss issues they perceive as salient to them. Topic guides have been adapted from those that have already been used to evaluate DAFNE courses in the past and will also be informed by views of the literature and emerging findings.

Analysis will be ongoing and iterative, starting once the interviews begin. The study will be informed by the principle of grounded theory (38) and the method of constant comparison (39), which involves concurrent data collection and analysis, together with systematic efforts to check and refine developing categories of data. Data will be analysed thematically with comparisons being drawn between the experiences and views of participants who attended CSII and MDI courses and over time, drawing upon the experience of the interviewers expertise in longitudinal analysis. Themes and hypotheses identified in the first set of interviews will inform areas of investigation in the follow-up interviews. Regular meetings between qualitative interviewers will explore respondents underlying reasoning which will help the researchers to reach agreement on recurrent themes and findings. Once consensus on themes has been reached, NVivo 8, a qualitative data-indexing package will be used to facilitate coding and retrieval. Numbers and demographics will be reported for any participants who withdraw from the interview process. So that any trend in individuals withdrawing may be analysed.

Health Economic Data Collection and Analysis Procedures

Patient costs will be calculated covering training, equipment, drugs and NHS contacts relating to the management of diabetes and its associated conditions. The cost of the training associated with the control and intervention groups will be calculated

through a survey of resource use and costs at each of the recruiting trusts. The survey will cover staff input, consumables, capital and overheads. Patient-level data will be collected for equipment, drugs and NHS contacts. These will be taken from the trial's case report forms and contact log.

Unit costs will be taken from standard sources (NHS Reference Costs, British National Formulary, and PSSRU) and combined with resource use data in order to calculate a cost for each patient within the trial. Mortality and health related quality of life will be available through other questionnaires used as part of the psychosocial study. EQ-5D will be scored using the UK tariff (Dolan). QALYs for each patient will be estimated by calculating the area under the curve defined by EQ-5D score, mortality and length of follow-up.

Two analyses, one within the trial, and another using a lifetime analysis based on the Sheffield Type 1 Diabetes Policy Model (currently in development through the NIHR Programme Grant), will be undertaken. For the within trial analysis (and hence those parameters that will subsequently be used in the Policy Model), missing data will be imputed with multiple imputation within STATA using ICE. An incremental cost effectiveness ratio (ICER) will be calculated with uncertainty around this characterised by plots on the cost-effectiveness plane and its associated cost-effectiveness acceptability curve and frontier. Deterministic sensitivity analysis will examine the effect of calculating QALYs using the SF-6D as based on the SF12 data. Sub-group analyses will be undertaken using the same populations as used within the clinical analysis, namely, for participants with HbA1c level below and ≥7.5% (58mmol/mol).

Site & Trial Closure Procedures

At the point at which all questionnaires and CRF's have been collected and entered (or participants have failed to respond despite reminders) and all data have been entered and cleaned, closure of the database will be approved. The end of the trial is defined by the point at which all questionnaires are returned and entered (not at last patient last visit) since the participants may return questionnaires after the visit. Questionnaire data will make up a significant proportion of the trial data.

Trial Pharmacovigilance

The safety of trial participants is of utmost importance and as such MHRA legislation and Sheffield CTRU SOPs will be followed in order to conduct the trial safely and to be able to assess any adverse events or serious adverse events that may occur during the trial. The following section outlines the methods for ensuring and assessing participant safety:

Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)- Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)-Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- Results in death
- Is life-threatening* (subject at immediate risk of death)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- 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***

*'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.
**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.
***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.

Adverse event inclusions and exclusions
Include:

- An increase in frequency of hypoglycaemia that is suddenly noticeable to the patient/patient's relatives
- A blood glucose reading >30 mmol/L
- Unexplained constantly raised blood glucose readings (3 consecutive readings >20mmol and over 12 hours)
- Suspicion of pump malfunction (This would be adjudicated by the educator).
- Pump site infection

Pregnancy will be recorded as an SAE so that any AEs may be identified if and when the child is born.

Do not include:
The following can occur in any patient with Type 1 diabetes and will not be classed as adverse events:

- Non-severe episodes of hypoglycaemia
- Ketonuria

<u>Classification of severe hypoglycaemia</u>
Defined as:
A hypoglycaemic episode leading to cognitive impairment sufficient to cause either coma or requiring the assistance of another person to recover.

Severe hypoglycaemic episodes requiring hospitalisation (as defined above) will be reported as SAEs.

<u>Classification of diabetic ketoacidosis (DKA)</u>
Hospitalisation and corroboration of Diabetic Ketoacidosis diagnosis will be reported as an SAE. Since all significant episodes of ketosis will need hospital admission we

can be confident of capturing all relevant episodes.

Assessment of Adverse Events

Adverse events will be assessed for relationship to the study drug (Yes/No) and for seriousness (Yes/No). Events assessed as serious will also be reported as an SAE.

SAEs will be assessed for; seriousness, frequency, intensity, relationship to study product and relationship to pump. Expectedness of SAE's will be assessed against the reference safety information in the SmPC for the type of insulin used in the arm of the study the patient is randomised to.

The following criteria will be used when assessing SAEs:
Intensity (severity):
- Mild - does not interfere with routine activities
- Moderate - interferes with routine activities
- Severe - impossible to perform routine activities

Relationship to the study product/pump:
- Unrelated - There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.
- Unlikely - There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
- Possible - There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
- Probable - There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- Definite - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
- Not assessable - There is insufficient or contradictory information which cannot be supplemented or verified.

Reporting Procedures

All trial participants will be encouraged to contact and inform their local diabetes educator if they experience any of the medical problems outlined under SAEs or relevant AEs included (above). Any that are not picked up through general contact will be identified at follow up visits through educators enquiring about problems that the patients have had.

Relevant non serious ARs/AEs/UARs - Educators will record events on the adverse event paper CRF and database.

Serious ARs/AEs/SUSARs - For any Serious Adverse Events an SAE paper CRF and database entry will be completed. The event will be assessed by the local Principal Investigator and the form faxed to the Sheffield Clinical Trials Research Unit (as delegated by the Sponsor) within 24 hours, except where exemptions from immediate reporting apply (see section below). In the absence of the PI, the form will be completed by the educator and faxed within 24 hours - when the PI becomes available a follow up form will be sent to the sponsor immediately. All SAE forms will be stored in the Site File.

Concomitant medications will only be recorded for SUSARs. In such cases

medications taken the 30 days prior to the event taking place will be reported.

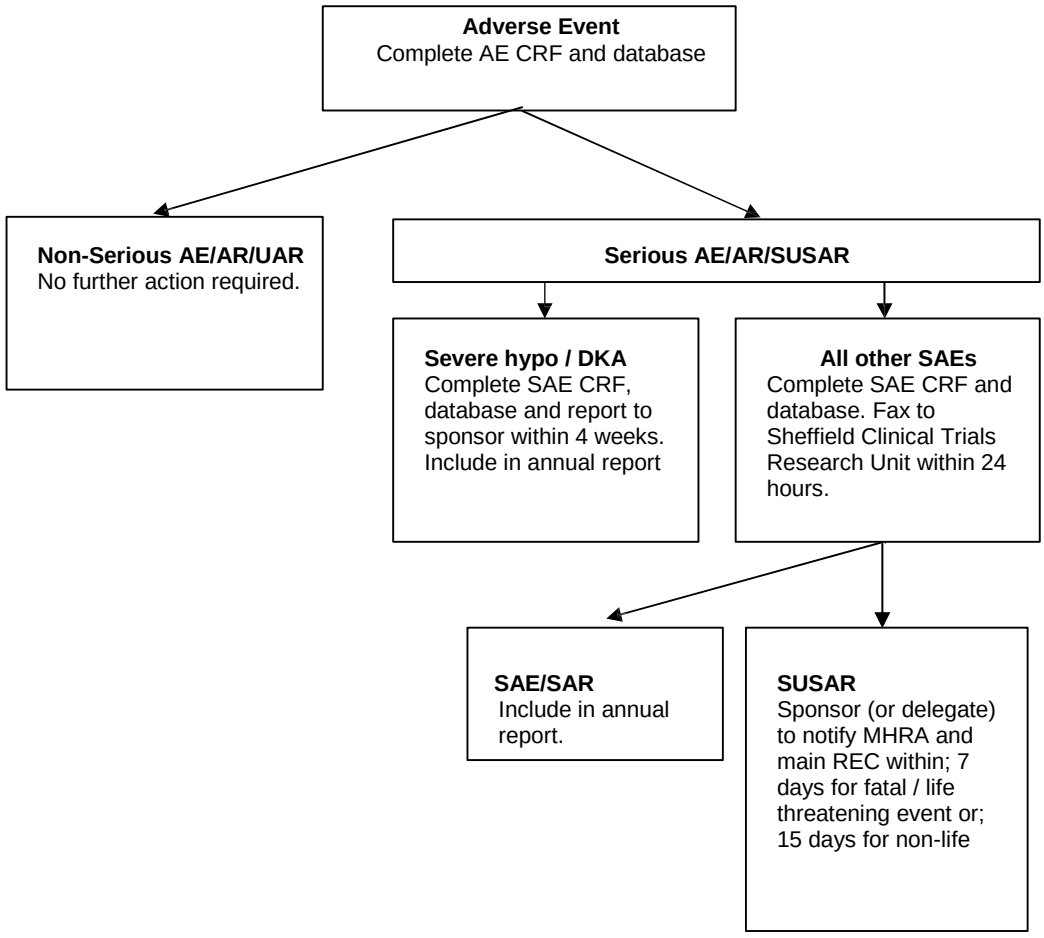
A follow up SAE form with additional information will be sent if the event has not been completely resolved at the time of reporting.

The sponsor will notify the Chief Investigator and Sheffield CTRU of all SAEs.
The sponsor (or delegate) will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and nonlife threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.

Exemptions from Immediate Reporting

Episodes of Severe Hypoglycaemia and Diabetic Ketoacidosis are expected to occur in some patients with Type 1 Diabetes. Therefore any of these episodes, defined as SAEs, will be exempt from immediate reporting to the sponsor. Pregnancies will also be exempt from immediate reporting, as these will not be related to the trial treatment. In these instances the Principal Investigator will fax the SAE form to the Sheffield Clinical Trials Research Unit (as delegated by the Sponsor) within 4 weeks of the event being discovered.

Figure 6. Procedure for AE/SAE Reporting



threatening event.

Safety & Efficacy Parameters

Safety and efficacy parameters may be used in IMP trials to stop the trial if one of the treatments seems to be less safe or is working more effectively than the other. For example, if during this trial, there are more frequent hypoglycaemic or diabetic ketoacidosis episodes in the pump arm then the study may be stopped prematurely. The decision to stop the trial would be made by the Data Monitoring and Ethics Committee in agreement with the Sponsor (see trial supervision section below for further details).

IMP Management and Labelling

In line with the three-level categorisation of clinical trial risk in the MRC/DH/MHRA report on Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products (CTIMPs) (40), (based on the classification by Brosteanu et al, 2009 (41)), this means REPOSE is classified as a Type A study: No higher than the risk of standard medical care. The trial treatment in REPOSE is licensed and administered according to its market authorisation. As such, according to the proposed by the MRC/DH/MHRA paper

Labelling
In accordance with the MRC/DH/MHRA guidance, REPOSE will not provide trial-specific labeling as the IMP, insulin, has a market authorisation in the UK, is being used within the terms of its marketing authorization during the trial, and is dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional and is labeled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/3194) Regulations that apply in relation to dispensed relevant medicinal products.

Tracking and Accountability Process
REPOSE is designed to determine whether the delivery mechanism (CSII/pump versus MDI) of the trial treatment, insulin, provides an added benefit over and above structured education (DAFNE). Thus, the IMP itself has no relationship with the data which are integral to the study endpoints. In addition, REPOSE is a trial of an authorised product with a design equivalent to standard care.

Insulin will be prescribed as per standard care and in line with its market authorisation. Given the lack of criticality of the IMP with the data analysis and trial results and the design of the trial being equivalent to standard care, there will be no IMP tracking and accountability undertaken during REPOSE.

9. Statistics

Sample Size

It is generally accepted that a difference of 0.5% in HbA1c is clinically worthwhile. To detect this difference with an SD of 1% at 80% power and 5% two sided significance using a t-test requires 64 patients per group for subjects ≥7.5% (58mmol/mol) HbA1c. In order to allow for a clustering effect of the educators and a within-course intra-class correlation coefficient (ICC) of 0.05, which is common in diabetes care, the sample size increases to 84. Allowing also for a 10% drop out, the sample size per group becomes 93. Audit of the DAFNE database shows that 75% of subjects have an HbA1c of over 7.5% (58mmol/mol). With this in mind we require 124 subjects per group, i.e. 248 in total. We plan to recruit 280 subjects which increases the power to 85% but which allows for some variation in drop-out rates and the proportion of

patients with HbA1c ≥7.5% (58mmol/mol).

We believe that we should include patients who experience frequent hypoglycaemia but who might have existing levels of HbA1c that are near the target range since they may reduce hypoglycaemic episodes and can therefore still provide important information about quality of life. Yet, since there will be no change in HbA1c levels for these participants, including this data would reduce our statistical power to establish improvement in our primary endpoint. We will therefore stratify those entering the trial based on HbA1c levels of ≥7.5% (58mmol/mol). The trial will be powered on the number of participants with an HbA1c ≥7.5% (58mmol/mol), in whom a fall would reflect worthwhile improvements in glycaemic control but we will also calculate the number of participants in each group who achieve a HbA1c <7.5% (58mmol/mol).

The DAFNE database shows that 25% of subjects currently experience 'problems' recognising hypoglycaemia and 45% of them experience at least one severe hypoglycaemic episode over 2 years. To demonstrate the benefit of CSII over MDI with this number of patients, the percentage of patients who experience at least one severe hypoglycaemic episode would need to fall to about 25% over 2 years (a change from control of about 12% per year if the events were independent) for 80% power and 2 sided 5% significance level, allowing for 10% drop-out (using a chi-squared test with continuity correction and allowing for an ICC of 0.05). We would have power to demonstrate smaller differences in moderate hypoglycaemia although we are unable to provide precise estimates due to a lack of published data using our chosen definition.

Review of HbA1c baseline data

The sample size calculation is based upon 75% of subjects having an HbA1c ≥7.5% (58mmol/mol). If the ratio of subjects with an HbA1c of ≥7.5% to <7.5% is substantially lower than the expected 75:25 ratio, then the sample size (N=280) will not be sufficient to detect a difference in the primary outcome. Therefore, a review will be undertaken after Course 2, 4 and 5 to examine the proportions of recruited participants who are in each HbA1c category (i.e. ≥7.5% or <7.5%). The trial statistician will look at the proportions in each category, and if the numbers of participants with an HbA1c ≥ 7.5% threatens the ability of the trial to detect a difference in primary outcome (i.e. there are substantially more subjects recruited with an HbA1c <7.5% than anticipated), then an additional inclusion criteria will be added to limit recruitment only to participants with an HbA1c of ≥7.5% in order to ensure the trial can detect a difference in the primary outcome.

Review of sample size in August 2012

In August 2012, a review of recruitment and retention to the trial took place. Recruitment to the trial was on target and most DAFNE courses were allocated with at least 7 participants (planned number of participants per course). However, a number of participant withdrawals (18 from 168 randomised) had also occurred post-randomisation but pre-DAFNE course delivery. The intention-to-treat population is participants who consent to take part in the trial **and** who attend their DAFNE course at least in part. As such participants recruited to the study who do not attend their DAFNE course do not count in the ITT population.

The study sample size of 280 participants allows for a ≤10% drop-out rate during the year follow-up. The current rate of participant withdrawal which has occurred exclusively prior to DAFNE course delivery is 11% and the mean number of participants per course is 6. The trial statistician undertook a review to determine the need for additional courses to maintain the study power based on the current drop-out rate. Scenarios were modelled based on current and predicted HbA1c population prevalence (≥7.5%) drop-out rate (10% or 15%) and size of

DAFNE course (4, 5, 6 or 7 participants). Assuming these variables remain similar to what has been currently observed (as of August 2012), the trial will need to run an additional two to seven courses in order to maintain power to determine the primary outcome.

Therefore, more than 280 participants will be recruited to the trial to replace participants who drop-out prior to attending their DAFNE course. The number of participants recruited will not exceed 340; however there will be no more than 280 in the ITT population.

As the last two course pairs run at a site, reserve participants who can step in to fill drop-out participant places should they occur on either of the last two courses to ensure these courses run with sufficient numbers of participants.

Data Analysis

An intention to treat analysis will be used primarily but the effect of switching to a per protocol analysis will also be explored.

Primary Analysis

The primary analysis will be a linear model of HbA1c at 2 years with baseline HbA1c as a covariate, (which will improve the power relative to the predicted power). Generalised estimating equations (GEE) will be used to control for clustering within course.

Secondary Analysis

Linear models of insulin usage, body weight, lipids and proteinuria will also be analysed at 2 years with baseline measures as covariates. We will use Poisson regression (or a zero-inflated Poisson regression if necessary) on the number of hypoglycaemic episodes in 2 years, which should also have more power than an analysis based on dichotomy of having experienced/not experienced an episode. Again, GEE will be used for these analyses to account for clustering.

Subgroup Analyses

The analyses outlined above will also be completed for sub-groups stratified at baseline by participants with HbA1c level < and ≥ 7.5% (58mmol/mol).

Primarily data will be analysed with missing data excluded. A secondary analysis will also be included using multiple imputation.

Quantitative Psychosocial Analysis

All variables will be subject to statistical analysis. Descriptive and inferential statistical analysis will be conducted using T-tests and ANOVA to compare means, crosstabs to explore individual variables, non-parametric tests including chi-square, correlational analysis and possibly multiple regression analysis. Statistical significance will be defined as $p \leq 0.05$ with 95% confidence intervals.

Primarily data will be analysed with missing data excluded. Secondary analyses will also be completed with a) a mean score for each missing questionnaire and b) a minimum score for each missing questionnaire.

A full Statistical Analysis Plan will be submitted at a later date in order to detail this section of the protocol.

10. Trial Supervision

Three committees are being established to govern the conduct of the study:
1. Trial Management Group (TMG)
2. Trial Steering Committee (TSC)
3. Data Monitoring and Ethics Committee (DMEC)

All committees are governed by Sheffield CTRU standard operating procedures. The TMG consists of the Chief and Principal Investigators, 3 educators and key staff within the CTRU. The role of the TMG is to implement all parts of the trial and to act on the recommendations from the TSC and DMEC. The TSC consists of the Chief Investigator, key staff within the CTRU, an independent chair, 2 independent members and a consumer representative. The roles of the TSC are to provide supervision of the protocol and statistical analysis plan, provide advice on and monitor progress of the trial, to review information from other sources and to consider recommendations from the DMEC. The DMEC will consist of an independent chair and 2 independent members including a statistician. The DMEC has responsibility for monitoring the results provided by the trial statistician to the plan described in the trial protocol with reference to efficacy and safety, reviewing information from other sources, providing recommendations to the TSC on why the trial might be modified or discontinued in terms of ethics and safety and considering adverse events. There will be no interim analysis for the trial unless the DMEC feels that this is necessary.

11. Data handling and record keeping

Participant confidentiality will be respected at all times. The educators will collect participant names and contact details so that participants can be contacted for the psychosocial interviews and to follow up on data. These will be immediately entered with an ID number on to an identification section of the database, which may be accessed by the educator or administrator who have entered the data, the psychosocial researchers for follow up on this element of the trial, and the study manager for follow up and verification of all data. Access will be controlled by usernames and encrypted passwords.

All other data will be anonymised and will only be identifiable by patient ID number. The CRF/questionnaires will have demographic details on them, including the first part of the participant's postcode. This will be used in analysis as an indicator of the participants' socioeconomic status. The blood samples that are sent to a central laboratory will be sent with patient ID and all results will be returned to the trust electronically with ID number and HbA1c result only. All data will be input by the administrators at each trust, on to a centralised database held within the CTRU. This section will also be controlled by usernames and encrypted passwords.

All consent forms, CRFs, HbA1c spreadsheets, questionnaires and interview transcripts will be kept in a locked filing cabinet in a secured area and will be destroyed at least 5 years after study completion. The consent forms will be kept in a separate place to the CRFs and questionnaires so that none of the data will be identifiable.

12. Data access and quality assurance

The study manager, data managers, PIs, educators, and administrators will have access to the anonymised data on the database through the use of usernames and encrypted passwords. In addition to this, access to hard copies of the CRF and questionnaire data will be required from the educators for study monitoring and audit purposes.

The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is required.

13. Publication

Results of the trial will be disseminated in peer reviewed scientific journals and clinical and academic conferences.

Details of the trial will also be made available on the SCHARR website. Summaries of the research will be updated periodically to inform readers of the ongoing progress.

14. Finance

The trial has been financed by the HTA and details have been drawn up in a separate agreement.

15. Ethics approval

The trial will be submitted to a Local Research Ethics Committee (LREC) through the IRAS central allocation system. The approval letter from the ethics committee and copy of approved patient information leaflet, consent forms, CRFs and questionnaires will be sent to the CTRU before initiation of the study and patient recruitment.

16. Regulatory approval

The trial will be covered by the clinical trial regulations from the Medicines and Healthcare Regulatory Agency (MHRA) and we will apply for authorisation from the MHRA before recruitment of any patient commences.

17. Indemnity / Compensation / Insurance

The University of Sheffield has in place insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical trial.

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