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Abstract

Improving management of type 1 diabetes in the UK: the Dose Adjustment For Normal Eating (DAFNE) programme as a research test-bed. A mixed-method analysis of the barriers to and facilitators of successful diabetes self-management, a health economic analysis, a cluster randomised controlled trial of different models of delivery of an educational intervention and the potential of insulin pumps and additional educator input to improve outcomes

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Background: Many adults with type 1 diabetes cannot self-manage their diabetes effectively and die prematurely with diabetic complications as a result of poor glucose control. Following the positive results obtained from a randomised controlled trial (RCT) by the Dose Adjustment For Normal Eating (DAFNE) group, published in 2002, structured training is recommended for all adults with type 1 diabetes in the UK.

Aim: With evidence that blood glucose control is not always improved or sustained, we sought to determine factors explaining why some patients benefit from training more than other patients, identifying barriers to successful self-management, while developing other models to make skills training more accessible and effective.

Findings: We confirmed that glycaemic outcomes are not always improved or sustained when the DAFNE programme is delivered routinely, although improvements in psychosocial outcomes are maintained. DAFNE courses and follow-up support is needed to help participants instil and habituate key self-management practices such as regular diary/record keeping. DAFNE graduates need structured professional support following training. This is currently either unavailable or provided ad hoc without a supporting evidence base. Demographic and psychosocial characteristics had minimal explanatory power in predicting glycaemic control but good explanatory power in predicting diabetes-specific quality of life over the following year. We developed a DAFNE course delivered for 1 day per week over 5 weeks. There were no major differences in outcomes between this and a standard 1-week DAFNE course; in both arms of a RCT, glycaemic control improved by less than in the original DAFNE trial. We piloted a course delivering both the DAFNE programme and pump training. The pilot demonstrated the feasibility of a full multicentre RCT and resulted in us obtaining subsequent Health Technology Assessment programme funding. In collaboration with the National Institute for Health Research (NIHR) Diabetes Research Programme at King's College Hospital (RG-PG-0606-1142), London, an intervention for patients with hypoglycaemic problems, DAFNE HART (Dose Adjustment for Normal Eating Hypoglycaemia Awareness Restoration Training), improved impaired hypoglycaemia awareness and is worthy of a formal trial. The health economic work developed a new type 1 diabetes model and confirmed that the DAFNE programme is cost-effective compared with no structured education; indeed, it is cost-saving in the majority of our analyses despite limited glycated haemoglobin benefit. Users made important contributions but this could have been maximised by involving them with grant writing, delaying training until the group was established and funding users' time off work to maximise attendance. Collecting routine clinical data to conduct continuing evaluated roll-out is possible but to do this effectively requires additional administrator support and/or routine electronic data capture.

Conclusions: We propose that, in future work, we should modify the current DAFNE curricula to incorporate emerging understanding of behaviour change principles to instil and habituate key self-management behaviours that include key DAFNE competencies. An assessment of numeracy, critical for insulin dose adjustment, may help to determine whether or not additional input/support is required both before and after training. Models of structured support involving professionals should be developed and evaluated, incorporating technological interventions to help overcome the barriers identified above and enable participants to build effective self-management behaviours into their everyday lives.

Trial registration: ClinicalTrials.gov NCT01069393.

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Contents

List of tables

List of figures

List of boxes

List of abbreviations

BGAT	Blood Glucose Awareness Training
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
CICS	Corporate Information and Computing Services
CIDS	Confidence in Diabetes Self-Care
CP	carbohydrate portion
CSII	continuous subcutaneous insulin infusion
CVD	cardiovascular disease
DAFNE	Dose Adjustment For Normal Eating
DAFNE 5 × 1 day	randomised controlled trial of DAFNE training delivered for 5 continuous days over 1 week vs. DAFNE training delivered for 1 day per week for 5 continuous weeks
DAFNE-HART	Dose Adjustment For Normal Eating Hypoglycaemia Awareness Restoration Training
DCCT	Diabetes Control and Complications Trial
df	degrees of freedom
DIG-AMI	Diabetes mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
DKA	diabetic ketoacidosis
DSQOLS	Diabetes-Specific Quality of Life Scale
DUAG	Dose Adjustment For Normal Eating Users Action Group
DUG	Dose Adjustment For Normal Eating User Group
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	estimated glomerular filtration rate
EQ-5D	European Quality of Life-5 Dimensions
EQ VAS	European Quality Visual Analogue Scale
ESRD	end-stage renal disease
FIIT	flexible intensive insulin therapy
GEE	generalised estimating equation
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – anxiety
HADS-D	Hospital Anxiety and Depression Scale – depression
HbA_{1c}	glycated haemoglobin
HDL	high-density lipoprotein
HFS-W	Hypoglycaemia Fear Survey Worry subscale
HTA	Health Technology Assessment
ICC	intracluster correlation coefficient
ICER	Incremental cost-effectiveness ratio
ITT	intention to treat
ITTP	Insulin Treatment and Training Programme
LDL	low-density lipoprotein
MDI	multidose injection (insulin)
MI	myocardial infarction
NICE	National Institute for Health and Care Excellence

NIHR	National Institute for Health Research
NPH	neutral protamine Hagedorn
NTCRN	North Trent Cancer Research Network
OLS	ordinary least square
PAID	Problem Areas in Diabetes
PMD	Personal Models of Diabetes
PPI	patient and public involvement
PROM	patient-reported outcome measure
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RE-AIM	Reach, Efficacy, Adoption Implementation, Maintenance
REPOSE	Relative Effectiveness of Pumps Over MDI and Structured Education
RfPB	Research for Patient Benefit
RQ	research question
ScHARR	School of Health and Related Research
SCI-R	Self-Care Inventory – Revised
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SF-12	Short Form questionnaire-12 items
SF-36	Short Form questionnaire-36 items
SMBG	self-monitoring of blood glucose
SMQ	self-management questionnaire
SSQ6	6-item Social Support Questionnaire
UKPDS	UK Prospective Diabetes Study
WESDR	Wisconsin Epidemiology Study of Diabetic Retinopathy
WHO-5	World Health Organization 5-item questionnaire
WTE	whole-time equivalent

Plain English summary

Many adults with type 1 diabetes cannot manage their diabetes effectively because they lack the skills to keep their glucose at near-normal levels. The result is an increased risk of premature death and complications because of long-term high glucose levels. This prompted our group to conduct the Dose Adjustment For Normal Eating (DAFNE) trial in 2002, which showed that structured training could help adults to self-manage their glucose more successfully. Over 20,000 people have been trained and the Department of Health have stated that all individuals with diabetes in the UK should be offered structured education.

However, courses do not always work well to help people improve their blood glucose levels. We therefore investigated why some patients benefit more than others and identified barriers that would help us to develop more effective programmes.

We found that courses often fail to help participants make these skills part of their everyday lives and skills were not maintained; DAFNE graduates often needed professional support in a more structured way. We developed a course to be delivered over 1 day per week for 5 weeks and will now offer both approaches to allow more people to be trained. We developed courses to train people to use insulin pumps and to help people whose blood glucose goes too low. We also found that people with diabetes made important contributions to the research but might be more effective if involved earlier.

We now intend to develop the DAFNE programme to help people incorporate skills into their everyday lives more effectively. We will develop more effective professional support and use modern technology to help achieve this.

Scientific summary

Background

Many people with type 1 diabetes develop severe microvascular complications and experience premature death from cardiovascular disease. The human cost in terms of loss of quantity and quality of life (QoL) is matched by the economic consequences. Around 2–3% of those with diabetes in the UK currently account for 10% of the NHS budget. The annual UK cost for managing kidney disease is around £150M in type 1 diabetes.

Keeping blood glucose close to non-diabetic levels reduces microvascular complications. In the Diabetes Control and Complications Trial, a reduction in glycated haemoglobin (HbA_{1c}; a measure of glucose control) of 2% halved the risk of diabetic complications. However, this evidence did not initially lead to improved clinical practice in the UK.

The main reason that tight metabolic control is difficult to achieve is that current methods of insulin delivery cannot reproduce physiological insulin release by the pancreas. Furthermore, the relentless behavioural and technical demands of calculating appropriate doses of insulin and adjusting for different situations (e.g. stress, exercise, carbohydrate consumption), attempting to reproduce normal physiology (in which correct amounts are released automatically), are very challenging. Using injected insulin to control glucose levels aggressively is also hazardous, with increased risks of hypoglycaemia, although the rewards are a reduced chance of microvascular complications and a prolonged life expectancy.

Despite these limitations, insulin therapy can control blood glucose effectively if patients can integrate different principles, including (1) understanding the effects of insulin, (2) appreciating which foods raise blood glucose and by how much, (3) recognising and treating hypoglycaemia and (4) anticipating exercise. Diabetes health-care professionals understand these principles and the crucial test is whether they can teach them to patients. In the 1980s the Düsseldorf Diabetes Centre developed a 5-day structured training programme in intensive self-management using these principles, which demonstrated markedly improved glucose control yet reduced hypoglycaemia.

In 2002, a multidisciplinary team, based in three centres and part of the group undertaking the work of this report, completed the Dose Adjustment For Normal Eating (DAFNE) trial, a randomised controlled trial (RCT) of the German intervention adapted for the UK. There were major improvements in QoL, sustained for up to 12 months (despite increased injections and blood tests), and falls in HbA_{1c} of 1.0% at 6 months and 0.5% at 12 months.

These results had a profound impact on the management of type 1 diabetes in the UK. They prompted the National Institute for Health and Care Excellence to evaluate structured education models in diabetes, acknowledging that the DAFNE approach, together with the German programmes, appeared to be effective. The approach was identified as one of the few interventions in type 1 diabetes that met criteria agreed by a Department of Health working group into structured diabetes education. This led to the formation of the DAFNE collaborative, with courses delivered to > 27,000 adults in > 70 centres across the UK and Ireland. There is an active user group, two members of whom sit on the executive; other patients have constructed an online website offering support, including an area where patients can obtain professional advice.

A review of the original DAFNE cohort showed that, after 4 years, the HbA_{1c} level was only 0.2% below the baseline level although psychosocial benefit was maintained. These data and others showing that around half of DAFNE graduates remain poorly controlled emphasised that DAFNE courses were just a start. More research was needed to improve the effectiveness of the intervention so that patients could manage their diabetes more effectively.

Objectives

The aim of the study was to use the DAFNE collaborative as a research test-bed to improve complex educational interventions for the management of type 1 diabetes and other long-term conditions.

Our objectives were to:

1. Develop an electronic database to record outcomes and progress in adults with type 1 diabetes undertaking structured education.
2. Undertake psychosocial studies to determine factors explaining why individuals do well or badly after structured education using linked qualitative and quantitative approaches. We aimed to:

    i. identify which aspects of the complex intervention do and do not promote improved biomedical and psychosocial outcomes
    ii. establish why some patients benefit more from DAFNE training than others
    iii. identify factors that explain why improved glycaemic control following DAFNE training tends to decline over time.

3. Undertake two RCTs (one pilot) to improve self-management and develop an additional intervention to address glycaemic outcomes.
4. Utilise user involvement to develop more effective interventions.
5. Measure the cost-effectiveness of interventions over the short and long term.

Objective 1: to develop an electronic database to record outcomes and progress, and explore whether or not it was possible to collect research data routinely in busy units

We constructed a database to record clinical outcomes and support other workstreams. Data were collected at baseline and annually on demographic, biomedical, health-related and psychosocial outcomes. From December 2008 we enrolled 2002 patients, 82% of whom were eligible. Follow-up data collection rates at 12, 24 and 36 months were 79%, 71% and 62%, respectively, at December 2013.

We established that creating a high-quality research database was feasible within clinical practice to evaluate educational interventions but to do this effectively requires additional administrator support and/or routine electronic data capture and input.

Objective 2: to undertake psychosocial studies to determine factors and experiences that explain why individuals do well or badly after DAFNE training

A combination of qualitative (interview and observation) and quantitative (questionnaire) assessment methods were employed with 262 adults with type 1 diabetes before commencing DAFNE training and at 1 year. The quantitative model developed in this study, based on social learning theory, explained between 14% and 20% of the variance in HbA_{1c} and between 28 and 62% of the variance in diabetes-specific QoL, over 1 year. Thus, demographic and psychosocial characteristics showed minimal explanatory power for glycaemic control but good explanatory power for diabetes-specific QoL. Qualitative data suggest that assessing numeracy, critical for insulin dose adjustment and carbohydrate counting, would help to determine whether or not additional training and support are required both before and during structured education. Analyses showed that, although DAFNE courses imparted knowledge and skills, they were less effective at helping participants establish key self-management practices such as regular diary keeping. Revising course curricula may facilitate the complex, ongoing behaviour change required to achieve effective self-management. Technological innovations to reduce the complexity and provide support while facilitating behaviour change domains are important areas to develop.

Objective 3: to undertake two randomised controlled trials (one pilot) to improve self-management of type 1 diabetes and develop an intervention for patients with hypoglycaemia problems

Developing and evaluating a course delivered for 1 day per week over 5 weeks

This was designed as a non-inferiority RCT. Adults with type 1 diabetes were randomised to receive either a standard 1-week DAFNE course or a 5-week DAFNE course. An embedded qualitative study helped understand and interpret outcomes. In total, 213 patients were randomised in seven centres across England and 160 completed the study procedures. For patients with a baseline HbA_{1c} of > 7.5%, the mean change was –0.20% at 6 months ($p = 0.016$) and –0.18% at 12 months ($p = 0.055$). Severe hypoglycaemic episodes fell by 82% in the 12 months after DAFNE training compared with the 12 months before (estimated relative risk 0.18; $p = 0.04$). Psychosocial outcomes improved significantly by 6 months and were maintained at 12 months. For all outcomes the difference between treatment arms was not significant. Qualitative interviews revealed that patients overwhelmingly preferred the format that they received. In conclusion, there were no major differences in outcomes between the 5-week course and the 1-week-course; glycaemic control improved less than in the original trial but severe hypoglycaemia was reduced. As participants valued both formats highly, and some found it easier to attend one type than the other, we will provide both in the future.

Feasibility/pilot study of a 5-day course providing both DAFNE and insulin pump training

We conducted a pilot feasibility study exploring the potential of a trial in which participants were randomised to DAFNE training involving either multiple insulin injections [multidose injection (MDI)] or insulin pumps. DAFNE educators developed a 5-day curriculum incorporating both DAFNE principles and the skills necessary to use a pump. Of 160 eligible individuals, 55 were randomised to either the pump course or the MDI course, of whom 47 both completed the course and attended the 6-month follow-up. HbA_{1c} levels improved in those attending the pump course, comparable to improvements in the original trial; severe hypoglycaemia was reduced and psychosocial outcomes improved. Participants generally remained on their allocated therapy over 6 months.

This pilot demonstrated the feasibility of the proposed full multicentre RCT, including a robust power calculation for the primary end point, and helped in obtaining Health Technology Assessment (HTA) programme funding for the full trial.

Developing an additional intervention for patients who experience hypoglycaemic problems after DAFNE training: DAFNE-HART (Hypoglycaemia Awareness Restoration Training)

Following recognition of the importance of hypoglycaemia to patients on the DAFNE programme in the psychosocial studies (see *Objective 2: to undertake psychosocial studies to determine factors and experiences that explain why individuals do well or badly after DAFNE training*), we collaborated with the diabetes research programme at King's College Hospital, London, in the design and piloting of a 6-week intervention that emphasised hypoglycaemia avoidance and addressed unhelpful beliefs concerning unawareness, incorporating motivational enhancement and cognitive–behavioural approaches. In total, 24 people with type 1 diabetes, impaired hypoglycaemia awareness and problematic hypoglycaemia attended pilot courses and were reviewed 3 months later. One was lost to follow-up. In the remaining 23, the Gold score (a measure of unawareness) improved (from 5.5 to 4.4; $p < 0.001$). The annualised rate of severe hypoglycaemia fell from a median (range) of 3.5 (0–70) to 0 (0–40) ($p = 0.14$), with a fall in moderate episodes from 14 (0–100) to 1 (0–11) per 6 weeks. Depression scores (Hospital Anxiety and Depression Scale) improved (from 5.4 to 4.6; $p = 0.04$) and HbA_{1c} remained stable. We conclude that this intervention helps individuals with impaired hypoglycaemia awareness to reduce hypoglycaemia that persists following DAFNE training.

Objective 4: to utilise user involvement to develop more effective interventions

Dose Adjustment For Normal Eating graduates were represented on different workstreams through the Dose Adjustment For Normal Eating Users Action Group (DUAG). DUAG consists of DAFNE graduates from across the country who have volunteered to contribute to further aspects of DAFNE work. This includes the creation of a website (DAFNE-online), liaison and representation on the DAFNE executive (which administers and supports the DAFNE collaborative) and participating in different research activities. The latter includes the DAFNE programme grant work and the trial of insulin pumps funded by the HTA programme [the Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) trial].

A longitudinal evaluation of their impact on the research programme was undertaken, including an evaluation of the initial training provided. We used a mixed-methods approach including (1) semistructured interviews and (2) non-participant observation at DAFNE meetings where users were present.

User involvement in the DAFNE research programme was not maximised because participants were not involved at the grant-writing stage and some DUAG members found it difficult to represent the spectrum of DAFNE participants.

Findings suggest that, if users are assigned to different workstreams, it is preferable to assemble the group first and deliver training on research methods later. This allows users to bond while the research team and users establish training needs.

The DUAG members gave important support to the work of the DAFNE-HART and 5 × 1-day trials. This included developing participant information and discussing inclusion and exclusion criteria while emphasising the contributions that service users can make.

At DUAG's request, users were not paid for their time but received expenses. The resulting difficulty in obtaining time off work might explain why users could not attend all meetings. In future programme grants, investigators should cost users' time to maximise attendance.

Objective 5: to use economic evaluation to assess the cost-effectiveness of interventions over the short and long term

The health economics workstream included development of a health economic model of type 1 diabetes, the re-estimation of the cost-effectiveness of DAFNE training compared with no DAFNE training using the new model, estimation of the cost-effectiveness of 5-week compared with 1-week DAFNE training and integration of psychological and behavioural characteristics into the model.

The key conclusions were that DAFNE training is cost-effective compared with no education, even with limited HbA_{1c} benefit, and that the 1-week and 5-week versions of the course have similar cost-effectiveness. Other results include a set of health-related QoL values for people with type 1 diabetes with varying degrees of diabetes-related complications and that predicting HbA_{1c} response to DAFNE training from individuals' psychosocial characteristics and restricting access to training based on these predictions would not be cost-effective. The Sheffield Type 1 Diabetes Policy Model can be used to answer future policy questions relating to the treatment and self-management of type 1 diabetes.

Key conclusions

1. DAFNE training confers major benefits in improving different aspects of QoL and is highly valued by participants but is less effective in improving and sustaining blood glucose control in the UK than in other European health-care systems.
2. Courses do not always help participants to instil and habituate key self-management practices such as regular diary/record keeping into their lives.

3. DAFNE graduates need structured professional support following training, which is currently unavailable or is provided ad hoc.
4. Demographic and psychosocial characteristics have minimal explanatory power in terms of predicting glycaemic control but good explanatory power regarding prediction of diabetes-specific QoL over 1 year of follow-up after DAFNE training attendance.
5. There were no major differences in outcomes between the 5-week and the 1-week DAFNE courses; glycaemic control improved by less than in the original DAFNE trial but severe hypoglycaemia was reduced.
6. The insulin pump pilot study demonstrated the feasibility of the proposed full multicentre RCT, including a robust power calculation for the primary end point. It also contributed to the success in obtaining HTA funding for the full trial.
7. The DAFNE-HART intervention may help individuals with impaired hypoglycaemia awareness to reduce the risk of hypoglycaemia.
8. DAFNE is a cost-effective intervention compared with no structured education (indeed, cost-saving in the majority of our analyses), even with limited HbA_{1c} benefit, and this supports its provision by the NHS to people with type 1 diabetes in the UK. The 1-week and 5-week versions of the course have similar cost-effectiveness.
9. User involvement was particularly useful in contributing to the trials but could have been maximised by involving users at the grant-writing stage. Training for users should be delayed until their participation is established. In future programme grants, investigators may need to ensure resource for users' time to maximise attendance.
10. It is feasible to run a research database of quality within clinical practice to evaluate self-management interventions such as DAFNE training but to do this effectively requires additional administrator support and/or routine electronic data capture and input.

Proposals for future work

1. Perhaps the most important finding of this programme was that teaching the rationale and skills of flexible intensive insulin therapy in a stand-alone intervention was insufficient to ensure that most individuals initiate and sustain effective self management. We now strongly believe that long-term conditions need integrated skills training and structured lifelong professional support. Thus, structured education in self-management needs to include a package that instils the principles of self-management and then supports individuals and their families to achieve success. This should be applied to other long-term conditions.
2. We should modify the current DAFNE curriculum to incorporate the emerging understanding of behaviour change to instil and habituate key self-management behaviour in addition to key competencies.
3. An assessment of numeracy, critical for insulin dose adjustment and carbohydrate counting, may help to identify the need for additional training/support.
4. Technological innovations to reduce the complexity of insulin dose calculations, record keeping and blood glucose pattern recognition combined with addressing behaviour change domains (knowledge, motivation and goal-setting) are important areas to incorporate into improved educational interventions seeking to improve diabetes self-management.
5. Models of structured follow-up involving professionals warrant development and evaluation. Technological interventions may contribute to overcoming the barriers identified above and enable participants to incorporate effective self-management strategies and behaviours into their everyday lives.
6. We should seek funding to conduct a multicentre RCT of the DAFNE-HART intervention for individuals with hypoglycaemia unawareness.
7. In future work we should ensure that users contribute to all elements of the research. This includes the different workstreams and how they should operate and the technological support needed.
8. We should ensure that future work includes a detailed assessment of the fidelity of educational interventions, including the extent to which educators maintain the principles on which DAFNE training is based.

Trial registration

This trial is registered as ClinicalTrials.gov NCT01069393.

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Chapter 1 Introduction

Background

Many people with type 1 diabetes develop severe microvascular complications including kidney failure, foot ulceration and deteriorating vision, and experience premature death from cardiovascular disease (CVD). The human cost in loss of quantity and quality of life (QoL) is matched by the economic consequences. Around 2–3% of those with diabetes in the UK currently account for 10% of the NHS budget.[1] The annual UK cost for managing kidney disease amounts to around £150M in type 1 diabetes.[2]

Keeping blood glucose levels close to non-diabetic levels reduces microvascular complications. In the Diabetes Control and Complications Trial (DCCT),[3] a reduction in glycated haemoglobin (HbA_{1c}, a measure of glucose control) of 2 percentage points halved the risk of diabetic complications. However, this evidence did not initially lead to improved clinical practice in the UK.

The main reason that tight metabolic control is difficult to achieve is that current methods of insulin delivery cannot reproduce physiological insulin release by the pancreas. Furthermore, the relentless behavioural and technical demands of having to calculate appropriate doses of insulin and adjust for different situations (e.g. stress, exercise, carbohydrate consumption) in a way that attempts to reproduce normal physiology (in which correct doses are released automatically) are very challenging. Using injected insulin to control glucose levels aggressively is also potentially hazardous, with an increased risk of hypoglycaemia,[4,5] although in the long term the rewards are a reduced chance of microvascular complications and a prolonged life expectancy.

Despite these limitations, insulin therapy can control blood glucose effectively if patients can integrate different principles, including (1) understanding the effects of insulin, (2) appreciating which foods raise blood glucose and by how much, (3) recognising and treating hypoglycaemia and (4) anticipating exercise. Diabetes health-care professionals understand these principles and the crucial test is whether or not they can teach them to patients. In the 1980s the Diabetes Centre in Düsseldorf developed a 5-day structured training programme in intensive self-management using these principles, which demonstrated markedly improved glucose control yet reduced hypoglycaemia.[6]

In 2002, a multidisciplinary team, based in three centres and part of the group undertaking the work of this report, completed the Dose Adjustment For Normal Eating (DAFNE) trial,[7] a randomised controlled trial (RCT) of the German intervention adapted for the UK. There were major improvements in QoL, sustained for up to 12 months (despite increased injections and blood tests), and falls in HbA_{1c} of 1.0% at 6 months and 0.7% at 12 months.

Principles of the complex educational intervention

One of the main principles underlying DAFNE flexible intensive insulin therapy (FIIT) is the separation of basal- and meal-related insulin. The basal or background insulin is a medium-acting insulin [neutral protamine Hagedorn (NPH), detemir or glargine), usually given as two doses, one just before bed and the other before breakfast. The doses are kept relatively constant to maintain the blood glucose within a given target range. The approach is designed so that the basal insulin doses should be able to keep the blood glucose reasonably controlled in the 'fasting state'. Participants are taught to adjust the basal dose every few weeks. The evening dose, given the night before, is altered based on the fasting blood glucose measured before breakfast on the following morning. The morning dose is altered according to the pre-evening meal blood glucose.

An important skill taught in the DAFNE programme concerns the calculation of the fast-acting insulin dose, given before meals. The dose required is determined by estimating the carbohydrate content of the food about to be eaten in terms of the number of 10-g carbohydrate portions (CPs) and multiplying this by an individualised ratio of the number of insulin units to each CP (often 1 : 1). A correction to the insulin dose may also be required if the relevant pre-meal blood glucose level is above the target range. Additional adjustment may also be made if the participant anticipates other activities such as exercise. DAFNE diaries are provided so that blood glucose levels can be written down, along with the carbohydrate content of the meals eaten and the insulin doses used. These records are designed specifically to aid reflection and refine future insulin dose adjustment.

Courses

Individual courses are led by two trained educators (usually one diabetes nurse specialist and one dietitian) in a group setting with six to eight adults with type 1 diabetes. The courses are run over 5 days with the participants attending between 09.00 and 17.00 Monday to Friday. Courses are held in a large room. Some centres have a designated education room whereas other centres hold courses in community centres. Centres organising DAFNE courses are free to choose which of their patients attend, although those with serious complications, those with very poor blood glucose control (and who are probably missing insulin for psychological reasons) and those who have a poor command of English are generally excluded. The age of participants varies between 18 and 80 years and the duration of diabetes of those participating can range from newly diagnosed to > 50 years. The curriculum has been built on adult education principles, emerging from the concept of therapeutic education (a principle advanced by Assal *et al.*[8] in the early 1980s), and adheres to the precept of social learning theory.[9] It encourages inclusivity and participation and involvement by all.

Group feedback sessions on insulin adjustment and achieving target blood glucose levels take place at the beginning and end of each day. During the course, there are additional sessions on the simple pathophysiology of diabetes, insulin types and their duration of action, blood glucose monitoring, managing hypoglycaemia, diabetes complications, the purpose of the annual review and managing diabetes in special situations, for example illness, alcohol and exercise.

A group follow-up session is offered to participants at 6–12 weeks after each course (often poorly attended) but follow-up thereafter is not specified and is left to individual centres.

Quality control

The DAFNE educators are required to teach on at least one course every 6 months to maintain their skills and are intermittently peer reviewed by educators from other centres who have had additional training. DAFNE centres are audited on a 3-year cycle on the process of delivering the DAFNE programme and on local outcomes, particularly recorded changes in HbA_{1c} levels.

Central organisation

The DAFNE programme is co-ordinated by a central organisation that is funded by annual payments from individual centres. DAFNE Central, hosted by North Tyneside General Hospital, is responsible for curriculum revision and training (all nurse/dietitian educators attend a 2-day course whereas doctors who support the DAFNE programme attend a 1-day workshop). The co-ordinating centre organises meetings of a DAFNE executive committee, carries out peer review for educators, conducts centre audits, supplies course materials, hosts a centralised database for audit of outcomes and hosts a website (see www.dafne.uk.com).

All participating DAFNE centres in the UK are invited to send representatives to the annual collaborative meeting, and regional educator meetings take place biannually. There is a patient support network called the Dose Adjustment For Normal Eating User Group (DUG) with a subgroup of elected representatives, the Dose Adjustment For Normal Eating User Action Group (DUAG), who nominate representatives to attend the DAFNE executive meetings and contribute to DAFNE planning and research development.

Outcomes

One of the principles underlying the DAFNE programme is that it is evidence based, quality assured and subject to audit. There is a commitment to ongoing research to improve diabetes education to benefit people with diabetes. DAFNE is not a fixed and unchanging educational package. Research and audit within the DAFNE organisation is facilitated by the programme being standardised, centrally organised and run collaboratively.

The results of the original trial had a profound impact on the management of type 1 diabetes in the UK. They prompted the National Institute for Health and Care Excellence (NICE) to evaluate structured education models in diabetes,[10] acknowledging that the DAFNE approach, together with the German programmes, appeared to be effective. The approach was identified as one of the few interventions in type 1 diabetes that met criteria agreed by a Department of Health working group into structured diabetes education.[11] This led to the formation of the DAFNE collaborative, with courses delivered to > 27,000 adults in > 70 centres across the UK and Ireland. There is an active user group, two members of whom sit on the executive; other patients have constructed an online website offering support, including an area where patients can obtain professional advice.

Rationale for the research programme

Despite the success of the DAFNE project, important questions remain unanswered. Many patients cannot sustain the approach and, in others, HbA_{1c} is unchanged or worsens after the course. These patients need additional input besides skills training to undertake effective self-management, perhaps a different course or undertaking it after specific pre-course preparation. A review of the original DAFNE cohort showed that, after 4 years, the HbA_{1c} level was only 0.2% below the baseline level, although psychosocial benefit was maintained.[12] These data and others showing that around half of DAFNE graduates remain poorly controlled emphasised that developing the DAFNE intervention was just a start and that more research was needed to both improve the effectiveness of the intervention and to support patients to manage their diabetes more effectively.

To improve the DAFNE programme, and indeed diabetes education in general, patients' experiences needed to be better understood. We were unsure of the 'active ingredients' that foster (or hinder) improved self-care and/or QoL in complex educational interventions. We did not know which factors are critical (or incidental) to success. Delivering diabetes education to groups may be more effective than delivering diabetes education to individuals,[13] but the reasons for this remain unclear. Given our limited understanding of how diabetes group education 'works', we may not have been using the most appropriate measures for its evaluation. To explore the DAFNE 'black box' we needed to record patient characteristics and psychosocial variables alongside an in-depth exploration of the problems and challenges encountered in sustaining intensive self-management over time.

In addition, the provision of a well-defined, quality-assured, educational and consistent programme delivered in centres across the UK allowed us to test the added benefit of new technologies in patients skilled in self-management. Thus, one of our workstreams involved the development of a model allowing us to measure the true benefit of continuous subcutaneous insulin infusion (CSII) in a RCT. Demonstrating the success of such an approach would allow us to establish the benefit of other emerging new treatments such as different forms of insulin delivery and techniques such as continuous glucose monitoring (CGM) in the future.

We recognise that type 2 diabetes is more common than type 1 diabetes and that the incidence of type 2 diabetes is increasing at a faster rate. However, when we initiated this work, the DAFNE collaborative was the only self-management programme for long-term conditions that has published evidence of effectiveness in a RCT and successfully rolled out care across the UK accompanied by a robust quality assurance programme with structured educator training and independent peer review. The work we proposed included a detailed exploration of factors determining success in a complex health educational intervention. Thus, we expected that the information gained from this approach would apply to both type 2 diabetes and other long-term conditions.

Objectives

The aim of this research programme was to use the DAFNE collaborative as a research test-bed to improve complex educational interventions in the management of type 1 diabetes and other long-term conditions.

Our objectives were to:

1. Develop a database to record outcomes and progress in adults with type 1 diabetes undertaking structured education.
2. Undertake psychosocial studies to determine factors explaining why individuals do well or badly after structured education using linked qualitative and quantitative approaches. We aimed to:

    i. identify which aspects of the complex intervention do and do not promote improved biomedical and psychosocial outcomes
    ii. establish why some patients benefit more from DAFNE training than others
    iii. identify factors that explain why improved glycaemic control following DAFNE training tends to decline over time.

3. Undertake two RCTs (one pilot) to improve self-management and develop an additional intervention to address glycaemic outcomes.
4. Utilise user involvement to develop more effective interventions.
5. Measure the cost-effectiveness of interventions over the short and long term.

Reports from the workstreams designed to address these objectives are presented in *Chapters 2–8*. Linkages between workstreams are indicated in the text.

Chapter 2 Research database

Abstract

The DAFNE project provides structured education for adults with type 1 diabetes. As one workstream within a National Institute for Health Research (NIHR) programme grant, we have set up a research database to study detailed outcomes from the DAFNE project with a view to assessing and understanding the effects of diabetes structured education and ultimately improving the intervention. In addition, one of the aims of the workstream was to assess whether or not it is possible to run an extensive database of this type in parallel with clinical practice with modest funding. The research database also supports data collection for other trials within the programme grant.

We describe the development and management structure of the research database. Data are collected at baseline and annually thereafter on demographics, biomedical and health-related outcomes, standard psychosocial and QoL outcomes and self-management, using a novel self-management questionnaire (SMQ). Since December 2008 we have enrolled 2002 patients, representing 82% of those eligible. Follow-up data collection rates at 12, 24 and 36 months are 76%, 64% and 48% respectively. Information held on the database has been the subject of 25 requests for downloads to date, most of these projects being currently in analysis.

We conclude that it is feasible to run a database of this extent and quality in parallel with clinical practice to evaluate outcomes from an intervention such as the DAFNE project. However, to do this effectively appears to require additional administrator support for the collection of follow-up data and/or a move towards electronic data capture and input.

Introduction

Historical background

A few pioneers have had the insight to recognise the potential of structured educational initiatives for people with type 1 diabetes to promote self-management by providing effective tools for insulin dose adjustment. Such educational programmes have been running in Germany (called the Insulin Treatment and Training Programme, ITTP) for many years[6,8] but were initially ignored in many other countries, including the UK. However, in the late 1990s a small group of British diabetologists were awarded funding by the British Diabetic Association to translate the ITTP (with the assistance of German colleagues) and modify it and evaluate its use in the UK in a feasibility RCT, which was known as the DAFNE project. The DAFNE programme was initially trialled in three centres and resulted in a significant improvement in diabetic control without an increased risk of hypoglycaemia and also greater treatment satisfaction and less impact of diabetes on QoL.[7] Following the success of the initial trial, the DAFNE programme was extended to seven further 'roll-out' centres with funding from the Department of Health's expert patient programme, commencing in 2002. It is currently provided in 71 centres in the UK and is also active in Ireland, Australia, New Zealand, Kuwait and Singapore.

A centralised DAFNE database was first established in 2002 to audit the effects of the DAFNE roll-out programme in centres beyond those taking part in the original trial. This resource contains pseudoanonymised baseline data, and annual biomedical and psychosocial data; these have generally confirmed the beneficial outcomes of the wider application of DAFNE education in the UK 2005 cohort.[14] However, as clinical data acquisition is labour intensive, there was inevitably a progressive decline in the rate of recurrent annual data collection with time. In addition, although the original data set was selected primarily to monitor the overall effectiveness of the DAFNE intervention, it was recognised that, on the one

hand, it was too complex and repetitive for routine audit use and yet, on the other hand, it was too limited in scope to be useful for addressing novel questions. Despite the success of the DAFNE programme, important questions remained unanswered. For example, it is not known why some people who undertake the DAFNE course gain substantial benefits whereas others find it difficult to sustain the approach and/or glycaemic control remains unchanged or even worsens. The DAFNE NIHR Research Group decided that analysis of a more comprehensive database of clinical observations could be of value in addressing these and other research questions (RQs) about diabetes education, or at least in generating testable hypotheses for future intervention studies. In addition, the DAFNE research arm required a database that could support data acquisition in prospective clinical trials. The DAFNE Executive and Research Groups therefore proposed a two-tier database, with collection of a comprehensive data set in certain selected centres and a simplified, routine audit database in the remainder.

Development of the DAFNE research database

The research database is an integral part of the NIHR Programme Grants for Applied Research for further investigation into the benefits and outcomes of DAFNE diabetes structured education. The rationale for the development of separate but linked research and clinical audit databases was described in the original NIHR grant proposal:

> *The current dataset is too complex for routine usage and needs developing to be a research resource.*
>
> *We will construct a two-tier web-based database consisting of i) basic biomedical data (HbA_{1c}, weight, severe hypoglycaemia, diabetic ketoacidosis, pregnancy, use of insulin pumps and death). All centres will enter these annually for all patients to allow us to compare outcomes between centres; ii) a more advanced database in 10 of the most active centres. These include the original 3 and an additional 7 which together account for over 75% of current DAFNE graduates (Annex 4) The extended database will:*
>
> - *include psychosocial measures [e.g. SF-36 (Short Form questionnaire-36 items) and DSQoL (Diabetes-Specific Quality of Life Scale)], insulin type, other therapy and adverse events. This will inform the psychosocial research and generate other data such as the effect of different insulins and highlight centres and educators producing better results*
> - *record adverse endpoints, including cardiovascular events, severe hypoglycaemia, ketoacidosis, laser therapy etc to allow economic modelling and identify individuals for further study*
> - *record data from the RCTs described below.*
>
> *This work will evaluate DAFNE as it rolls-out, part of developing a complex educational intervention. We are collaborating with others delivering structured education in Type 1 diabetes and such a database could record outcomes for all individuals in the UK participating in such programmes.*

As stated in the original grant application, the database was intended to underpin the following projects:

(a) development, practicality and utility of a research database
(b) a health economics study incorporating biomedical outcomes, psychosocial measures (QoL) and diabetes-related adverse events
(c) a prospective, psychosocial study of QoL, including in-depth analysis of the factors predicting individual benefit from DAFNE and of the dynamics of group education
(d) a prospective randomised study comparing outcomes from a DAFNE course provided on 1 day per week over 5 weeks with outcomes from the standard course delivered over 5 consecutive days
(e) a pilot study comparing the outcomes from DAFNE education in patients continuing with multiple daily injections of insulin and patients provided with an insulin pump
(f) development of a small pilot 'repeaters course' designed to provide follow-up education.

As studies (b)–(f) are described elsewhere, this chapter refers largely to project (a).

One aspect of NIHR programmes is to determine whether or not findings may be applicable in other clinical areas. An additional aim was therefore to use the DAFNE research programme to investigate it, in ordinary clinical practice and with modest additional investment, it is possible to set up and maintain a database that can produce output of research quality. This is clearly of potential importance in evaluating other clinical interventions.

For the future, the database could potentially be used as a source of information when planning other research, as it clearly describes a large and typical cohort of people with type 1 diabetes undergoing structured education, and might also be used to help design nested trials.

Methods

Management, funding, organisation and infrastructure

The overall responsibility for the DAFNE database and custodianship of the research database lies with the DAFNE National Programme Director who is accountable to the DAFNE Executive Group. Development and oversight of both the audit and research arms of the DAFNE database are provided by the DAFNE Clinical and Research Database Committee, which reports both to the DAFNE Research Committee and to the DAFNE Executive. The Database Committee is multidisciplinary with representation from diabetologists, diabetes specialist nurses, dieticians, health economists, clinical psychologists, statisticians, administrators, the database host and DAFNE service users and in addition to the research project managers, the database manager and the DAFNE National Programme Director.

The combined audit and research database is jointly funded from two sources. The National DAFNE Programme, which obtains an annual contribution from all DAFNE centres, funds the database hosting and technical support costs for the audit database, along with half of the 1.0 whole-time equivalent (WTE) database manager's salary. Funding from the NIHR programme grant then covers the research database development costs, the other half of the database manager's salary and support costs to the database centres to facilitate local data collection and entry.

The database manager was appointed jointly by the DAFNE National Programme Director and the DAFNE Database Committee Chair. The database manager delegated responsibility for implementing developments and for maintenance of the database. Specifically, these duties include ensuring that data were being entered in a timely fashion at the research database centres, checking for obvious errors and completeness of data entry, cleaning data as required and preparing reports and data dumps for analysis. The database manager was also responsible for arranging secure access to the database by suitably appointed staff at the research database centres.

The 10 research database centres were chosen as being some of the most active DAFNE sites, with an identified local diabetes physician having an interest in research and being both willing and able to act as a local investigator to oversee the project. When the NIHR grant proposal was written, these 10 centres were providing DAFNE courses to > 700 patients per year and it was anticipated that most of these patients would consent to inclusion. The research database centres and investigators are provided in *Appendix 1*. The centres are geographically widespread with representation from both university hospitals and district hospitals. From the NIHR programme grant, each diabetes research centre received funding to employ an administrator (0.05 WTE) to provide additional resources to staff already involved in clinical audit data collection for the DAFNE programme. It was left to each centre to determine how its administrator should work, whether in co-ordination, collection or input of research database data. This depended on local arrangements for data collection, and on the skills and expertise of the appointee at each centre.

At the time of applying for the DAFNE NIHR programme grant, the then current DAFNE clinical audit database was hosted by an independent company, Living Media (Liverpool, UK). In 2008 we were informed that this company could no longer support the DAFNE database and so it was transferred to

Ecommnet Ltd (Newcastle upon Tyne, UK), which provided services for a number of other clinical databases on behalf of Northumbria Healthcare NHS Foundation Trust, the site of the central DAFNE offices. During development of the DAFNE research database it became apparent that it would be preferable for the database to be hosted by an organisation with greater expertise in research. In addition, some difficulties were experienced in redeveloping the database in view of historical in-built structural idiosyncrasies. After a lengthy NHS tendering process, the DAFNE database (for both clinical audit and research) was transferred in 2010 to the School of Health and Related Research (ScHARR) at the University of Sheffield. The database has been improved to provide automated reports on, for example, the current number of patients enrolled and ascertainment at follow-up.

Ethics, confidentiality and safety

The DAFNE research database has approval from the National Research Ethics Service through the Trent Research Ethics Committee. Patients are required to give written informed consent before their data are collected and entered. Patients at research centres who have not given consent and all those at other centres are registered on the clinical audit database. The intention was that all patients undertaking DAFNE courses in the relevant time period should be invited to participate in the research database study.

The data held on the research database is pseudoanonymised, with patients having a unique numeric identifier. Within each centre, the diabetes clinical team can identify its own patients from DAFNE code numbers through the person or persons responsible for database administration. However, these personal details are not held in the central database and so cannot be accessed by other DAFNE sites and they do not appear in any data extracts.

The research database is accessed via a dedicated web-based data capture system. All data are stored in a PostgreSQL database (PostgreSQL Global Development Group) on virtual servers hosted by Corporate Information and Computing Services (CICS) at the University of Sheffield. Industry-standard security measures are employed, including the use of Secure Socket Layer/Transport Layer Security (SSL/TLS) to encrypt data transmissions. Access is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature is used to ensure that users have access only to the data required to complete their tasks. The web server is protected both by a local firewall and by an additional network firewall managed by CICS. Remote administrative access is possible only through connection to the university's Virtual Private Network (VPN), and access to this is controlled using usernames and passwords. The web server is configured to perform automated daily backups of all data and these are retained daily for 7 days, weekly for 5 weeks, monthly for 12 months and yearly indefinitely (unless earlier deletion is required).

Research database content

The data set collected for the research database has three principal components comprising biomedical outcomes, psychosocial questionnaires and an assessment of self-management behaviours. The biomedical data collection form and the SMQ in particular were discussed at length by the multidisciplinary DAFNE Database and Research Groups and underwent several iterations before arriving at the final versions. There is a 'window' of 3 months either side of the due date for the collection of annual follow-up data for the research database.

Biomedical data collection form

The biomedical data collection form, to be completed at baseline, has the following sections and data items:

(a) *Demographics*: date of data collection, year of birth, year of diagnosis of diabetes, DAFNE course date, country of birth, whether or not English is the first language, gender, ethnicity, smoking status, whether diabetes care is provided mainly by the general practitioner (GP) or by a specialist and postcode (minus the final two letters to prevent identification), which can be used as a marker of deprivation.

(b) *Biochemical tests*: HbA_{1c}, creatinine, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol subfractions and estimated glomerular filtration rate (eGFR).
(c) *Clinical*: date of last full diabetes annual review, date of last retinal screening, weight, height and blood pressure.
(d) *Insulin regimen and medications*: current insulin regimen, frequency of injection, insulin types and usual doses, if a patient is being considered for insulin pump therapy, presence of lipohypertophy at insulin injection sites and use of lipid-lowering, antiplatelet or antidepressant medication.
(e) *Health outcomes*: past and current pregnancies, the presence of any pre-existing complications of diabetes, any hospital admissions for diabetes-related problems within the past year with reasons for admission and duration of stay, and numbers of telephone and face-to-face contacts with health-care professionals.
(f) *Blood glucose recording and hypoglycaemia*: number of capillary blood glucose monitoring tests undertaken in the previous 2 weeks and whether or not these are recorded; information on hypoglycaemia, including the occurrence and number of any severe hypoglycaemic episodes within the previous 12 months and, if so, whether these episodes required paramedic assistance and/or attendance at hospital; and whether symptoms of hypoglycaemia typically occur at a blood glucose concentration > 3 mmol/l or < 3 mmol/l, or there is absence of such symptoms.

A very similar biomedical form is completed at annual follow-up visits.

Psychosocial and quality of life questionnaires

Both at baseline and at the annual follow-up, patients are requested to complete a series of questionnaires. These are the Hospital Anxiety and Depression Scale (HADS),[15] the Problem Areas In Diabetes (PAID) scale[16] and the DSQOLS,[17] and the measurement of health status provided by the European Quality of Life-5 Dimensions (EQ-5D)[18] and the Short Form questionnaire-12 items (SF-12).[19]

Self-management questionnaire

The aim of the SMQ was to determine the extent to which DAFNE participants had adopted and implemented the behavioural aspects of self-management demonstrated and rehearsed during structured education. The SMQ was developed using an iterative process. The initial draft was drawn up by a group of nine diabetes educators, social scientists and clinicians. This was reviewed and amended by a group of eight DAFNE educators and piloted with 70 adults with type 1 diabetes who had undertaken a DAFNE course and who were asked to provide feedback, in particular on the relevance of the questions, clarity of the instructions and response formats, and whether or not phrasing was suitably non-judgemental. Further amendments were then made in discussion with the original group of researchers and clinicians to arrive at the final version. The SMQ is completed at annual follow-up appointments only as it contains concepts that may not be familiar to patients before participation in a DAFNE course. The SMQ was designed to study the degree to which patients continue to follow the principles of diabetes self-management enshrined in the DAFNE course, and also to investigate the degree to which learnt behaviours correlate with outcome. The SMQ includes questions on frequency of measurement and recording of self-monitored blood glucose levels, usage of carbohydrate 'counting' of foods eaten and recording, 'reflection' on diabetes management and achieved glycaemia using a diary, and adjustment of insulin doses to correct for preprandial blood glucose concentrations that are outside recommended target levels.

Data collection

Currently, all of the above information is collected on paper forms and questionnaires at individual research database centres. The acquired data are then entered locally into a web-based centralised database (the DAFNE research database). Centres undertake regular audits of the completeness and accuracy of data entry and have an annual monitoring visit from the DAFNE NIHR research manager and the database manager. The database also has inbuilt checks on data entry with limits on many fields

(range of absurdities). Error messages are flagged if the limits are breached. As a check of the accuracy of data entry, individual research centres were required to repeat data entry in a 10% sample, followed by independent verification by the project manager or database manager.

One of the hypotheses being tested with the research database was whether or not it is possible to run a database of this size and complexity in ordinary clinical practice. We did not specify the process by which data collection should take place at individual centres as it was felt to be important that each centre should decide how this could best be integrated with their existing clinic and administrative arrangements. DAFNE centres provide pre-course visits shortly before the week-long DAFNE education course and so consent and baseline data were often obtained on these occasions. The methods of collection of follow-up data were rather more variable. Many centres obtained follow-up questionnaire data by post. The demographic and biomedical data collection form was variably completed from hospital records, by telephone or face-to-face, in some centres in specific DAFNE follow-up clinics. Many centres adopted a combination of approaches.

To share ideas and good practice on data collection, a Research Database Administrators Subgroup was set up; this group met occasionally, including at the annual DAFNE collaborative meeting.

Inevitably, a considerable range of methods was used and there were differences in the completeness of follow-up data acquisition and entry between centres. This led to a best practice review, run by the database manager. This was planned to obtain an understanding of the processes used by individual research centres when recruiting and collecting/entering data, and also to identify if certain processes were associated with improved results during recruitment, data collection and entry, and data validation. An initial questionnaire was sent to all 10 research database centres to ascertain an outline of the processes of data collection. We also identified the three most and three least successful centres in terms of how well they were managing recruitment, and data collection and entry, and in particular the percentage of due follow-up data obtained. Once these six centres had been identified, additional information was sought, along with clarification of some of the previous questions. In particular, we sought to understand how the different processes of data acquisition took place at the various centres, including recruitment and consent, baseline and follow-up data collection, data entry and data verification. In particular, we identified whether or not educators, administrators or clinicians undertook the various tasks and who provided leadership for the project.

Use of the database for projects

Application for the use of data from the DAFNE research database is available not only to members of the DAFNE Research Group but also to the wider DAFNE collaborative and indeed other health professionals not involved in the DAFNE programme who wish to undertake specific audit or research projects.

A series of potential database studies with lead investigators and other contributors was devised and agreed at an open meeting of the DAFNE Research and Database Groups in 2009. Future studies outside this list require peer review to ensure that their aims are valid and novel, that the project is feasible and that there is minimal overlap between the proposed study and other projects already under way.

A process has been drawn up to consider requests for data from the research database. Lead investigators are required to complete two forms made available by the DAFNE NIHR Project Office. The first incorporates a series of questions including the rationale for the request, where researchers will have access to the data, where the data will be stored and arrangements for security, how the findings of the project will be disseminated and the timescale for analysis and publication. There is an extended version of this form for novel projects requiring peer review and a shortened version for previously agreed projects. The second form asks for specific details about the data set required for the project.

Applications are reviewed by the Database Committee Chair, with peer review organised as necessary, and are approved on behalf of the DAFNE Research Group. The Database Group and database manager are then available for ongoing practical assistance and advice. Except when individual database centres request to use only their own data for audit purposes, the applicant is required to sign an agreement, prepared by the custodian, outlining the terms for permission to use the data. In a standard agreement, the applicant must agree:

- to provide written interim reports (at least one within the first 6 months) appropriate to the planned duration of the analysis
- that a member of the DAFNE Database Group act as a guarantor for the use of the data and be a co-author on any subsequent publication
- that, if satisfactory progress on data analysis has not taken place within the planned time frame, rights to usage of the data and publication will be withdrawn and the data will revert back to the DAFNE Database Group
- to the data not being used for any other purpose than that in the agreement without further reference to and written agreement from the DAFNE Research Group and custodian
- not to transfer the data or share the data with anyone other than those stipulated in the agreement without the prior authorisation and written agreement of the DAFNE Research Group and custodian.

Once the written agreement has been signed, the database manager will prepare an anonymised data extract (i.e. DAFNE centre and patient number omitted) from the database. The researchers will keep the data for the period of the study and thereafter for the period specified by their institution to comply with research governance regulations and/or publication requirements.

For all usage of the data from the research database, we require that interim reports are submitted at regular intervals, appropriate to the planned duration of the analysis, to the Database Group. It is anticipated that final results will be distributed within the public domain through dissemination at meetings and publication in peer-reviewed journals. Results will also be reported to the NIHR as appropriate.

Research database project applicants are also required to provide a brief 'lay' summary of their proposed study at the time of requesting the data. This information is uploaded onto the DAFNE website along with the results of investigations as these follow.

Database projects

The research database is intended as a resource for exploratory studies. A meeting of the DAFNE Database and Research Groups in Nottingham in January 2009 was made open to the wider DAFNE collaborative to discuss ideas about how the information contained in the database could most profitably be used to explore areas of education and management in people with type 1 diabetes. Various outline projects and workstreams emerged and project leaders were identified. The projects fell naturally into three groups: A – those that were self-contained within the data contained in the database; B – those that would require some additional information; and C – those that would require considerably more external data and/or collaboration. The projects identified as being of potential interest are described in the following sections.

Group A

- Psychosocial questionnaire scores and outcomes after DAFNE education.
- Rates of hypoglycaemia and ketoacidosis before and after DAFNE education.
- Do the outcomes after DAFNE education vary depending on the type of basal insulin used?
- Does ethnicity affect outcomes after DAFNE education?
- Do outcomes after DAFNE education differ between centres?
- Evaluation of the SMQ.
- Insulin pump usage after DAFNE education.
- Are outcomes after DAFNE education affected by duration of disease?

Group B

- Assessment of patients who do not attend for follow-up after DAFNE education.
- Pregnancy outcomes.
- International comparisons of outcomes after structured education.

Group C

- Effect of changes in diet and outcomes after DAFNE education.
- Does diabetes knowledge influence outcomes?
- What are patient expectations of DAFNE education and do these correlate with outcomes?

Since that time, additional projects have been initiated that use information contained on the database.

Results

Recruitment

The first patients were recruited onto the research database study in December 2008. Recruitment numbers from then until the end of March 2013 are shown in *Table 1*. The total number of patients recruited with data entered is 2002. The numerical contributions from the 10 different database centres range from 83 to 351, with 82% of eligible subjects consenting overall (range between centres 65–99%). Five centres achieved recruitment rates of ≥ 90%.

The numbers of patients with follow-up data collected at 12, 24 and 36 months are shown in *Tables 2–4* respectively. The overall 1-year follow-up collection rate for the biomedical data is 76% (range 52–91%). Five centres achieved a 1-year follow-up data collection rate of > 80%. At 24 months the follow-up rate was 64% (range 35–88%) and at 36 months the follow-up rate was 48% (range 14–96%) (see *Chapter 9* for updated details of ascertainment).

TABLE 1 Number of DAFNE courses run, number of subjects attending, number and percentage consenting to the research database study and number with any data collected at baseline by research database centre, December 2008–March 2013

Centre	No. of courses	No. of subjects	No. consented	% consented	No. with data collected
A	46	332	217	65	208
B	20	119	87	73	83
C	43	268	181	68	181
D	31	212	190	90	190
E	55	380	351	92	351
F	37	239	182	76	181
G	24	152	116	76	116
H	32	205	204	99	204
I	34	235	213	91	210
J	46	307	278	91	278
Total	368	2449	2019	82	2002

TABLE 2 Number of subjects with 12-month post-DAFNE data collection due, and number and percentage with any data actually collected and entered by research database centre, up to the end of March 2013

Centre	No. with data due	No. with data collected	% with data collected
A	183	95	52
B	73	60	82
C	150	101	67
D	156	141	90
E	261	190	73
F	118	107	91
G	87	68	78
H	139	121	87
I	161	105	65
J	207	173	84
Total	1535	1161	76

TABLE 3 Number of subjects with 24-month post-DAFNE data collection due, and number and percentage with any data actually collected and entered by research database centre, up to the end of March 2013

Centre	No. with data due	No. with data collected	% with data collected
A	138	48	35
B	48	23	48
C	90	62	69
D	104	92	88
E	185	96	52
F	60	50	83
G	55	39	71
H	90	77	86
I	99	49	49
J	128	100	78
Total	997	636	64

TABLE 4 Number of subjects with 36-month post-DAFNE data collection due, and number and percentage with any data actually collected and entered by research database centre, up to the end of March 2013

Centre	No. with data due	No. with data collected	% with data collected
A	95	13	14
B	22	8	36
C	28	17	61
D	50	48	96
E	116	27	23
F	23	16	70
G	37	20	54
H	43	33	77
I	47	22	47
J	63	45	71
Total	524	249	48

There is not a clear correlation between the rate of baseline data collection at recruitment and the rates of follow-up data collection at different centres. The figures given in *Tables 2–4* for the rates of data collection are for any data entry. In some cases, particularly at follow-up, data collection is incomplete. For subjects for whom biomedical follow-up data are present, in approximately one-fifth of cases psychosocial and SMQ data are missing.

Verification of data entry

All 10 centres have re-entered some data for verification. For baseline data entry, five centres re-entered data from more than the required 10% of forms and five re-entered data from less than 10% of forms. Centres undertook re-entry and verification of follow-up data. Following data re-entry, across all centres, 74% of the original forms were judged to have been entered completely accurately, with 19% having between one and five field inaccuracies and 7% having more than five errors. For reference, the biomedical form has up to 168 data fields and the DSQOLS up to 80 fields. There was inevitably some variation between centres but, for eight centres undertaking this exercise, $< 8.5\%$ of the data forms had more than five field discrepancies in the database. A large proportion of the data discrepancies on the biomedical form in particular were not of clinical significance, for example minor differences in how dates of tests or events had been entered.

Best practice survey

The best practice survey identified that centres had more difficulty with follow-up data collection and verification than with baseline data collection and verification. However, there was no clear relationship between the processes of data collection, and the success of data acquisition and entry in that there did not appear to be one single method or combination of methods associated with better results. However, it was clear that centres with a single dedicated and interested person with adequate time and resources to organise data collection tended to have better results. In addition, some centres did not have an identifiable second person to undertake the required verification of 10% of the data entered. The provisional recommendations of the best practice survey were that consideration should be given to having a dedicated central administrator to contact patients and collect data by telephone and that there could be a roving administrator who could carry out data entry or validation at all centres.

Data requests with outcomes

By March 2013, all group A projects had taken place, one of the B projects, international comparisons, had proceeded and the more complex category C projects would be considered further in the future. There had been 25 requests for data for projects relating to the DAFNE research database. These represented 18 different projects, which are described in brief below, together with request numbers and references for any published articles or abstracts:

1. A comparison of clinical and demographic factors in those consenting to the DAFNE psychosocial study and those declining participation (data request DR002).
2. Long-term cost-effectiveness modelling of DAFNE education (DR003, DR005, DR013, DR017, DR024) and analysis of changes in utility over time in DAFNE graduates (DR016). These requests were for data to support development of the health economics model for type 1 diabetes and the DAFNE intervention, which are described more fully in *Chapter 8*.[20]
3. Psychometric validation of the DSQOLS in English (DR004). Data from the DAFNE database were used to demonstrate the validity of the English-language version of the DSQOLS.[21]
4. Development of a SMQ (DR006) and development and validation of the DAFNE SMQ (DR009). Data were downloaded to assess the results of the patient SMQ. The results were used to evaluate the degree to which self-management behaviours were maintained 12 months after DAFNE education and whether such behaviours are associated with greater improvements in glycaemic control or in QoL.[22]
5. DAFNE psychosocial study – DSQOLS (DR007) (see *Chapter 3*).
6. A research database for structured diabetes education (DAFNE) (DR008). Data were required to demonstrate the use of the DAFNE research database at the 2011 Diabetes UK Professional Conference.[23]
7. Evaluation of the DAFNE pump pilot study (DR010). The database was used to collect and store data for a pilot project evaluating the possibility of a larger-scale trial of insulin pump therapy in conjunction with DAFNE education.
8. DAFNE 5 × 1 day (a RCT of DAFNE training delivered for 5 continuous days over 1 week vs. DAFNE training delivered for 1 day per week for 5 continuous weeks) baseline data (DR011) and improving management of type 1 diabetes in the UK: the DAFNE programme as a research test-bed – 5 × 1-day RCT (DR019). The database was used to collect and store data for a RCT comparing the outcomes from DAFNE education provided on 5 consecutive days over 1 week compared with the outcomes from DAFNE education provided for 1 day per week for 5 weeks (see *Chapter 4*).
9. Duration of diabetes and outcomes after DAFNE education (DR012). This project showed that outcomes after DAFNE education are broadly independent of the duration of diabetes, such that structured education can be beneficial even to those with long-standing diabetes.[24]
10. Comparative exploration of patient behaviours and outcomes following structured education programmes for people with type 1 diabetes in Ireland, the UK and Germany (DR014, DR025). Data extracts were required to support the ongoing project evaluating outcomes from diabetes education programmes in three separate countries. Glycaemic control after structured education may be better in Germany than in the UK or Ireland and this project is planned to investigate detailed outcomes with psychosocial input to investigate reasons for differences.
11. The effectiveness of DAFNE education in the management of type 1 diabetes in ethnic minority groups (DR015). This project was designed to investigate the uptake of and outcomes after DAFNE education in different ethnic minority groups.[25]
12. Types and frequency of injection of basal insulin related to outcomes in diabetes structured education (DR018). This project was designed to investigate whether or not outcomes after DAFNE education vary depending on the types and frequency of injection of basal insulin used by individual patients.
13. Improvements in hypoglycaemia following DAFNE training (DR020). This study compared rates of severe hypoglycaemic episodes and admissions with ketoacidosis in the 12 months before and the 12 months after DAFNE education, finding a considerable reduction in events and health service costs after DAFNE education.[26]

14. Which patients switch to insulin pump therapy after DAFNE education and what are the benefits? (DR021). Many studies of outcomes in patients transferring to insulin pump therapy are difficult to interpret as either there are no control subjects or control subjects have had less educational input than cases. Some patients transfer from multiple dose insulin injections to insulin pump therapy within a year of undertaking DAFNE education. This allows an investigation of outcomes in those using insulin pumps and those on conventional injection therapy among a large group of patients, all of whom have recently received structured diabetes education.[27]
15. The impact of DAFNE structured education on the requirement for CSII as determined by UK (NICE) guidance (DR022). According to NICE criteria, patients may be considered for insulin pump therapy if they have recurrent severe hypoglycaemia or they do not attain adequate diabetic control on conventional insulin therapy. This project was devised to determine any reduction in the proportion of patients who might meet the criteria for insulin pump therapy after DAFNE education.[28]
16. An analysis of the variability of outcomes after DAFNE education according to the providing centre to determine if there are differences in outcomes and if there are messages relevant to improvement and standardisation (DR023).

Discussion

We have set up and run a database to evaluate outcomes after DAFNE education in accord with one of the workstreams of the original NIHR grant. The value of the research database is threefold. First, it provides a resource of data for research studies prescribed in the NIHR programme, in particular the psychosocial and health economics studies. Second, the database has been used to assimilate and store data from the randomised trials incorporated within the NIHR grant, including the DAFNE 5 × 1-day trial and the insulin pump pilot study (see *Chapters 4* and *5*). Third, the information held within the database is increasingly being used for novel, self-contained projects, as described earlier.

It took approximately 18 months from the start of the NIHR grant period until the first patients were enrolled into the database. Considerable time was spent, first, in agreeing the broad content of the data set and, then, in refining the details of the demographic and biomedical and the SMQs, which are specific to this project. There was a further delay in preparing and submitting the Integrated Research Application System application. We were also working with the constraint that the new database had to be modified from the already existing DAFNE database, which had some idiosyncratic features that made development difficult. Finally, we were twice required to change database hosts, which inevitably introduced delays and required considerable development work. However, the database is now hosted by an academic institution that functions in effect more as a collaborator than as a contractor, which is a more satisfactory arrangement.

The database project is clearly of interest to patients, as the consent and recruitment rate at baseline was 82% of all those eligible. The recruitment rate is therefore much as predicted, that is, a high proportion of the nearly 700 patients attending for DAFNE education at the 10 research centres combined were recruited. The 1-, 2- and 3-year follow-up rates are rather less but are still substantial, with 76%, 64% and 48% of initially consenting patients, respectively, providing biomedical data and the majority of these also providing psychosocial data. It is difficult to find a similar study to compare follow-up rates. Ascertainment rates are of course usually higher than this in more generously funded clinical trials. Outside such a setting, we cannot identify any other multicentre diabetes database projects that collect such an extensive data set assessing outcomes in response to an intervention, as opposed to being purely epidemiological surveys. A German quality circle assessed outcomes after structured education in 59 centres with high follow-up rates,[29] but this was with a limited biomedical data set and follow-up was for 1 year only, and we

understand that, presently, this quality assurance programme is currently much diminished (U Müller, University of Jena, Germany, September 2012, personal communication). Longer-term follow-up rates after diabetes structured education in certain studies can be > 90%, but generally this is only in single-centre studies and with a restricted data set.[30,31] The comprehensive Epidemiology of Diabetes Complications (EDC) study has high long-term follow-up rates, but this is an epidemiological study in a restricted geographical area.[32]

The projects that were originally proposed to investigate outcomes of DAFNE education using the research database were grouped into those that were independent and did not require additional information (group A), those that required limited additional information (group B) and those that required considerable data outside those stored on the database and/or collaboration (group C). All of the stand-alone projects in group A are under way, at least to the extent that there is an identified lead, a firm plan and data have been downloaded, and some projects have progressed to report on data analysis. Only one of three projects in group B (international comparison of outcomes) and none of those in group C has progressed beyond the stage of an initial idea. This reinforces the perhaps self-evident concept that self-contained projects are more likely to be successful. This emphasises the planning that is required for a database of this complexity. In a diabetes database, some data items will always be included (e.g. HbA_{1c}), but many items are discretionary. Ideally, in any future such project, RQs and the necessary data set required to answer those questions should be agreed before the details of data collection and the content of the database are finalised. The great majority of the database projects have produced some output and potentially useful information. In view of the delay in developing the database and the length of time required for data accumulation, most of the output is currently in abstract form, with full publications pending.

The research database study has significant positive aspects. The project has produced very comprehensive information about the outcomes of DAFNE education, which is being used to evaluate and potentially refine the structured education programme. There are close interactions between the database and other aspects of the NIHR research programme, including the health economics and psychosocial studies and also the clinical trials. The data are derived from a large number of patients in several widespread centres in the UK and so they should have broad applicability. Although difficult to quantify, the project has benefited from the more academic partnership with the current database hosts and from having a database manager.

There are certain problems with the research database as it currently operates. It is generally underfunded and runs on a great deal of goodwill. In particular, the time allowance (about 4 hours per week) for administrators for data collection and data entry at individual centres, although seemingly appropriate at set-up, has become inadequate because of the increasing numbers of recruits and the recurrent annual follow-up. This is potentially the primary reason for the fall in follow-up ascertainment rates with time, consistent with the observation of widely differing follow-up rates between centres. In future, the administrator time required at each centre could potentially be reduced by greater use of electronic rather than paper forms for data collection and/or by scanning and automatic reading of completed paper questionnaires.

One question we began with was to investigate if, in ordinary clinical practice and with modest additional investment, it is possible to set up and maintain a database that can produce output of research quality. We feel that the answer is a qualified yes. Clearly, data collection can be achieved, but this has relied heavily on goodwill and could probably be better achieved and with higher follow-up rates with additional funding for administrator time and/or by using more refined methods of data collection and entry. It is too early to say whether or not the data collected are, in their own right, of research quality, as opposed to being suitable only for supporting other projects, although ongoing funding is clearly an issue in maximising ascertainment and entry of data.

For the future, there is an effective infrastructure in place for the maintenance and further development of a DAFNE research database. Eight of the original centres are continuing with collection of a reduced data set consisting of the biomedical data form and the EQ-5D only, with the dual purpose of maintaining the infrastructure and providing longer-term follow-up data for the health economics study. There then remains the possibility of rebuilding on the existing infrastructure, perhaps including new centres, to develop a further version of the research database. This could be used for long-term biomedical follow-up of existing patients and to answer new questions. These could include the utility of different psychosocial instruments, a revised self-management assessment tool, using the information contained within patients' own DAFNE diaries to assess individual behaviours and responses to meals and exercise to try and improve glycaemia management and supporting other trials based on DAFNE.

Chapter 3 Qualitative and quantitative evaluation of the DAFNE intervention: the psychosocial study

Abstract

Evaluations of diabetes structured education consistently report improved HbA_{1c}, well-being and diabetes-specific QoL. However, it is unclear which elements are critical to achieving and sustaining these outcomes. This study aimed to identify factors influencing changes in glycaemic control and QoL following DAFNE training, to improve future courses, including providing professional support and perhaps matching participants to different programmes.

A combination of qualitative (interview and observation) and quantitative (questionnaire) methods was employed in 262 adults with type 1 diabetes, new to DAFNE training, with assessments at baseline and regularly over 1 year. The quantitative model developed for this study, based on social learning theory, explained 14–20% of the variance in HbA_{1c} and 28–62% of the variance in QoL at 1 year.

The selected demographic and psychosocial characteristics showed minimal explanatory power for glycaemic control but good explanatory power for QoL. Qualitative data suggest that assessing numeracy, critical for insulin dose adjustment, would help to determine additional training needs and support needed before and following courses. Quantitative and qualitative analyses showed that DAFNE courses imparted knowledge and skills but were less effective at helping participants to habituate key self-management practices such as regular diary/record keeping. There is merit in revising course curricula to facilitate the complex and ongoing behaviour change necessary for effective self-management. Technological innovations to aid carbohydrate counting, insulin dose adjustment, diary/record keeping and pattern recognition plus addressing individual behaviour change domains (knowledge, motivation and goal setting) offer potential for development.

Introduction

Few adults with type 1 diabetes in the UK maintain tight glucose control. The result is a high risk of complications resulting in morbidity, mortality and a substantial financial drain on the NHS. The DAFNE programme was introduced in the UK in response to the difficulties that people with type 1 diabetes experience in undertaking and sustaining effective self-management. Based on the ITTP developed in Düsseldorf in the late 1970s, DAFNE draws on theories of empowerment, and uses goal-setting and problem-based learning to promote self-efficacy and self-care.[33,34]

The 5-day DAFNE course promotes FIIT, separating basal insulin from prandial, rapid-acting insulin, plus a flexible and varied diet with no forbidden foods. Participants are taught to count carbohydrates (expressed as 10-g CPs) and to calculate quick-acting mealtime insulin dose requirements as ratios to the number of CPs consumed.[35,36] Patients are advised to undertake regular reviews of self-monitoring of blood glucose (SMBG) readings (normally taken pre meal and pre bed) and are instructed how to interpret patterns and/or changes in readings to calculate and adjust mealtime ratios and basal insulin dose requirements to meet or maintain pre-prandial and bedtime targets. Patients also learn how to use corrective insulin or additional CPs to help maintain blood glucose readings within target ranges (5.5–7.5 mmol/l before breakfast, 4.5–7.5 mmol/l before other meals, 6.5–8.0 mmol/l before bed in the DAFNE programme).[37,38] Patients attend in groups of six to eight and courses are facilitated by a diabetes specialist nurse and dietitian. Patients are given the opportunity to attend a group booster session 6 weeks post course, with some DAFNE centres also offering group-based follow-ups at 6 and/or 12 months. NICE guidance[39] states that 'people with diabetes and/or their carers receive a structured educational programme that fulfils the

nationally agreed criteria from the time of diagnosis, with annual review and access to ongoing education'. The need for ongoing support after educational programmes is recognised[40] but, currently, DAFNE and other structured education courses offer unstructured support that varies widely across the country.

The original DAFNE trial,[7] which was funded by Diabetes UK and undertaken in 2000–1, demonstrated improved QoL up to 12 months (despite patients being required to perform more injections and SMBG tests) and reductions in HbA_{1c} of 0.7% at 6 months and 0.5% at 12 months. Follow-up of the trial cohort found that glycaemic control was only partially maintained but that the marked improvement in diabetes-specific QoL was fully maintained for up to 4 years.[12] The ability to demonstrate external validity of interventions such as DAFNE education is critical to their adoption into routine care. However, the published data from evaluated roll-outs and observational studies of DAFNE education suggest that initial improvements in glycaemic control are not sustained.[14]

Despite the success of the original trial, other important questions remain unanswered. For example, many patients cannot sustain the FIIT regimen taught on DAFNE courses and, for others, HbA_{1c} readings remain unchanged or worsen after their course (20% of DAFNE graduates have $HbA_{1c} > 9\%$).[12] Furthermore, the importance of QoL in sustaining the intensive self-care behaviours required to manage diabetes has only recently been acknowledged.[41] Hence, the reasons for improvements in QoL outcomes following diabetes structured education are unclear as these interventions are generally not spcifically designed to improve QoL. Relatively few studies have identified determinants of either glycaemic control or QoL in adults with type 1 diabetes as most research in this area has focused on childhood and adolescence or on type 2 diabetes.[42,43] To our knowledge, only one study to date has examined determinants of glycaemic control after diabetes structured education.[42]

Although the outcomes of diabetes structured education programmes are relatively consistent across studies,[6,7,38,44,45] it remains unclear which elements of these programmes are critical to success or whether specific patient characteristics or experiences predict those with optimal and suboptimal outcomes. If it is possible to determine subgroups who are more likely to benefit from, or struggle with, DAFNE training, it may also be possible to develop an adapted course and/or to tailor follow-up support to ensure that more people derive and sustain benefits in outcomes. Furthermore, although delivering diabetes education to groups has been shown to be more effective than didatic approaches,[46] the reasons for this remain unclear. As others have observed, structured education programmes are complex interventions; hence, it is difficult to determine what exactly their 'active' and 'vital' ingredients are.[7,47,48] It is important to develop an understanding of how such interventions work to offer opportunities for refining and improving them in relation to key outcomes[7,48] and to ensure that the most appropriate measures are being used for their evaluation.

Aims and objectives (as stated in the grant application)

Linked qualitative and quantitative approaches were developed to address the following aims and objectives:

Aims

(a) To identify which aspects of the DAFNE intervention do and do not promote improved biomedical and psychosocial outcomes (including HbA_{1c} and QoL).
(b) To establish why some patients benefit more from the DAFNE programme than others in terms of biomedical and psychosocial outcomes (including HbA_{1c} and QoL).
(c) To identify the factors that determine why improvements in glycaemic control following DAFNE attendance tend to decline in the long term and whether or not this relates to psychosocial outcomes such as QoL.

Objectives

1. To inform development of future programmes, including follow-up.
2. To identify and/or develop appropriate measures for the evaluation of future programmes.
3. To devise ways of matching patients to appropriate education programmes on the basis of initial psychological assessments.

Research questions

At the outset of the NIHR programme, a series of RQs was developed to address the study aims and objectives. These questions were devised following regular meetings between members of the psychosocial team and consultations with the steering group, coinvestigators, collaborators and other clinicians involved in the DAFNE programme.

- RQ1: What were patients' pre-course circumstances and motivations for attending the DAFNE programme?
- RQ2: How do DAFNE courses work and why? What are the active and vital ingredients of DAFNE courses? What do patients like/dislike about the courses?
- RQ3: Are the improvements in glycaemic control and diabetes-specific QoL reported in research evaluations of DAFNE also found when the intervention is delivered as part of routine UK health care?
- RQ4: What are the determinants of glycaemic control following participation in diabetes structured education?
- RQ5: What are the determinants of QoL following participation in diabetes structured education?
- RQ6: What are patients' experiences of self-management post course and over time, and what barriers and facilitators do patients encounter?
- RQ7: How could patients be better supported to sustain course learning/a FIIT approach over time?

Methods

Ethical approval for this study was obtained from King's College Hospital Research Ethics Committee (ref.: 08/H0808/53). Relevant local approvals were obtained from the 12 individual trusts participating in the study.

The methodology developed for this aspect of the NIHR programme consisted of two linked components:

1. a quantitative study comprising questionnaires delivered to approximately 250 patients pre course and 3, 6 and 12 months post course
2. a qualitative study comprising observation of six DAFNE courses, interviews with DAFNE educators ($n = 12$) and in-depth interviews with patients ($n = 30$) conducted after completing the observed courses and 6 and 12 months later.

The time points for follow-up (6 and 12 months) in the two study arms were selected to allow qualitative and quantitative findings to be mutually informing and illuminating. Two research fellows – one quantitative (DC) and one qualitative (DR) – were employed to undertake data collection and be involved in data analysis.

Recruitment, data collection and data analysis were successfully executed in both arms of the study as detailed below – and in line with the original study protocol. In the protocol we had originally allowed 12 months for the recruitment of 250 participants into the study. A total of 200 is the minimum sample size recommendation for the type of statistical modelling planned and it was anticipated that 250 would need to be recruited to take into account attrition by 12 months' follow-up. Delays in obtaining research

and development approval meant that initial recruitment was slower than expected. The recruitment period was extended to 15 months to ensure that sufficient numbers were recruited. It was not possible to halt recruitment as soon as 250 participants had been recruited as recruitment took place at 12 sites from a number of different courses and consent was not obtained until a written, signed consent form had been returned by post. Hence, of the 494 people that were approached by the centre to participate, the total sample recruited was 269; however, it was discovered subsequently that seven people had not attended the DAFNE course and so they were not included (*Figure 1*). This gave a 54% response rate. Anonymised basic demographic and clinical data were available, allowing a comparison between those who had declined participation in the study or whom we had been unable to contact about participating ($n = 254$) and those who were consented and recruited ($n = 262$). There were no differences between the two groups regarding duration of diabetes [$t = -0.44$, degrees of freedom (df) = 511, $p = 0.66$] or gender

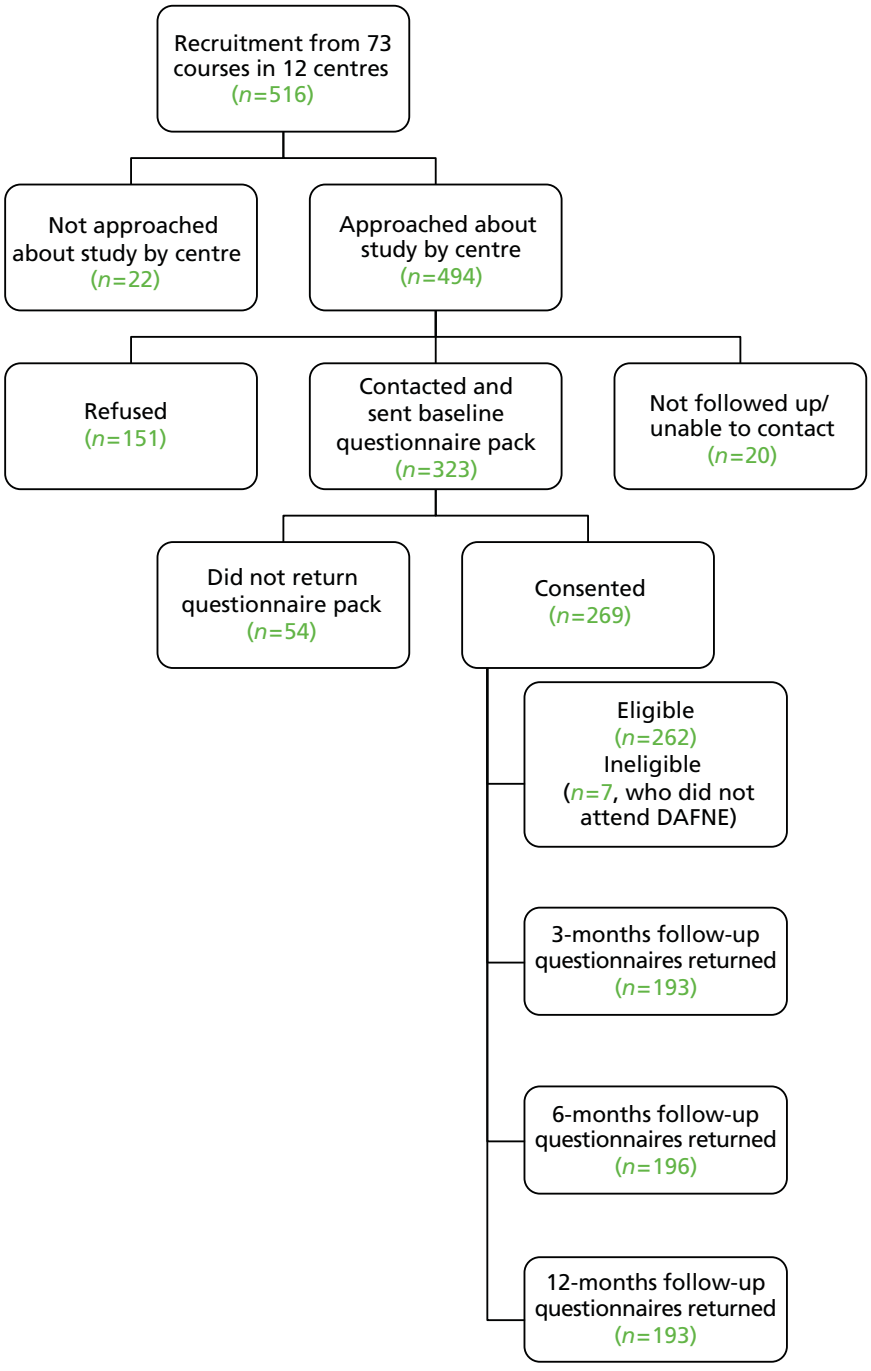

FIGURE 1 Flow chart documenting recruitment and study follow-up rates.

($\chi^2 = 0.13$, df = 1, $p = 0.72$). The group including those who declined participation in the study or whom we had been unable to contact had a significantly higher baseline HbA_{1c} level [mean 8.8%, standard deviation (SD) 1.6%, or 73 mmol/mol] than the group consented into the study (mean 8.5%, SD 1.5%, or 69 mmol/mol; $t = 2.32$, df = 501, $p = 0.02$).

Quantitative component

Research design and methods

Recruitment to the questionnaire study took place from July 2008 to October 2009 using an opt-in method (*Figure 2*). Prospective participants who had agreed to take part in a DAFNE course and who had not previously attended structured education were invited to participate by their educators. If they agreed to be approached, the research fellow (DC) contacted them to explain the study and take consent. Participants were recruited from 73 courses at 12 hospitals. Sites were selected to ensure a fair representation of well-established centres where DAFNE courses had been offered for some time ($n = 8$) and centres where DAFNE courses had been introduced more recently ($n = 4$). The following eligibility criteria, identical to those used for entry to the DAFNE programme, were used:

- type 1 diabetes for at least 6 months (and/or post 'honeymoon', i.e. still producing endogenous insulin)
- ≥ 18 years
- $HbA_{1c} < 12\%$ (at discretion of referring educator)
- motivated to improve diabetes control
- need for flexibility of eating/insulin regimen
- willing to inject insulin and check blood glucose levels at least five times per day
- able to speak/understand/read English
- absence of 'end-stage' diabetes complications, that is, renal failure
- able to attend a full 5-day course and a follow-up session 6 weeks later.

The clinical and demographic characteristics of the study participants are presented in *Table 5*. The mean age of participants was 40 years and the average diabetes duration on entry to the study was 18 years. The mean HbA_{1c} level at baseline was 8.5%. Participants were in relatively high status occupations with 47% of the sample in professional occupations. The follow-up rates for questionnaire completion at each time point remained stable at 74–5%.

Measures

Demographic and clinical variables

Glycated haemoglobin data were collected from routine patient records up to 8 weeks before commencing structured education and at 6 and 12 months post course. Demographic data such as age, gender, socioeconomic status and diabetes duration were collected by patient self-report.

Psychosocial measures

Questionnaire data were collected up to 2 weeks before enrolment on the DAFNE course and at 3, 6 and 12 months after completion of the course. At the point of recruitment, participants were also asked to state their reasons for attending the DAFNE course and these were documented. The follow-up periods were selected as they were most likely to coincide with points at which HbA_{1c} data were routinely collected at outpatient clinic appointments. In addition, the 3-month follow-up was included because we reasoned that this would allow sufficient time after the booster session (at 6 weeks) to see improvements in the psychosocial variables assessed. In an attempt to boost recruitment rates and reduce attrition at follow-up, participants were given the option of completing the questionnaires electronically (via e-mail) or

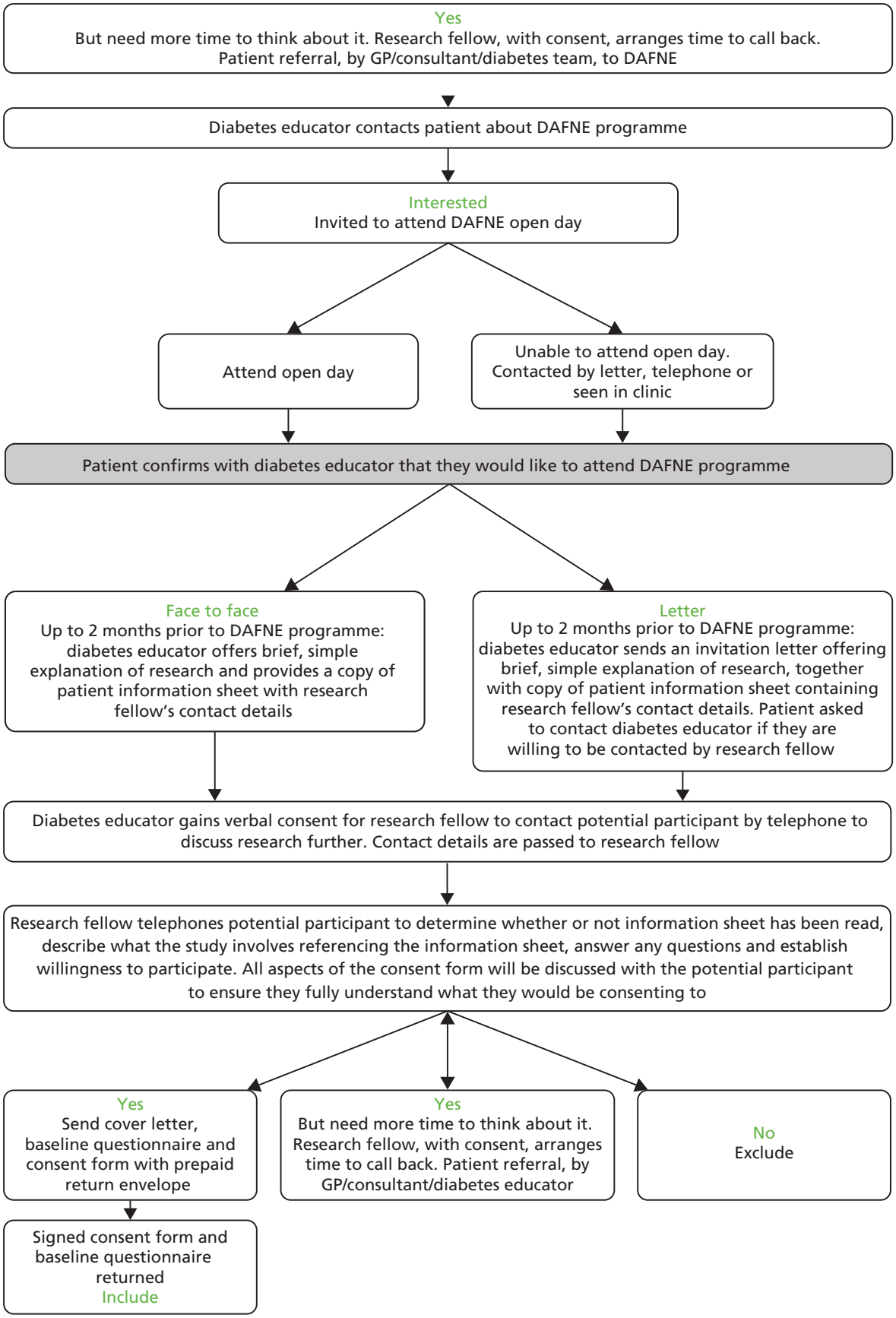

FIGURE 2 The DAFNE study consent flow chart. Note: The process for consent into the study did not begin until the patient had confirmed with the diabetes educator that he or she wanted to attend the DAFNE programme (shaded box). All of the boxes above the shaded box outline what happens in terms of normal service delivery for the DAFNE programme.

TABLE 5 Clinical and demographic characteristics of study participants

Characteristic	Value
Age (years), mean (SD), range	39.9 (13.9), 17–73
Gender female, *n* (%)	131 (50)
Diabetes duration at baseline (years), mean (SD), range	18.4 (13.1), 6 months–55 years
Occupation (at baseline), *n* (%)	
Professional (health, education, etc.)	124 (47)
Semi-skilled	72 (27)
Unskilled	32 (12)
Student	24 (9)
Unemployed	9 (3)
HbA_{1c} (%); IFCC HbA_{1c} (mmol/mol), mean (SD), range	
Baseline	8.5 (1.5), 5.4–14.2; 70 (16), 36–132
6 months	8.1 (1.4), 5.5–15.2; 65 (15), 37–143
12 months	8.3 (1.5), 5.7–16.0; 67 (17), 39–151
Questionnaire completion, *n* (%)	
Baseline	262 (100)
3 months	193 (74)
6 months	196 (75)
12 months	193 (74)

IFCC, International Federation of Clinical Chemistry and Laboratory Medicine (harmonising HbA_{1c} testing).

in paper format (by post). A meta-analysis has demonstrated the equivalence of paper compared with electronic administration of patient-reported outcome measures (PROMs).[49] The questionnaire comprised a number of standardised scales:

- Personal Models of Diabetes (PMD[50,51]): 10 items comprising two subscales: perceived treatment effectiveness and perceived seriousness of diabetes. Each item is scored on a 5-point Likert scale with higher scores indicating greater beliefs. The reliability coefficients for the two scales are acceptable for 5-item scales (perceived seriousness of diabetes $\alpha = 0.6$; perceived treatment effectiveness $\alpha = 0.7$). This measure has been used to predict self-management behaviours, supporting its validity.[52,53]
- The Self-Care Inventory – Revised (SCI-R):[54] 15 items measuring perceived adherence to diabetes self-care recommendations. Higher scores indicate greater levels of self-care. Internal consistency is high ($\alpha = 0.9$) and responsiveness has been demonstrated, with improvements in scores following a psychoeducational intervention.[54]
- The Confidence in Diabetes Self-Care (CIDS) scale:[55] 20 items designed to assess diabetes-specific self-efficacy in adults with type 1 diabetes. Higher scores indicate greater levels of self-efficacy. The scale has high internal consistency ($\alpha = 0.9$; 33) and has demonstrated responsiveness following cognitive–behavioural therapy.[56]
- The 6-item Social Support Questionnaire (SSQ6):[57] an abbreviated version of the original 27-item questionnaire providing a measure of the number of supportive relationships available and an indication of the level of satisfaction with that support, with higher scores indicating greater levels of satisfaction with social support. It has high internal consistency ($\alpha = 0.90$–0.93) and retest reliability.[58]

- The World Health Organization (WHO)-5 Well-Being Index:[59] a 5-item questionnaire measuring general emotional well-being using positively worded items. The WHO-5 has been shown to be a valid instrument for detecting depressive symptoms in people with diabetes.[60,61] It has good internal consistency ($\alpha = 0.70–0.85$). Higher scores indicate greater well-being.
- Hypoglycaemia Fear Survey Worry subscale (HFS-W):[62] a 13-item subscale assessing anxieties related to hypoglycaemia, with higher scores indicating more worry. The HFS-W has been shown to have acceptable-to-good internal consistency and reliability ($\alpha = 0.60–0.84$) in a review of seven studies.[63] The scale has also demonstrated responsiveness with reduced scores following interventions designed to minimise frequency and fear of hypoglycaemia.[64]
- The DSQOLS was designed specifically to evaluate the Düsseldorf ITTP, on which the DAFNE programme is based.[17] Work to validate the scale in English (UK) was undertaken using the current data set and data from two other DAFNE studies[65,23] and is reported elsewhere.[21] The DSQOLS includes 57 diabetes-specific items, which form six subscales: social aspects, fear of hypoglycaemia, dietary restrictions, physical complaints, anxiety about the future and daily hassles. The subscales have excellent internal consistency ($\alpha = 0.74–0.94$). Higher scores correspond to better outcomes in each area. Notwithstanding the identification of six distinct subscales, these are moderately to strongly positively intercorrelated ($r = 0.50$ to 0.72) and can be combined to form a single scale – total diabetes-specific QoL – with higher scores indicating more optimal QoL.

Data analysis

In terms of developing the model for hypothesis testing, the goal of diabetes structured education is to help people take control of their own condition by improving their knowledge and providing the competencies and skills to make informed choices for self-directed behaviour change, enabling them to integrate self-management into their daily lives and ultimately reduce the risk of complications. The DAFNE course draws on a number of educational theories and models, primarily social learning theory.[9] Our decision about which factors to assess was driven by social learning theory and evidence in the research literature about variables that are associated with diabetes-specific QoL and HbA_{1c} levels.

Data are presented as mean (SD) or number (%). To examine change over time in each of the psychosocial variables examined, estimated means and SDs were calculated from fitting a model with an unconstrained variance–covariance matrix. Likelihood ratio tests of mean differences compared the chi-square value for the model in which the means are constrained to be equal with that in which they are not constrained.

In terms of HbA_{1c}, we analysed change from baseline to 6 months and, separately, change from 6 months to 12 months using piecewise growth models.[66] Piecewise growth models within a latent variable modelling framework have some advantages over simple difference scores in terms of handling missing data, for which we used direct maximum likelihood.[66] In general, there were large changes from baseline to 6 months but little change from 6 months to 12 months, and this non-linear pattern could not be modelled as a single function over the 12-month period but was better described by looking at the two periods separately. The models were specified so that we could also look at predictors of HbA_{1c} at baseline.

We found marked changes in QoL between baseline and the 3-month follow-up but little or no change thereafter. Piecewise growth models were used to model change between baseline and 3 months and then the linear change from 3 months to 12 months. Differences were computed as the score at the later time minus the score at the earlier time. The models were specified so that we could also look at predictors of QoL at baseline.

Qualitative component

Research design and methods

The original research plan was adhered to throughout the study and the proposed sample was achieved in full. As planned, DR undertook non-participant observation of six complete DAFNE courses at five diabetes centres; these centres having been selected to include diversity in terms of location (e.g. rural vs. urban) and educator experience of delivering DAFNE courses. All aspects of these courses (including teaching sessions, breaks and informal interactions) were observed in their entirety to enable DR to construct detailed descriptive field notes accompanied by interpretive comments. These observational field notes were used to inform the topics and areas explored with patients and educators in their post-course interviews and to contextualise and inform interpretation of their responses.

Patients already enrolled onto designated courses and who were taking part in the quantitative arm of the study were provided with recruitment packs by DAFNE educators before their courses commenced and invited to opt in to the qualitative study. In total, 30 adult patients from the six courses observed by DR were recruited, with the last two courses purposively sampled to ensure that people of a different gender and age, and with a different occupation, duration of diabetes and HbA_{1c} readings were represented in the final sample (*Table 6*). Before each interview, DR explained that the qualitative team were not health-care professionals and gave reassurances that all information shared in the interviews would be kept strictly confidential.

TABLE 6 The DAFNE psychosocial qualitative sample: demographic characteristics, domestic arrangements and glycaemic indicators of 30 adult patients recruited to the interview study

Characteristic	Value
Age (years), mean (SD), range	36.1 (11.6), 18–56
Gender female, %	53.3
Diabetes duration at baseline (years), mean (SD), range	16.5 (10.3), 1–45
Occupation (at baseline), %	
Professional (health, education, etc.)	30
Semi-skilled	36.7
Unskilled	20
Student	10
Unemployed	3.3
Domestic arrangements, %	
Living with partner	60
Living with parents/family members	13.3
Living alone (or in a shared house)	26.7
HbA_{1c} (%); IFCC HbA_{1c} (mmol/mol), mean (SD), range	
Baseline	8.8 (1.9), 5.4–12.7; 73 (20), 36–15
12 months	8.2 (2.0), 6.0–14.1; 66 (22), 42–131
Interview participation, *n* (%)	
Baseline	30 (100)
6 months	28 (93.3)
12 months	27 (90)

IFCC, International Federation of Clinical Chemistry and Laboratory Medicine (harmonising glycated haemoglobin testing).

In-depth interviews were conducted with patients in the week immediately after their course (baseline) and again at 6 and 12 months' follow-up. There was minor attrition as one patient withdrew and two others were unable to be contacted over time. Twelve educators (two from each course) were recruited using a similar opt-in procedure. Educators were interviewed once on completion of their course.

Patient interviews were conducted from July 2008 to February 2010. Baseline interviews mainly took place face to face, with follow-up interviews conducted by telephone. Interviews were informed by topic guides, literature reviews, course observations and consultations with collaborators, co-investigators and course educators and were revised in response to ongoing data analysis, in line with the principles of grounded theory research.[67] Patients were asked at baseline about their understandings and experiences of the course attended; changes in knowledge/attitudes about diabetes and its management; perceived future needs; and views on the development of a 5-week version of the DAFNE course (*see Chapter 4*). Topic guides used at follow-up explored patients' application of DAFNE principles over time; any changes to dietary practices; issues and difficulties with sustaining the new regimen; and need for further support. Follow-up topic guides were also tailored to explore issues raised by patients during earlier rounds of data collection. Educator interviews were also informed by topic guides and were used to explore their views about delivering DAFNE courses; difficulties experienced by patients in sustaining the regimen; and development of a new 5-week curriculum (see *Chapter 4*). All interviews were audio recorded, averaged 60 minutes and were transcribed in full.

Data analysis

The method of constant comparison[67] was used to develop a framework of themes that were used to code and further analyse the data. To do this, DR and JL each performed an independent thematic analysis by reading each patient's three rounds of interviews sequentially and by cross-comparing these to identify continuities, and relationships between and changes in participants' accounts over time. The researchers met at regular intervals to compare interpretations, resolve any differences in understanding and reach an agreement on recurrent and overarching themes. A coding framework was devised and data were coded using a qualitative software programme (QSR-N6; QSR International, Melbourne, Australia). Data sets were then subject to further analyses.

Results

Findings are presented under the RQs developed for the programme. We have also indicated when qualitative and quantitative data were drawn on to address specific questions.

Research question 1: what were patients' pre-course circumstances and motivations for attending the DAFNE programme?

Circumstances

Analysis of patients' baseline qualitative interviews highlighted that, before course attendance, most had a poor and fragmented understanding of their diabetes and how to manage the condition effectively. This typically resulted from patients being diagnosed in childhood or adolescence and not retaining information imparted at that time; patients being restricted to brief appointments in adult clinics and/or lack of staff continuity in these clinics; the receipt of conflicting and contradictory information over time; or patients using out-of-date information that had not been updated by health professionals.[68] Patients also came to their courses with different skills, experiences and approaches to diabetes management in place, because of differences in clinical practice across the UK and the different lengths of time since they had been diagnosed with diabetes. At one extreme there were those, typically diagnosed in childhood or adolescence, who, before their course, continued to manage their diabetes using the practice, taught at diagnosis, of matching their food intake to fixed insulin doses. Others, normally those already on regimens comprising both

quick-acting and background insulin, described how, in light of common-sense understandings of how insulin worked and/or health professional guidance, they would sometimes attempt to alter insulin doses according to portion sizes and/or the type of meal consumed, albeit in a haphazard way.[69] Some also described having previously received instruction from health professionals on carbohydrate counting, but without having generally received complementary training on how to alter quick-acting insulin doses. Very few had been given any instruction on how exactly to determine and make adjustments to background insulin doses or meal-time ratios. Given these backgrounds and pre-course circumstances, all patients reported benefiting from the education and skills management training received on their course, as reported in more detail below.

Agendas

At baseline, when consenting into the quantitative element of the study, patients highlighted a range of agendas for attending a DAFNE course, the most common reason being that it had been recommended by a health-care professional, friend or relative, or because they had read about the programme in Diabetes UK's *Balance* magazine. Participants often gave more than one reason for course attendance. Other common reasons given (in order) were to improve glycaemic control and hypoglycaemia symptoms (38%); increase skills around adjustment of insulin/counting carbohydrates/managing weight and exercise (29%); increase knowledge/education (24%); improve lifestyle, for example dietary freedom (19%); improve self-management skills (10%); decrease worry and the likelihood of developing long-term complications (9%); improve hypoglycaemia symptoms (8%); improve QoL (mood swings, tiredness, depression; 7%); to obtain a pump (6%); to help with recent changes in a treatment regime, for example moving to a basal–bolus regime (6%); or to increase the chances of becoming pregnant (3%). These findings were reinforced by those arising from an analysis of patients' interview accounts. These interviews also highlighted that, whatever patients' primary agenda(s) for attending a DAFNE course were, all hoped and expected course attendance to help them improve their blood glucose control and all welcomed the opportunity that DAFNE presented to eat or adopt a more flexible diet.[70]

Research question 2: how do DAFNE courses work and why? What are the active and vital ingredients of DAFNE courses? What do patients like/dislike about the courses?

To answer this question we undertook an analysis of patients' and educators' post-course interviews as well as drawing on quantitative data. Patients, in their post-course (i.e. baseline) interviews, were uniformly positive about the courses and struggled to suggest ways in which the curriculum could be changed or improved, albeit some indicated that it would have been easier to have attended a course over 1 day per week for a number of weeks because of their employment or personal circumstances. A similar finding is reported in the DAFNE 5 × 1-day RCT (*see Chapter 4*). Because of their knowledge deficits before course attendance (see RQ1), all attendees also praised DAFNE's comprehensive and diverse educational curriculum, and all claimed to have acquired a much better understanding of their diabetes and how to manage it effectively as a result of course attendance.[71] This finding was reflected in the questionnaire arm of the study in which significant improvements were found in diabetes knowledge using the Michigan Diabetes Knowledge Test (Michigan Diabetes Research and Training Center, University of Michigan, Ann Arbor, MI, USA) from pre course (mean 20.1, SD 2.0) to 3 months' follow-up (mean 20.7, SD 1.9; $\chi^2 = 14.4$, df = 1, $p < 0.01$); these improvements were maintained at the 6- and 12-month follow-ups. Possible scores on the Michigan Diabetes Knowledge Test range from 0 to 23. Ceiling effects are apparent on this scale, with high mean scores and low SDs at each study time point. The differences found are unlikely to be clinically significant. The problem with this scale is that it does not provide an accurate assessment of the specific knowledge and skills imparted within the DAFNE curriculum. More sensitive tools to assess individuals' understanding of carbohydrate counting, correction doses and so on are required. Work at King's College Hospital and the Bournemouth Diabetes and Endocrine Centre is under way to develop such a tool.

Although patients and educators suggested that the comprehensive educational curriculum was a vital ingredient of DAFNE, as other studies of structured education programmes have similarly highlighted,[72] they also described a synergistic interaction between the course's curriculum and other aspects of its delivery, most critically the use of a group-based format. As patients and educators suggested, delivering education in a group setting:

(a) promoted patients' sense of enjoyment during their courses and hence their ability to concentrate[71]
(b) enhanced learning by virtue of patients being able to draw on one another's experiences and to use these experiences to illustrate, prove and convince themselves, and others, that course teaching and guidelines were correct[71]
(c) presented opportunities for more apprehensive and anxious patients to observe other course attendees make insulin dose adjustments and see these have a positive impact on blood glucose levels.[71]

Patients also described valuing and gaining confidence from attending daily sessions at which their blood glucose readings were reviewed, and they received input, feedback and reassurance from the course educators and fellow patients. The benefits of having clear guidelines and course 'rules' to follow were also highlighted.[71] In addition, patients suggested that coming together in a group had helped them to overcome feelings of isolation and offered reassurance that they were not alone in their efforts to self-manage their diabetes.[71]

The vital ingredients of the DAFNE course are thus its educational content, its group-based approach and the use of course rules/educator oversight. However, as the above findings suggest, what made these vital ingredients 'active' was the synergistic interaction between them, an observation that, in part, may help to explain why group-based educational approaches tend to be more efficacious than traditional didactic teaching styles (see, for example, Trento *et al.*[73]). However, although the courses were effective at imparting knowledge and DAFNE skills training, they appeared less effective at habituating self-management practices, particularly diary/record keeping. This latter finding is apparent in the quantitative arm of the study, which found that, although there were significant improvements in diabetes-specific self-care behaviours from pre course (mean 59.3, SD 12.7) to 3 months' follow-up (mean 70.2, SD 10.2; $\chi^2 = 129.5$, df = 1, $p < 0.01$), there was a slight but statistically significant deterioration in scores on the diabetes self-care behaviours measure from 3 to 12 months (mean 70.2, SD 10.2 vs. mean 67.5, SD 11.5; $\chi^2 = 13.9$, df = 1, $p < 0.01$). Additional reasons for this slippage in self-care practices over time are considered under RQ6. Possible scores on the SCI-R – the measure of self-care behaviours used in this study – range from 0 to 100. The improvement in scores reported here is higher than that reported in another study, which showed that a mean difference score of 9.7 on the SCI-R was associated with improvements of $\geq 0.5\%$ in HbA_{1c} levels.[54]

Research question 3: are the improvements in glycaemic control and diabetes-specific quality of life reported in research evaluations of DAFNE also found when the intervention is delivered as part of routine UK health care?

Quantitative research methods were employed to address this question. A before-and-after evaluation of the DAFNE intervention was conducted to assess its impact on glycaemic control and diabetes-specific QoL for 1 year after receiving the structured education ($n = 262$).[74] One-quarter ($n = 65$) of the sample had a HbA_{1c} level of $< 7.5\%$ (< 58 mmol/mol), which was regarded as acceptable because further improvement would increase the risk of severe hypoglycaemia. This subgroup was excluded from an analysis of people with suboptimal HbA_{1c}. Linear mixed models were run with direct maximum likelihood to account for missing data. In the whole group ($n = 262$), there was significant improvement in HbA_{1c} from baseline to 6 months (mean 8.5%, SD 1.5% vs. mean 8.2%, SD 1.5%; $p < 0.001$), which was maintained at 12 months (mean 8.3%, SD 1.6%; $p < 0.001$), although there was a slight deterioration from 6 to 12 months ($p < 0.05$).

In the subgroup with a HbA_{1c} level of ≥ 7.5%, there was a clinically and statistically significant improvement in HbA_{1c} from baseline (mean 9.1%, SD 1.6%) to both follow-up points (6 months: mean 8.6%, SD 2.0%, $p < 0.0001$; 12 months: mean 8.8%, SD 2.5%, $p < 0.01$), with a slight deterioration from 6 to 12 months ($p < 0.001$). Each of the diabetes-specific QoL subscales (social aspects, fear of hypoglycaemia, dietary restrictions, physical complaints, anxiety about the future and daily hassles) and the total score showed significant improvements by 3 months, all of which were maintained at 6 and 12 months in the total sample.[74]

The group with suboptimal baseline HbA_{1c} levels showed a, clinically significant, 0.5% reduction in HbA_{1c} level by 6 months, reflecting a small effect size. The initial improvement in QoL at 3 months was equivalent to just under a medium effect size. The maintenance of effects from baseline to 12 months suggests that improvements in HbA_{1c} and QoL were attributable to the DAFNE intervention. The reduction in the magnitude of change compared with the original DAFNE RCT may reflect the higher proportion of participants with baseline HbA_{1c} values closer to target. DAFNE audit data demonstrate significant improvements in the frequency of severe hypoglycaemia and hypoglycaemia awareness. These benefits are only seen by not restricting the DAFNE programme to people with suboptimal HbA_{1c}.

Research question 4: what are the determinants of glycaemic control following participation in diabetes structured education?

Quantitative data were used to address this RQ. As described in *Data analysis*, the DAFNE programme draws on a number of educational theories and models, primarily social learning theory.[9]

There were few predictors of change in HbA_{1c}, either from baseline to 6 months or from 6 months to 12 months, and in the multivariate analysis effects only approached significance. Male gender and greater frequency of SMBG at baseline predicted improvements in HbA_{1c} from the 6-month to the 12-month follow-up period, and stronger beliefs in perceived treatment effectiveness at baseline predicted improvements in HbA_{1c} from baseline to 6 months. The effect for gender was also found in the univariate analyses but those for frequency of SMBG and perceived treatment effectiveness were not. In the multivariate analysis, estimated R^2 values showed that the proportion of variance explained by the model was 20% at baseline, 16% at 6 months and 14% at 12 months.

Thus, the baseline demographic and psychosocial variables assessed had minimal explanatory value in terms of improvements in HbA_{1c} at follow-up. Greater frequency of SMBG did predict improvements in HbA_{1c} and this is consistent with previous research.[3,42] The finding that men were more likely to achieve improvements in HbA_{1c} from 6 months to 12 months fitted with previous findings that being female was associated with poorer glycaemic control 3 years after structured education.[42] At baseline, greater perceived treatment effectiveness predicted HbA_{1c} improvements at 6 months, consistent with other work in this area.[51]

Changes in the psychosocial variables examined were also assessed to determine whether or not they were associated with improvements in HbA_{1c}. Improvement in diabetes-specific QoL was associated with improvement in HbA_{1c} from baseline to 6 months. An increase in the perceived seriousness of diabetes was associated with improvements in HbA_{1c} from baseline to 6 months, but an improvement in HbA_{1c} from 6 to 12 months was associated with perceiving diabetes to be less serious. Increases in perceived treatment effectiveness also predicted reductions in HbA_{1c} from 6 to 12 months. Improvements in diabetes-specific self-efficacy from 6 to 12 months predicted reductions in HbA_{1c} over the same period although this only approached statistical significance. Change in the other psychosocial variables examined was not associated with change in HbA_{1c}.

Research question 5: what are the determinants of quality of life following participation in diabetes structured education?

Quantitative data were used to address this RQ. As described in *Data analysis*, the DAFNE programme draws on a number of educational theories and models, primarily social learning theory.[9]

When we examined what baseline factors predicted improvements in QoL during the initial period from baseline to 3 months, several factors were significant in univariate analyses: male gender, perceiving diabetes as more serious, lower levels of self-efficacy, lower levels of self-care behaviours, more worry about hypoglycaemia and lower levels of well-being. However, only one of these relationships was significant in the multivariate analysis, possibly reflecting the fact that correlation among these variables is such that they do not have an independent effect. Perceiving diabetes as more serious at baseline was associated with greater improvements in QoL from baseline to 3 months. This is assessed using three items from Sarah Hampson's PMD scale,[50,51] which asks participants to rate how serious their diabetes is, how worried they are about developing diabetes complications and the extent to which they have changed daily activities (work, social life, hobbies) because of their diabetes. Consistent with the absence of significant linear change in QoL after 3 months' follow-up, there were few baseline factors predictive of improvements in QoL during the latter part of the study period from 3–12 months. In the univariate analyses, having a higher HbA_{1c} and lower levels of self-care behaviours were significant. However, in the multivariate analyses, no baseline variables were significant. In the multivariate analyses, estimated R^2 values showed that the proportion of variance in QoL explained by the model was 62% at baseline and 28%, 34% and 38% at 3, 6 and 12 months, respectively.

Analyses were also conducted to examine whether or not change in predictor variables was associated with change in QoL. We modelled change in QoL using the piecewise growth model, as before, and then used as predictors the differences in HbA_{1c} and in the psychosocial variables. This model fitted the data well ($\chi^2 = 55.11$, df = 36, $p < 0.001$, confirmatory fit index = 0.978, root mean square error of approximation = 0.045, standardised root mean square residual = 0.027). From baseline to 3 months, as the HbA_{1c} level reduced, QoL improved over the same period. Perceiving diabetes as less serious, improvements in diabetes-specific self-efficacy, reductions in fear of hypoglycaemia and improvements in well-being also predicted improvements in QoL over this initial period. These results were supported in both the univariate and the multivariate analyses. For the period from 3 to 12 months, reductions in fear of hypoglycaemia and improvements in well-being and diabetes knowledge were all predictive of improvements in QoL over the same period, in both the univariate and the multivariate analyses. Only improvements in diabetes knowledge approached statistical significance. Change in the other psychosocial variables examined was not significantly associated with change in diabetes-specific QoL.

Research question 6: what are patients' experiences of self-management post course and over time, and what barriers and facilitators do patients encounter?

Patients' three rounds of qualitative interviews were analysed to answer this RQ, with particular attention paid to continuities and changes in experiences, and self-management practices over time and the reasons for these.

Overview

On course completion, and over time, patients reported feeling motivated and committed to sustaining use of FIIIT. This was because this regimen was seen as providing a more logical, precise and effective approach to diabetes self-management than former treatments, with patients experiencing improved blood glucose readings and/or reporting feeling better. Furthermore, despite the increased demands of SMBG and diary/record keeping, patients described a FIIT approach as more liberating than other treatments, such as those requiring them to consume meals at regular intervals with fixed carbohydrate contents to accompany fixed insulin doses.[75] However, despite the perceived benefits of the FIIT regimen, all patients, to varying degrees, reported difficulties with implementing and sustaining self-management practices, considered in the following sections. These findings were also reflected in the quantitative work (see RQ2).

Habits and routines

Patients who tended to find it most easy to integrate and sustain a FIIT regimen into everyday life were normally those who already led routinised lives, with predictable work hours (e.g. 09.00–17.00) and regular mealtimes. Patients described how such routinised lifestyles helped foster habituation of key self-management practices and behaviours, such as undertaking regular SMBG. Patients who followed, or were able to develop, routines also reported achieving more stable and predictable blood glucose readings than those, for instance, who worked irregular shifts (resulting in unpredictable levels of physical activity and/or irregular meal times) or who experienced major life disruptions/changes during the year of follow-up, for example because of a change in job, pregnancy or having to care for a chronically ill family member.[75] Major life changes not only disrupted patients' routines but also could affect their insulin requirements, necessitating dose adjustments. They also disrupted their motivation for and confidence in carrying out the complex behavioural demands of living with type 1 diabetes. This often meant reviewing background insulin doses or meal-time ratios as these often needed adjusting in response to altered insulin resistance (see *Dose adjustments and health service contact*).

Food and eating practices

Routinisation and behavioural restriction became particularly apparent in patients' accounts of their food and eating practices over time. Despite DAFNE's ethos of promoting dietary freedom, 6- and 12-month interviews revealed that most patients had only made, or sustained, limited changes to their diet and, in some instances, their food choices and meal timings had become more restricted and regimented.[70] For instance, patients described how the requirement to match insulin to food could limit the temptation to snack on sugary foods, as most wished to avoid having to have an extra injection, particularly when they were not at home (see also Casey *et al.*[76]). Patients also highlighted a growing sense of tedium, which arose from having to weigh foodstuffs such as rice, pasta and cereals to calculate the carbohydrate content accurately, and ongoing difficulties estimating the carbohydrate content of food when dining out or when meals were prepared by others. To address these difficulties, patients described preferring or feeling that they had to stick to eating the same kinds of meals on a regular basis, dining out less (or always selecting the same menu items) and/or purchasing more processed and labelled, pre-packaged foods to facilitate accurate carbohydrate determination. Some patients also experienced a changed relationship with food over time in which, increasingly, they fixated on carbohydrates rather than calories and which could lead to inadvertent, unhealthy food choices. In addition, a small minority attempted to eat a low/zero carbohydrate diet because of anxieties about miscalculating the carbohydrate content, injecting too much insulin as a consequence and exposing themselves to risk of hypoglycaemia.[70]

Managing hypoglycaemia and using blood glucose targets

Indeed, despite DAFNE training leading to reductions in the incidence of severe hypoglycaemia,[7,77] and patients receiving comprehensive instruction on how to self-treat hypoglycaemia during their course, many continued to worry about, and to overtreat, hypoglycaemia post course and over time. For instance, patients reported how the physical experiences and sensations of hypoglycaemia – such as confusion, disorientation and an insatiable hunger – could make it difficult to consume treatments such as Lucozade® and sweets in course-recommended fixed quantities. Some also described how, when they felt disoriented and confused, they tended to (albeit unintentionally) revert back to habituated (pre-course) overtreatment practices. Panic reactions from family and friends who were exposed to an episode of hypoglycaemia could also mean that patients were encouraged to overtreat; this finding reflects similar outcomes from the evaluation of Dose Adjustment For Normal Eating Hypoglycaemia Awareness Restoration Training (DAFNE-HART) (see *Chapter 6*), suggesting that future interventions may need to be targeted at significant others as well as at patients.[78]

Alongside physical reasons for overtreatment of hypoglycaemia, patients also highlighted more complex, psychological explanations. Some patients, for instance, recounted earlier, traumatic, pre-course experiences of hypoglycaemia involving seizures and hospital admissions and which had endangered their own lives and sometimes also the lives of others. These experiences were described as having left patients very risk adverse. As a consequence, such patients not only tended to overtreat hypoglycaemia as soon as they experienced early warning signs[78] but many also reported making upwards revisions to course-recommended blood glucose targets over time, particularly pre-bed targets, to avoid (nocturnal) hypoglycaemia.[79]

Indeed, although patients did find use of course-recommended blood glucose targets intrinsically motivational, particularly when they were successfully attained, their 6- and 12-month accounts often revealed slippage in the targets used over time, normally in an upwards directions (see *Chapter 4*) and with a potential detrimental impact on their long-term glycaemic control. As well as elevating targets to mitigate worries about (nocturnal) hypoglycaemia as described above, some patients, typically those who struggled to attain blood glucose readings within target ranges, also upwardly revised them to make them more achievable and sustainable and thereby mitigate feelings of personal failure. Poor recollection of targets, and/or a desire to make them more memorable by simplifying them (e.g. by rounding figures up, or using the same targets throughout the day), were also observed in some patients' 6- and 12-month accounts. Furthermore, as clinical review sessions tended to focus on HbA_{1c} readings rather than diary records of SMBG results (particularly when these were led by non-DAFNE-trained staff), patients' misuse of targets was not always identified and addressed[79,80] during the year of study follow-up. Lack of appropriate clinical follow-up could also impact on patients' insulin dose adjustment practices, as will now be considered.

Dose adjustments and health service contact

Following their courses, most patients described needing to make further adjustments to quick-acting insulin ratios and background insulin doses as they had not yet attained blood glucose levels within the target range. In addition, as already indicated, changes in patients' lives and circumstances (e.g. pregnancy, moving from a manual to a sedentary occupation) could also result in their insulin requirements changing over time. Although post course, and over time, most patients found that it was relatively easy to determine and adjust quick-acting insulin doses (particularly when they were using 1 : 1 ratios or when food choices were simplified), making adjustments to background doses and/or mealtime ratios presented more challenges. After leaving the supervisory arena provided on their courses, only a minority of patients described having the confidence and ability to review blood glucose readings independently, identify patterns/problems and make adjustments to basal insulin doses or mealtime ratios without seeking input from a health professional. These individuals all described themselves as having good numerical skills and an aptitude for problem-solving, which was often reflected in their career paths (typically finance and information technology).[69]

In many cases, patients described lacking the confidence or mathematical ability, or both, to alter basal insulin doses or mealtime ratios without seeking or receiving input from medical staff.[69] Although some contacted their course educators after their courses to seek advice, others reported difficulties with soliciting educator support (e.g. because of telephone calls not being returned) or described being reluctant to initiate contact with health professionals between scheduled appointments because of their worries about staff already being overstretched and not wishing to overburden them.[80] Patients also reported that the opportunity to seek support with interpreting blood glucose readings and determining insulin dose adjustments was limited if routine care and reviews were provided by medical staff (e.g. GPs, nurses and hospital consultants) who were not DAFNE trained. Specifically, such patients described how routine clinical review appointments tended to focus on HbA_{1c} readings, whereas many now felt, in light of their DAFNE training, that they wanted, and needed, a more holistic appraisal that included a review of daily SMBG readings.[80]

Although patients generally continued to undertake regular SMBG, they not only failed to solicit/receive input from health professionals in interpreting readings, but also many struggled, over time, to keep diary records. This could lead patients to fixate on their most recent results and could lead to a failure to spot patterns and trends in blood glucose readings. Patients' poor diary keeping and the difficulties that they confronted when attempting to independently address problems with blood glucose readings meant that many became increasingly reliant on the use of corrective doses over time to try to keep their readings within (self-determined) target ranges.[69]

Some patients who struggled with maths reported how, rather than attempting to change mealtime ratios to address repeated out-of-target readings, they would adopt simpler strategies such as sticking to a 1 : 1 ratio and reducing their insulin dose by 1 unit.[70]

Research question 7: how could patients be better supported to sustain course learning/a flexible intensive insulin therapy approach over time?

Patients' three rounds of interviews and educator interviews were analysed to address this RQ.

Given their difficulties with independently determining and making complex dose adjustments, patients also highlighted a need for ongoing input, support and clinical review from health professionals, specifically from those with DAFNE training. Although patients highlighted some benefits to receiving follow-up in groups – including receiving empathy and emotional support from fellow patients – most indicated a preference, or need, for at least some individualised and tailored support following their course that was responsive to their individual needs and to (changes in) their personal circumstances and lifestyle.[80] Similarly, patients who participated in the DAFNE 5 × 1-day RCT, as well as patients in the Irish DAFNE study,[77] indicated the need for individualised and tailored follow-up support (see *Chapter 4*). Patients also highlighted the need to be able to access this health professional support as soon as problems manifested or if questions and/or concerns about blood glucose readings arose, without having to worry about overburdening staff. To address these needs, some patients suggested that it would be beneficial to have a dedicated emergency or 24-hour helpline/e-mail service delivered by staff with DAFNE training. Several patients also discussed how having a structured appointment system in place following their course might help address concerns about overburdening staff with requests for help. Finally, patients described how the provision of refresher courses delivered by DAFNE-trained health professionals could address several needs, including opportunities to access top-up or new information, and re-education to aid patients' recall and use of information that had not been fully retained since course attendance (e.g. effects of sickness and physical activity on blood glucose control).[80]

Although most patients saw diabetes self-management as their responsibility pre and post course, virtually all sought at least some support from partners, family and friends/colleagues, particularly with hypoglycaemia management. In addition, patients reported an increased use of family support networks after their course, largely because of their own and others' increased enthusiasm for diabetes management.[81] To support patients effectively, members of these networks could also benefit from instruction on course-recommended approaches to managing (mild) hypoglycaemia.[78] Also, given that family/partners are often involved in food preparation, they might also benefit from training in CP counting.

Patients also highlighted how support received from parents was influenced by the age at which they were diagnosed, with those diagnosed during childhood generally receiving much more support from their parents than those diagnosed in adulthood. However, some patients also reported that their parents struggled to provide relevant support because the DAFNE approach ran counter to historic and out-of-date ways in which they had been taught to manage their child's diabetes.[81]

Educators also recognised that patients often wanted one-to-one follow-up support from DAFNE-trained health professionals to be available as and when needed but also described the difficulties that this would incur for their already busy work lives. Aware of constraints on their time, several educators suggested establishing regular DAFNE-specific drop-in clinics that patients could attend without an appointment to seek support and clarification on course-related topics. Others suggested that more regular contact, initiated by educators, possibly using e-mail systems to enable review of blood glucose results, might prompt patients to get in touch and arrange clinic appointments if they were experiencing difficulties or required further support with DAFNE principles.

Conclusion

As the above sections serve to highlight, we have been successful in answering all of the RQs developed for this component of the programme. Indeed, as a consequence of undertaking the linked qualitative and quantitative studies, we now have a much better understanding of how DAFNE courses work and why. In terms of predicting glycaemic control following structured education, individual participant characteristics as measured by the questionnaires used in this study offer little explanatory power.

Regarding prediction of QoL following structured education, our models had good explanatory power. Reductions in HbA_{1c}, perceiving diabetes as less serious, improvements in diabetes-specific self-efficacy, reductions in fear of hypoglycaemia and improvements in well-being predicted improvements in QoL. Improvements in these different factors are implicit at the moment within the DAFNE curriculum. If these were targeted explicitly, we hypothesise that greater effects on both QoL and glycaemic control would be obtained. This reflects evidence emphasising the importance of QoL in sustaining intensive self-care behaviours required to manage diabetes.[41] Outcomes centred on QoL and psychological well-being are still assessed relatively rarely in evaluations of self-management interventions. Few self-management programmes incorporate aspects of emotional management, coping, and the continual adjustment and adaptation required to live well with diabetes. We conclude that an explicit emphasis on these areas is necessary and likely to be beneficial.[82] Our research also identified reasons why patients may struggle to sustain self-management practices after their course and, relatedly, why the original trial and subsequent work have shown glycaemic drift over time.[7,12] We have also identified new and potentially better ways in which patients could be supported to sustain a FIIT approach after their course, which could be trialled/explored in future research programmes, and we have developed better insights into the kinds of variables that would need to be measured to evaluate future programmes most effectively. Finally, study findings also show that, although the effects on glycaemic control do attenuate, it is possible to achieve sustainable improvements in HbA_{1c} and QoL among adults with type 1 diabetes during routine delivery of structured education within the UK health-care system.

The following sections return to the original study objectives in more detail.

Objective 1: to inform the development of future programmes, including follow-up

Our findings lend empirical support to international guidelines and studies[34,83,84] that recommend that continuing support is provided to graduates of diabetes self-management education programmes to help sustain the benefits from their course training and education over time. Our findings also offer insights into what this continuing support should comprise. Despite growing interest in the use of group-based follow-up support to promote self-management of diabetes and other chronic conditions, our results, alongside those of others,[85,86] raise questions and concerns about promoting group-based support in routine clinical practice, particularly if this type of support is offered in isolation from other inputs and interventions. This is because a group-based approach may be incompatible with type 1 diabetes patients' need for individualised input from health professionals post course. In addition, pre-scheduled group-based appointments may not be compatible with patients' need to access health professional input as and when it is required.

Patients in our study indicated a preference and need for individualised and tailored inputs post course, both to accommodate their unique and personal experiences of applying a FIIT regimen in everyday life and to troubleshoot issues of concern, particularly with regard to the interpretation and application of daily SMBG readings. To this end, graduates of DAFNE and similar programmes may benefit from being offered a 'menu' of support options post course and over time, which could be evaluated in a future research study or pilot intervention. Such a menu could incorporate differing degrees of professional input tailored to patients' personal requirements and which are responsive to changes in their lifestyle and personal circumstances. As part of this menu, consideration could be given to patients' suggestion of providing a telephone and/or e-mail-based support service, alongside opportunities to attend educational 'top-ups'

and refresher courses. In addition, patients with poor numeracy skills might benefit from being provided with bolus calculators, particularly those who are not on, or who need to change from, 1 : 1 mealtime ratios. Indeed, bolus calculators are already readily available to those on pump therapy and it has been shown that they can lead to better glycaemic control.[87] Our findings also suggest that some patients who have had previous traumatic experiences of hypoglycaemia might benefit from tailored psychological support to help overcome treatment mismanagement (including consumption of very-low-carbohydrate diets) and habituated practices. Research on the use of psychological interventions to reduce the fear of hypoglycaemia, and hence, potentially, practices of overtreatment, remains in its infancy. However, as others have recommended, further work to develop and evaluate interventions such as those involving cognitive–behavioural therapy[88] or referral to a clinical psychologist or psychiatrist[89] might benefit some people, as could pilot interventions exploring better integration of diabetes and psychological medicine teams.[89] In light of these recommendations, findings from the psychosocial study were used to inform the development of the DAFNE-HART feasibility study, an intervention that incorporates psychological support in the provision of structured education to patients with hypoglycaemia unawareness (see *Chapter 6*).

There may also be benefit in developing and offering a dedicated glycaemia support service to future cohorts of course graduates. An essential feature of such a service would be to enable patients to confer with health professionals who are highly trained and competent in the use of FIIT. This service would need to instil confidence in patients choosing this approach, to share and discuss blood glucose readings and determine if, what and why adjustments to basal bolus insulin doses and mealtime ratios may be required. Although some patients already actively seek out this kind of support, others, such as those who fail to identify problems with blood glucose readings or those who drift into unintended overuse of corrective insulin doses, may not solicit assistance as soon as it is required. Hence, the ideal glycaemia support service should be able to accommodate 'on the spot' enquires, as well as having systems in place to ensure regular follow-up of all patients. Furthermore, to address patient concerns about overburdening staff, it is vital that any such follow-up support be presented as an integral part of the care package and, hence, as something that patients can expect and feel entitled to ask for.

Although DAFNE courses were found to impart knowledge and skills training to patients, they were less effective at helping patients to instil and habituate key self-management practices, such as regular diary/recording keeping, into their everyday lives. We believe that there is a strong case for revising course curricula to facilitate the complex and ongoing behaviour change required to support effective self-management practices. Technological innovations to reduce the complexity of CP counting, insulin dose adjustment, diary/record keeping and pattern recognition combined with the application of individual behaviour change domains (knowledge, motivation and goal setting) offer useful areas for further exploration.

Objective 2: to identify and/or develop appropriate measures for the evaluation of future programmes

At the design stage of the study, the best measures available were selected to assess the factors hypothesised as affecting outcomes (QoL and HbA_{1c}). The need for PROMs has increasingly been recognised, particularly with the recent introduction by the Department of Health of a mandated collection of PROMs for key elective procedures (see www.ic.nhs.uk/proms; accessed August 2014). Ten years ago, Glasgow[90] urged attribution of the same importance to behavioural outcomes in diabetes as is accorded to biological outcomes. This message has been reiterated again in a consensus of outcomes for diabetes education.[91] The importance of evaluating structured education programmes in diabetes has been highlighted in the Department of Health/Diabetes UK Improvement Toolkit for Commissioners and Local Diabetes Communities (see www.diabetes.org.uk/upload/Professionals/NHS_commissioning_toolkit_diabetes_2d.pdf; accessed 18 September 2014) and the NICE guidance for patient education models.[10] At the outset of the study it became apparent that existing questionnaire tools were not always up-to-date or appropriate. For example, existing measures of diabetes self-care behaviour do not accurately capture diabetes self-management because they have not been updated to include key recommendations that now form part of diabetes care, such as dose adjustment and CP counting.[54,92,93] Similarly, questionnaire measures assessing diabetes

knowledge and diabetes-specific self-efficacy have the same limitations. Acknowledging the limitations of existing measures of diabetes self-care behaviours, the research team submitted and obtained a Research for Patient Benefit (RfPB) grant to develop a new questionnaire tool. Development of an updated questionnaire to assess diabetes self-care behaviours would enable precise assessment of the contribution of patients to insulin adjustment and self-care. This would permit evaluation of the effectiveness of existing structured education programmes at producing desired changes in behaviour. Assessment of how well people are able to carry out these behaviours can help people with diabetes and their health-care team to identify areas in which additional input or support may be needed to initiate or maintain changes in behaviour. An early version of this new questionnaire tool was included in our study but we decided not to include it in our modelling work as it had not yet been validated. The RfPB work is now complete. Preliminary analyses of 611 adults with type 1 diabetes who participated in survey and validation work for this study have shown that specific self-care behaviours, as recommended by the DAFNE programme and other similar structured education programmes, explain 23% of the variance in HbA_{1c} after controlling for type of insulin therapy [multidose injection (MDI) or pump] and diabetes duration.

When designing this study, the most relevant diabetes-specific QoL questionnaire identified in the literature had been validated only in the German language. The DSQOLS[17] was designed specifically to evaluate the Düsseldorf ITTP, on which the DAFNE programme is based. Work to validate the scale in English (UK) was undertaken using the current data set and data from two other DAFNE studies, one of which is also part of this programme grant and used the database study.[23,69] The UK English-language validation has been published.[21] The DSQOLS includes 57 diabetes-specific items, which form six subscales: social aspects, fear of hypoglycaemia, dietary restrictions, physical complaints, anxiety about the future and daily hassles. The subscales have excellent internal consistency ($\alpha = 0.74$–0.97). Higher scores correspond to better outcomes in each area. Notwithstanding the identification of six distinct subscales, these are moderately to strongly positively intercorrelated ($r = 0.50$–0.72) and can be combined to form a single scale – total diabetes-specific QoL – in which higher scores indicate better QoL.

The new questionnaire to assess diabetes-specific self-care behaviours is available for use. The findings of the qualitative study will also be critical in determining the nature and content of future evaluations of diabetes structured education. This work could not necessarily have been anticipated at the outset of the study but it served to highlight how powerful and influential contextual factors can be for people's self-management practices and, hence, whether or not they are able to sustain a FIIT approach over time (and also, potentially, whether they are able to achieve and sustain good glycaemic control over time). A key contextual factor in this regard is health service contact, specifically and most crucially whether people receive their clinical reviews from staff with DAFNE training or not. In light of this finding, development of a measure of health service contact post DAFNE course (i.e. when, where and from whom one receives one's diabetes care and clinical reviews) would be recommended. The use of a measure of numerical competency in any future work should also be considered when seeking to explore why some people might do 'better' than others in terms of glycaemic control following their course.

Objective 3: to devise ways of matching patients to appropriate education programmes on the basis of initial psychological assessments

As reported earlier, the model developed and used in this study explained between 14% and 20% of the variance in HbA_{1c} levels at different time points. The proportion of the variance in HbA_{1c} levels explained corresponds almost exactly to that in previous research (16–17%), although the variables hypothesised as affecting glycaemic control differ somewhat.[42,43] The demographic and psychosocial characteristics explored in this study showed minimal explanatory power in terms of glycaemic control, which may reflect the strength of the intervention and that people will derive benefit whatever their background characteristics. However, the results do suggest that screening people before participating in diabetes structured education programmes to select those who are more likely to gain the most in terms of improvements in glycaemic control is unwarranted, particularly if current demographic and psychosocial characteristics are used. Although these characteristics have minimal explanatory power, qualitative findings suggest that it would be helpful to undertake an initial assessment of patients' numerical skills to

determine whether or not they may require additional training and support before or during their course.[94] The possibility of developing an adapted course for such patients, with a heavier mathematical teaching component, might also be considered. This kind of assessment may be especially important in the UK context, given the particularly low levels of numeracy in this country [an estimated 75% of the UK working population had literacy skills below that equivalent to a pass at General Certificate of Secondary Excellence (GCSE)], an issue that, as others have highlighted, is a particular cause for concern.[95]

The demographic and psychosocial characteristics investigated showed minimal explanatory power in terms of glycaemic control and good explanatory power in terms of diabetes-specific QoL. Qualitative data suggest that an assessment of numeracy, critical for insulin dose adjustment and carbohydrate counting, would be helpful to determine whether or not additional training and support are required both before and during structured education. Quantitative and qualitative analyses showed that, although DAFNE courses imparted knowledge and skills training, they were less effective at helping participants to instil and habituate key self-management practices such as regular diary/record keeping into their everyday lives. There is merit in revising course curricula to facilitate the complex and ongoing behaviour change required to support effective self-management practices. Technological innovations to reduce the complexity of CP counting, insulin dose adjustment, diary/record keeping and pattern recognition combined with the application of individual behaviour change domains (knowledge, motivation and goal setting) might also offer useful areas for further exploration.

Chapter 4 A cluster randomised controlled trial comparing a 5-day DAFNE course delivered over 1 week with DAFNE training delivered over 1 day per week for 5 weeks: the DAFNE 5 × 1-day trial

Abstract

Introduction

Dose Adjustment For Normal Eating structured education courses have traditionally been delivered over 5 consecutive days (1 week). In this randomised controlled non-inferiority trial we compared the outcomes of this format with the outcomes of the alternative of DAFNE training for 1 day a week for 5 consecutive weeks (5 weeks).

Methods

Adults with type 1 diabetes were individually randomised, using a random block size and stratified by centre, to receive either a 1-week or a 5-week DAFNE course. A qualitative study was embedded within the trial to help understand and interpret outcomes.

Results

In total, 213 patients were randomised and 160 patients completed the study procedures. The mean change in HbA_{1c} at 12 months was not significant [–0.07%, 95% confidence interval (CI) –0.22% to 0.08%; $p = 0.382$]. For those patients with a baseline HbA_{1c} of ≥ 7.5%, the mean change in HbA_{1c} was –0.20% (95% CI –0.37% to –0.04%) at 6 months ($p = 0.016$) and –0.18% (95% CI –0.37% to 0.004%) at 12 months ($p = 0.055$). Episodes of severe hypoglycaemia were decreased by 82% in the 12 months after DAFNE training compared with the 12 months before training (relative risk 0.18, 95% CI 0.03 to 0.936; $p = 0.042$). The psychosocial outcomes improved significantly by 6 months and were maintained at 12 months. For all outcomes, the difference between the treatment arms was not significant. In particular, for HbA_{1c}, for all subjects and also for those with a baseline HbA_{1c} of ≥ 7.5%, all 95% CIs for the difference between the 1-week course and the 5-week course were within the ±0.5% HbA_{1c} set for non-inferiority. Qualitative interviews revealed that patients were overwhelmingly in favour of the format that they received.

Conclusions

We have demonstrated that the 5-week and 1-week DAFNE courses are equivalent in terms of glycaemic control. However, the change in HbA_{1c} over 6 and 12 months is less than in the original DAFNE RCT. As participants valued both course formats highly, and some find it easier to attend one type rather than the other, we are persuaded to provide both 5-week and 1-week courses in the future.

Introduction

The key importance of structured education for patients with diabetes is now recognised, although access to structured education programmes is not universal.[96] The DAFNE training course was highlighted by NICE in their initial guidance on structured education.[97] It was developed and trialled in three English secondary care centres (Sheffield, Newcastle, and King's College London) and the results of the RCT were published in 2002.[7] It was adapted from a German programme that had reported markedly improved HbA_{1c} levels with increased dietary freedom while reducing the risk of hypoglycaemia.[38]

This was in contrast to the DCCT,[3] which found that the risk of microvascular complications was reduced by improving glycaemic control but at the expense of much higher rates of severe hypoglycaemia. However, an equally important stimulus for adapting the German model of structured education was an increasing realisation that British patients with type 1 diabetes required formal structured training to assist them to self-manage their diabetes.

Following the publication of the positive outcomes of the DAFNE trial, the programme has been successfully rolled out to 76 centres and self-management skills have been taught to > 27,000 patients across the UK, as well as in centres in Ireland, Australia (Oz DAFNE), New Zealand, Kuwait and Singapore. Even in centres not providing DAFNE training, many now provide structured education, albeit of varying duration, content and quality.[98] Quality assurance, both internal and external, is an essential component of the DAFNE programme (and a required element of training in a Department of Health report[11]), but is rarely systematically included in other courses.

Nevertheless, the DAFNE consortium has been criticised for providing training only over 5 days, from Monday to Friday[99] (1-week course). It has been argued that providing courses over 1 day a week over a longer period may improve access for those in full-time work. To our knowledge there is only one RCT in which structured education was delivered for 2.5 days spread over 6 weeks; interestingly, there was no improvement in biomedical outcomes.[99] Observational data from longer courses in single centres have reported comparable outcomes to those of the DAFNE trial[100] but are prone to bias.

The possibility that delivering the course in different ways may result in different outcomes is underpinned theoretically. A 1-week course may provide more intense bonding among participants and the mutual support could conceivably facilitate the incorporation of self-management skills. Alternatively, a 5-week course may enable participants to practise and embed competencies and enable more effective integration of self-management into everyday life.

To address these important issues, and to explore an additional mode of delivery that might enable us to provide skills training to more individuals, we conducted a RCT in which outcomes following 5-day DAFNE training delivered over 1 week were compared with those following a course delivered over 1 day a week for 5 consecutive weeks.

Objectives

The DAFNE 5 × 1-day RCT was designed to meet the following objectives:

1. to compare the effectiveness of DAFNE delivered over 1 week and over 5 weeks in terms of both biomedical outcomes and QoL outcomes
2. to determine the cost-effectiveness of the 1-week compared with the 5-week course (see *Chapter 8*)
3. to understand and interpret any differences and similarities in biomedical and psychological outcomes in participants
4. to ascertain patient preference for one format over the other
5. to provide recommendations for the future delivery of DAFNE courses.

Objectives 3 and 4 were primarily achieved by building a qualitative substudy into the trial. More details of the substudy are provided later (see *Qualitative Study*).

Methods

The protocol of this trial has been previously reported.[101]

This multicentre trial involved seven of the 74 DAFNE centres in the UK. Participants were recruited through DAFNE waiting lists at each centre and in some centres by information evening meetings. Participants were informed of a pair of course dates (a 1-week and a 5-week course) for which they would need to be available. After obtaining written consent, participants were randomised to attend either the 1-week course or the 5-week course.

The inclusion criteria were as follows: adults with type 1 diabetes for at least 6 months, aged 18–80 years, not previously attended a DAFNE course, $HbA_{1c} < 12\%$ (108 mmol/mol), prepared to undertake intensive insulin therapy with multiple SMBG, happy to undertake CP counting and insulin self-adjustment and holding no strong views on attending either a 1-week course or a 5-week course.

The exclusion criteria were as follows: severe diabetic complications (including renal replacement therapy, severely impaired vision), unable to communicate in English, a strong preference for either a 1-week course or a 5-week course (and so would be unlikely to complete the study if randomised to his or her least favoured arm), severely needle phobic, unenthusiastic about undertaking SMBG and insulin self-adjustment or could not give informed consent.

The sample size was calculated on the following basis. The trial was designed to test non-inferiority between the two different formats of course delivery. Based on a non-inferiority margin in HbA_{1c} of 0.5%, a SD of 1.5%, seven to eight participants per course, 80% power at the one-sided 5% significance level and an intracluster correlation coefficient (ICC) of 0.05, it was calculated that 150 participants were required to complete the trial. Assuming a 10% dropout rate, this meant randomising 166 participants. Each centre was originally required to run four courses, that is, two pairs of 1-week and 5-week courses. However, as the trial proceeded the dropout rate was higher than anticipated between randomisation and course attendance and we therefore requested one centre to run an extra pair of courses.

The control arm was the standard DAFNE 1-week course delivered from Monday to Friday. The intervention arm was the 5-week course, delivered over 1 day per week for 5 consecutive weeks. To reduce bias, both formats of the course were delivered by the same two DAFNE educators so that enthusiasm, skill or teaching style did not influence the outcomes. In both arms, as for non-trial DAFNE participants, a participant was deemed to have completed the course if they attended at least 4 full days out of the total of 5. Also, as per normal procedures, if a participant missed a part of the course attempts were made by the educators to try to cover the missed material on an individual basis.

Development of the 5-week curriculum

The content of the 5-week curriculum was identical to that of the standard 1-week DAFNE course in terms of skills training and educational subject matter; however, some minor adaptations were made to take account of the course being delivered over 5 weeks rather than 1 week. To make these adaptations, patients and educators who took part in the earlier psychosocial study of the DAFNE programme (see *Chapter 3*) were asked, during their post-course interviews, how, if at all, they thought the 1-week course curriculum should be adapted for the 5-week variant of the course to maximise learning, effectively use daily review sessions and ensure patient retention.

After these data had been analysed using a thematic approach, the qualitative researchers met with four experienced educators to feed back findings and exchange ideas; the final consensus on adaptations was reached by e-mail. A key adaption was to give those attending a 5-week course their workbook each day that they attended as opposed to receiving their entire workbook on the first day. It was hoped that this would reduce the potential dropout rate over the 5 weeks as some patients in their interviews had speculated that 5-week course participants might drop out of the course after the first few weeks if given

all of the material in one go. In addition, blood glucose diaries were altered to give more space to record physical activity and events in more detail to aid review of a whole week of blood glucose results. Blood glucose readings for the preceding week were reviewed at the beginning of each day as opposed to twice a day on the 1-week course. To minimise potential risks to patients there was no insulin dose adjustment information provided on day 1. Instead, the course was structured so that day 1 incorporated most of the information needed to enable patients to count carbohydrates effectively. Patients were also asked to record food diaries between weeks 1 and 2. This was to enable review of their CP counting skills after day 1 of the course. Dose adjustment review sessions then took place on days 2–5, after patients had received education on insulin dose adjustment principles. Patients were provided with educator contact details so that if need be they were able to contact them between weekly sessions. The revised curriculum was tested in three pilot courses at two different centres and, as a consequence, minor changes were made to two of the sessions before commencement of the RCT.

After baseline data collection, randomisation of participants was performed individually into either a 1-week course or a 5-week course using a random block size, stratified by centre, and a blinded web-based remote randomisation system. The allocation sequence was generated using the computer program RANDLOG (University of Southampton, Southhampton, UK).

Data collection

Data including HbA_{1c} readings, lipid profile, weight, number of severe hypoglycaemic episodes, number of hospital admissions and psychosocial questionnaires were collected at baseline, and 6 and 12 months after completion of the courses. The primary outcome was change in HbA_{1c} level from baseline to 6 and 12 months; it was measured at local laboratories that were DCCT aligned. Secondary outcomes were change in HbA_{1c} or those participants with a baseline $HbA_{1c} \geq 7.5\%$ (this is because some patients choose to undergo DAFNE training to increase dietary freedom or to decrease the number of episodes of hypoglycaemia as opposed to reducing HbA_{1c}), number of episodes of severe hypoglycaemia (defined as needing assistance of a third party to recover), changes in lipid profile/eGFR and differences in psychosocial outcomes (for a full list of psychosocial questionnaires used please refer to the protocol paper[101]). In light of the early findings of the qualitative substudy (see *Qualitative substudy*) an extra questionnaire was developed to assess patients' abilities to sustain DAFNE principles (see *Appendix 2*) at 12 months' follow-up.

Statistical analysis

The primary analysis utilised a linear model of HbA_{1c} at 12 months with baseline HbA_{1c} as a covariate (which improves the power relative to the predicted power), using generalised estimating equations (GEEs) to control for clustering within courses. The ICC was estimated using the method of moments. A negative binomial model was used for the number of severe hypoglycaemic episodes over 12 months, which has more power than a dichotomy of having/not experiencing an episode, again using GEEs to account for clustering. A per-protocol analysis was performed, as appropriate for a non-inferiority study.[102] An intention-to-treat (ITT) analysis was also undertaken, with missing data from dropouts addressed using multiple imputations. The full analysis set for the ITT analysis included all patients for whom baseline data were collected.

A full economic analysis was undertaken, the method of which is detailed in the protocol paper.[101] The results of this analysis are provided in *Chapter 8* of this report.

Qualitative substudy

In view of earlier psychosocial work involving participants on standard 1-week DAFNE courses, described in *Chapter 3*, it was decided to explore 5-week course participants' experiences of and views about their course, and their post-course experiences, so that direct comparisons could be made between 5-week and 1-week course participants' accounts. The inclusion of this qualitative work in the DAFNE 5 × 1-day trial followed the NICE recommendation that RCTs should involve a qualitative evaluation of the intervention.[10] As indicated earlier, this qualitative substudy was developed to address trial objectives 3 and 4.

Study design

(a) Observation of 5-week DAFNE courses to inform issues and areas explored in patients' post-course interviews and identify any unanticipated issues arising from the adaptation of DAFNE training and delivery of courses over 5 weeks.
(b) Post-course interviews with 5-week course participants to explore their experiences of, views about and likes/dislikes with regard to the 5-week course; whether they thought that future DAFNE courses should be offered in a 1-week and/or a 5-week format (and why); any changes made to their diabetes management/self-care practices in light of the course (and why); their hopes, expectations and (any) short- and long-term treatment goals set; and (if relevant) reasons for not completing the course.
(c) Follow-up interviews with 5-week course participants at 6 months to explore whether, and why, they had been able or unable to sustain their skills training in intensive insulin therapy and any issues that they thought would help promote/support them to undertake effective self-management in the future. As the follow-up interviews were undertaken at 6 months, it was possible for these data to be directly compared with the accounts of 1-week course participants who had been involved in the earlier psychosocial study (see *Chapter 3*). This earlier psychosocial research had also highlighted that, by 6 months, sufficient time should have elapsed to establish whether, and for what reasons, patients had been able or unable to put their skills training into practice and sustain the intensive approach to disease self-management taught on the course.
(d) Interviews with the educators who had delivered the 5-week course ($n = 11$) to establish and explore whether or not they had encountered any difficulties delivering the DAFNE course over 5 weeks and their views about whether or not any further adaptions would need to be made to the curriculum before roll-out of the 5-week variant, should roll-out be a recommendation arising from the trial. As these data are not immediately relevant to addressing trial objectives 3 and 4, they are not reported further in this chapter. However, we do note here that all educators reported positive experiences of, and no unanticipated problems arising from, delivering DAFNE training over 5 weeks, and all were supportive of offering future cohorts of patients the opportunity to attend 5-week courses after trial completion.

Data collection

Field notes were written up at the end of each day of course observation by one of the qualitative researchers. Topic guides were used to inform all interviews to ensure that the discussion stayed relevant to the study aims and objectives while allowing participants to raise and discuss issues that they perceived as salient to them. These topic guides were adapted from those used in the qualitative evaluation of standard 1-week DAFNE courses to allow for data comparisons. Baseline interviews with patients were normally undertaken face to face and at a time and location of their choosing (normally in patients' own homes). Follow-up interviews were conducted by telephone unless a patient requested a face-to-face interview. Each interview lasted around an hour and, subject to consent, interviews were audio recorded and transcribed in full to permit in-depth analysis. Recruitment of 5-week course participants continued until data saturation occurred, that is, until no new findings or themes emerged for any new data collected. Purposive sampling was used to ensure diversity in the patient sample in terms of demographic and clinical characteristics. The study was informed by the principles of grounded theory[103] and the method of constant comparison,[67] which involves concurrent data collection and analysis, together with systematic efforts to check and refine developing categories of data. A key aspect of the final analysis involved comparison of 5-week course participants' accounts with those patients who had attended standard DAFNE courses delivered over 1 week. The two qualitative researchers held regular meetings to discuss cases and reach agreement on recurrent themes and findings. NVivo 9 (QSR International, Warrington, UK), a qualitative data-indexing package, was used to facilitate data coding and retrieval.

'Booster' qualitative substudy

Early analysis of 5-week course participants' accounts of their courses revealed a strong and consistent preference for courses to be offered *only* in a 5-week format in the future, with patients often speculating that it would be very difficult to attain the same educational, clinical and behavioural benefits from the use of a 1-week format. As the research team recognised that this strong preference for the 5-week format could have been an artefact of patients taking part in a clinical trial and experiencing what has been termed the 'therapeutic misconception' in trials literature[104] (i.e. patients believing that the course to which they were randomised was the best course), a decision was made to include a booster sample in the qualitative substudy. This sample comprised patients who had attended the 1-week course in the 5 × 1-day trial. These patients were purposively sampled to match the 5-week course participants in terms of demographic and clinical characteristics, and were interviewed once only, on completion of their course. These post-course interviews were scaled-down versions of the interviews undertaken with 5-week course participants and explored patients' experiences of, views about and likes/dislikes with regard to the 1-week course and whether they thought that future DAFNE courses should be offered in a 1-week and/or a 5-week format (and why). Interviews were digitally recorded with consent, transcribed and included in the main analysis to address objective 4. Recruitment of patients to this booster study continued until data saturation had occurred.

Ethical considerations

Written informed consent was obtained from all participants with additional written consent secured for those undertaking the qualitative substudy. Ethical approval for the trial and subsequent amendments for the booster study and extended self-care questionnaire were obtained from the Derbyshire Research Ethics Committee (ref.: 09/H0401/91). The study sponsor was Sheffield Teaching Hospitals NHS Foundation Trust and all components of the trial were approved by the local research and development departments of all participating centres. The trial is registered as ClinicalTrials.gov NCT01069393.

Results

In total, 217 patients were assessed for eligibility and 213 were randomised from May 2010 to May 2011 to either a 1-week course or a 5-week course. Virtually equal numbers of patients in each arm failed to attend their baseline data collection visit and a small number in each arm then failed to attend the course. Thus, 180 patients commenced the course and 168 (93%) completed the intervention, which was in line with the target of 166. Of these, eight were lost to follow-up and therefore 160 completed the study procedures (89%). The flow of participants through the trial is shown in the Consolidated Standards of Reporting Trials diagram[105] in *Figure 3*. All results quoted in the following tables represent per-protocol analyses; ITT analyses have also been performed (data not shown with the exception of HbA_{1c} as there were no significantly different findings between the two types of analysis).

The average age of the whole cohort was 41.6 years and the average duration of diabetes was 18.5 years; the remainder of the baseline summary statistics are summarised in *Table 7*.

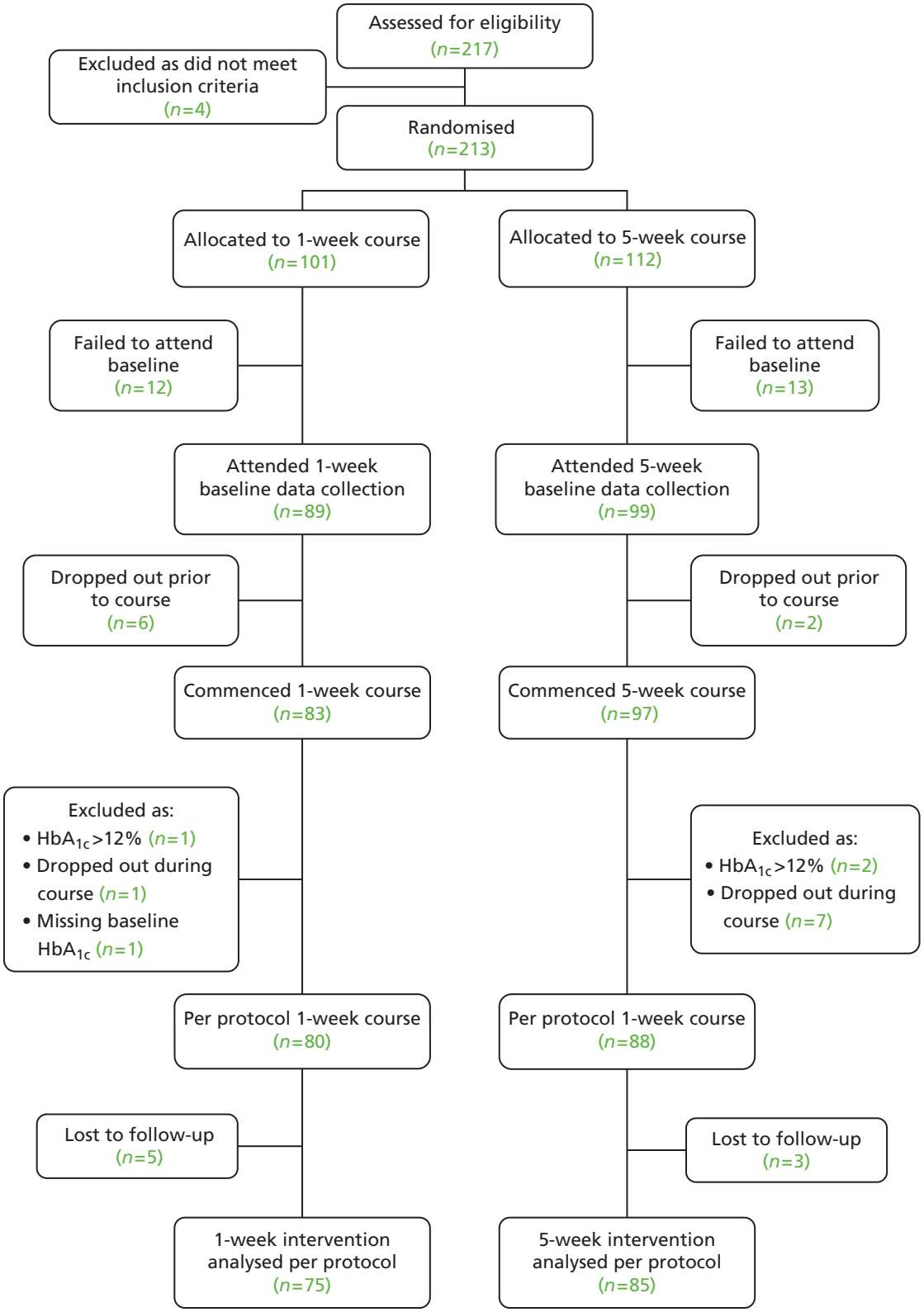

FIGURE 3 Consolidated Standards of Reporting Trials diagram: participant flow through the DAFNE 5 × 1-day RCT.

TABLE 7 Baseline summary statistics of participants

Characteristic	Treatment arm									
	1-week course ($n = 80$)					5-week course ($n = 88$)				
	n	Mean	SD	Min.	Max.	*n*	Mean	SD	Min.	Max.
Age (years)	80	40.7	13.2	19.0	73.0	88	42.4	12.9	19.0	72.0
Age at diagnosis (years)	79	20.1	12.8	2.0	65.0	88	26.1	14.8	2.0	65.0
Duration of diabetes (years)	79	20.9	13.7	0.0	51.0	88	16.3	12.0	0.0	48.0
Weight (kg)	76	78.3	15.7	51.0	135.4	88	78.3	15.3	54.5	127.5
Height (cm)	77	170.2	8.5	152.0	190.5	87	171.6	8.7	152.5	190.0
BMI (kg/m^2)	76	27.0	4.6	19.0	39.0	87	26.5	4.6	19.8	44.7
Systolic blood pressure (mmHg)	76	132.0	18.7	103.0	224.0	86	127.4	18.2	90.0	198.0
Diastolic blood pressure (mmHg)	71	75.3	9.8	55.0	100.0	86	74.0	10.2	44.0	100.0
Total cholesterol (mmol/l)	76	4.6	0.9	2.8	7.7	84	4.3	0.7	2.5	6.5
Triglycerides (mmol/l)	55	1.2	0.6	0.4	3.4	66	1.3	1.0	0.4	5.5
HDL (mmol/l)	65	1.6	0.5	0.6	3.2	80	1.5	0.4	0.8	2.9
Gender, *n* (%)										
Male	41 (51.2)					56 (63.6)				
Female	39 (48.8)					32 (36.4)				
Ethnicity, *n* (%)										
White	77 (96.3)					83 (94.3)				
Other	3 (3.8)					5 (5.7)				
eGFR (ml/minute), *n* (%)										
< 60	5 (6.3)					1 (1.1)				
≥ 60	71 (88.8)					73 (83.0)				
Missing	4 (4.9)					14 (15.9)				

BMI, body mass index, max., maximum; min., minimum.

Outcomes: glycated haemoglobin (primary and secondary)

Across the entire cohort, the improvements in HbA_{1c} were small. For those patients with a baseline HbA_{1c} of ≥ 7.5%, the mean change in HbA_{1c} was –0.20% at 6 months ($p = 0.016$) and –0.18% at 12 months ($p = 0.055$) (*Table 8*).

The mean changes in HbA_{1c} from baseline to 6 and 12 months were not significantly different between the two arms of the trial. Non-inferiority is established if the 95% two-sided CI for the difference between the 5-week course and the 1-week course is entirely above the non-inferiority margin (i.e. entirely above –0.5). For both the per-protocol and the ITT analyses of the primary end point and the secondary outcome of change in HbA_{1c} from baseline to 6 and 12 months for those patients whose baseline HbA_{1c} was ≥ 7.5%, the 95% CIs for the differences between the 5-week course and the 1-week course are entirely above the non-inferiority margin (*Table 9*). The ICC for HbA_{1c} at 12 months was –0.02 (95% CI –0.10 to 0.12).

TABLE 8 Mean change in HbA_{1c} across the entire trial cohort and for patients with a baseline HbA_{1c} of ≥ 7.5%

Group	Follow-up (months)	*n*	Unadjusted mean change (%)	95% CI (%)	*p*-value
Entire cohort	6	166	–0.08	–0.21 to 0.06	0.277
	12	167	–0.07 (from 8.46 to 8.39)	–0.22 to 0.08	0.382
Baseline HbA_{1c} ≥ 7.5%	6	127	–0.20	–0.37 to –0.04	0.016
	12	126	–0.18 (from 8.96 to 8.78)	–0.37 to 0.004	0.055

TABLE 9 Per-protocol and ITT analyses of change in HbA_{1c}

Analysis	Follow-up (months)	1-week course		5-week course		Model summary coefficient[b] (95% CI)
		n	Mean change[a] (95% CI)	*n*	Mean change[a] (95% CI)	
Per protocol						
Whole population	6	70	–0.09 (–0.30 to 0.12)	84	–0.08 (–0.27 to 0.11)	0.03 (–0.22 to 0.28)
	12	72	–0.14 (–0.37 to 0.10)	84	0.00 (–0.22 to 0.22)	–0.08 (–0.36 to 0.20)
Baseline HbA_{1c} ≥ 7.5%	6	59	–0.16 (–0.41 to 0.08)	58	–0.25 (–0.50 to 0.00)	0.04 (–0.24 to 0.31)
	12	61	–0.21 (–0.48 to 0.06)	56	–0.14 (–0.44 to 0.16)	–0.11 (–0.46 to 0.25)
ITT						
Whole population	6	75	–0.09 (–0.20 to 0.11)	91	–0.07 (–0.26 to 0.13)	0.03 (–0.21 to 0.27)
	12	77	–0.16 (–0.38 to 0.06)	90	0.01 (–0.19 to 0.22)	–0.13 (–0.39 to 0.13)
Baseline HbA_{1c} ≥ 7.5%	6	64	–0.15 (–0.38 to 0.070	63	–0.25 (–0.50 to –0.01)	0.06 (–0.19 to 0.32)
	12	66	–0.23 (–0.48 to 0.02)	60	–0.13 (–0.42 to 0.16)	–0.14 (–0.47 to 0.19)

a Unadjusted mean change.
b Difference between treatment groups, adjusted for baseline value and cluster effect. A positive value indicates that the 5-week course has a better outcome.

Secondary outcomes: biomedical

Episodes of severe hypoglycaemia were decreased in the 12 months after DAFNE training compared with the 12 months before training. The estimated relative risk for before training compared with after training is 0.18 (95% CI 0.03 to 0.936; $p = 0.042$). This shows that, regardless of treatment arm, patients have an 82% reduced risk of severe hypoglycaemia after DAFNE training compared with before DAFNE training. The interaction between treatment arm before compared with after DAFNE training is not significant ($p = 0.939$). Therefore, the decrease in risk of severe hypoglycaemia after DAFNE training compared with before DAFNE training is the same in both treatment arms.

There were some small differences in other biomedical outcomes between the two arms. The mean decrease in weight at 12 months was higher in the 5-week arm than in the 1-week arm (–1.61 kg vs. –0.07 kg). This was associated with a bigger decrease in body mass index (BMI) (–0.54 kg/m^2 vs. 0.01 kg/m^2), diastolic blood pressure (–2.72 mmHg vs. 0.46 mmHg) and triglycerides (–0.12 mmol/l vs. 0.30 mmol/l) in the 5-week arm than in the the 1-week arm at 12 months (*Table 10*).

TABLE 10 Per-protocol analysis of change in secondary outcomes

Outcome	Follow-up (months)	1-week course		5-week course		Model summary coefficient[b] (95% CI)
		n	Mean change[a] (95% CI)	*n*	Mean change[a] (95% CI)	
Weight (kg)	6	65	–0.95 (–2.13 to 0.23)	75	–1.20 (–2.19 to –0.20)	0.14 (–1.14 to 1.41)
	12	65	–0.07 (–1.49 to 1.35)	78	–1.61 (–2.79 to –0.44)	1.72 (0.10 to 3.33)
BMI (kg/m^2)	6	65	–0.30 (–0.70 to 0.09)	74	–0.40 (–0.74 to –0.06)	0.15 (–0.31 to 0.61)
	12	65	0.01 (–0.48 to 0.50)	77	–0.54 (–0.95 to –0.14)	0.74 (0.17 to 1.30)
Systolic blood pressure (mmHg)	6	59	–1.32 (–6.61 to 3.97)	70	–0.96 (–4.44 to 2.52)	2.64 (–4.13 to 9.41)
	12	54	–1.33 (–6.74 to 4.08)	72	1.82 (–1.92 to 5.56)	0.05 (–6.46 to 6.57)
Diastolic blood pressure (mmHg)	6	59	–2.41 (–5.14 to 0.32)	70	–2.99 (–6.25 to 0.28)	1.00 (–3.08 to 5.09)
	12	54	0.46 (–2.69 to 3.62)	72	–2.72 (–5.60 to 0.15)	4.91 (0.04 to 9.78)
Total cholesterol (mmol/l)	12	61	0.04 (–0.17 to 0.26)	71	0.15 (0.01 to 0.29)	–0.06 (–0.24 to 0.12)
Triglycerides (mmol/l)	12	43	0.30 (0.00 to 0.65)	54	–0.12 (–0.31 to 0.07)	0.31 (0.03 to 0.59)
HDL (mmol/l)	12	48	–0.01 (–011 to 0.10)	61	0.05 (–0.01 to 0.12)	–0.02 (–0.13 to 0.08)

a Unadjusted mean change.
b Difference between treatment groups, adjusted for baseline value and cluster effect. A positive value indicates that the 5-week course results in a better change.

Secondary outcomes: psychosocial

The psychosocial outcomes were improved following DAFNE structured education. For all psychosocial outcomes, scores improved significantly by 6 months, the improvement was maintained at 12 months and the 5-week intervention was non-inferior to the 1-week intervention. For example, the mean score on the PAID scale (which measures diabetes distress on a scale from 0 to 100, with higher scores indicating greater distress) decreased on average by 9.5 points from baseline to 6 months and by 10.2 points from baseline to 12 months, with no significant difference between the arms (*Table 11*).

Similar improvements in results were achieved and maintained across a range of other scales [HADS, CIDS, DSQOLS (all subscales), HFS-W and EQ-5D, shown in *Tables 12–16* respectively]. There was no difference between treatment arms except for the HFS-W, for which participants in the 5-week arm had lower scores than participants in the 1-week arm at 6 months, with no difference between the two arms at 12 months.

TABLE 11 Per-protocol analysis of change in PAID scores

Outcome	Follow-up (months)	1-week course		5-week course		Model summary coefficient[b] (95% CI)
		n	Mean change[a] (95% CI)	*n*	Mean change[a] (95% CI)	
PAID	6	63	–10.04 (–14.41 to –5.66)	72	–9.11 (–12.11 to –6.11)	–2.21 (–7.27 to 2.86)
	12	62	–8.78 (–13.30 to –4.27)	74	–11.30 (–14.30 to –8.30)	3.18 (–1.31 to 7.66)

a Unadjusted mean change.
b Difference between treatment groups, adjusted for baseline value and cluster effect. A positive value indicates that the 5-week course results in a better change.

TABLE 12 Per-protocol analysis of change in HADS scores

Outcome	Follow-up (months)	1-week course		5-week course		Model summary coefficient[b] (95% CI)
		n	Mean change[a] (95% CI)	*n*	Mean change[a] (95% CI)	
Anxiety	6	63	–0.65 (–1.38 to 0.08)	71	–0.86 (–1.58 to –0.14)	0.08 (–0.96 to 1.12)
	12	62	–1.11 (–1.98 to –0.24)	75	–1.88 (–2.75 to –1.02)	0.71 (–0.44 to 1.85)
Depression	6	63	–0.87 (–1.61 to –0.13)	71	–0.88 (–1.34 to –0.43)	–0.10 (–1.05 to 0.86)
	12	62	–0.93 (–1.66 to –0.20)	74	–1.23 (–1.85 to –0.60)	0.15 (–0.71 to 1.01)

a Unadjusted mean change.
b Difference between treatment groups, adjusted for baseline value and cluster effect. A positive value indicates that the 5-week course results in a better change.

TABLE 13 Per-protocol analysis of change in CIDS scores

Outcome	Follow-up (months)	1-week course		5-week course		Model summary coefficient[b] (95% CI)
		n	Mean change[a] (95% CI)	*n*	Mean change[a] (95% CI)	
CIDS	6	56	7.36 (4.50 to 10.22)	71	5.41 (3.31 to 7.51)	–1.11 (–3.60 to 1.39)
	12	54	5.16 (2.13 to 8.19)	73	5.66 (3.45 to 7.87)	0.88 (–1.98 to 3.75)

a Unadjusted mean change.
b Difference between treatment groups, adjusted for baseline value and cluster effect. A positive value indicates that the 5-week course results in a better change.

TABLE 14 Per-protocol analysis of change in DSQOLS scores

Outcome	Follow-up (months)	1-week course		5-week course		Model summary coefficient[b] (95% CI)
		n	Mean change[a] (95% CI)	*n*	Mean change[a] (95% CI)	
Social aspects	6	63	–5.42 (–9.67 to –1.17)	72	–4.09 (–6.80 to –1.37)	–1.50 (–5.27 to 2.28)
	12	62	–6.02 (–9.55 to –2.49)	75	–5.92 (–8.60 to –3.24)	0.37 (–3.08 to 3.83)
Fear	6	63	–9.72 (–14.63 to –4.80)	72	–9.10 (–13.01 to –5.20)	–1.40 (–5.74 to 2.95)
	12	62	–11.36 (–16.43 to –6.30)	75	–9.83 (–14.22 to –5.45)	–1.03 (–6.36 to 4.31)
Diet	6	62	–18.25 (–23.09 to –12.60)	72	–15.56 (–19.82 to –11.29)	–3.43 (–9.33 to 2.48)
	12	62	–19.04 (–24.66 to –13.42)	75	–18.55 (–23.08 to –14.02)	0.51 (–4.91 to 5.93)
Physical complaints	6	63	–7.47 (–12.04 to –2.89)	72	–6.53 (–9.41 to –3.65)	–1.00 (–5.08 to 3.07)
	12	62	–7.58 (–11.63 to –3.52)	75	–8.85 (–11.88 to –5.81)	1.10 (–1.40 to 3.61)
Anxiety	6	63	–15.99 (–22.14 to –9.85)	72	–12.53 (–17.13 to –7.92)	–4.12 (–11.21 to 2.96)
	12	62	–14.13 (–20.27 to –7.99)	75	–15.99 (–20.36 to –11.62)	2.34 (–4.00 to 8.68)
Hassles	6	63	–14.46 (–20.04 to –8.87)	72	–8.72 (–13.36 to –4.09)	–4.94 (–11.49 to 1.61)
	12	62	–15.87 (–21.97 to –9.77)	75	–12.79 (–17.67 to -7.91)	–1.15 (–7.19 to 4.90)
DSQOLS total	6	63	–10.07 (–14.09 to –6.04)	72	–8.24 (–10.97 to –5.52)	–2.04 (–6.13 to –2.06)
	12	62	–10.75 (–14.44 to –7.06)	75	–10.45 (–13.34 to –7.57)	0.27 (–3.42 to 3.96)
Preference-weighted treatment satisfaction score	6	58	9.43 (5.75 to 13.11)	65	7.57 (4.21 to 10.93)	–1.22 (–4.42 to 1.98)
	12	60	6.26 (2.80 to 9.73)	71	7.49 (4.55 to 10.42)	1.76 (–1.26 to 4.78)

a Unadjusted mean change.
b Difference between treatment groups, adjusted for baseline value and cluster effect. A positive value indicates that the 5-week course results in a better change.

TABLE 15 Per-protocol analysis of change in HFS-W scores[a]

Outcome	Follow-up (months)	1-week course		5-week course		Model summary coefficient[c] (95% CI)
		n	Mean change[b] (95% CI)	*n*	Mean change[b] (95% CI)	
Worry	6	58	–0.80 (–2.35 to 0.75)	73	–3.50 (–5.71 to –1.29)	2.01 (0.59 to 3.43)
	12	56	–2.63 (–4.92 to –0.33)	76	–4.01 (–6.39 to –1.63)	0.33 (–2.21 to 2.86)

a All items scored from 1 (never worry) to 5 (always worry). Minimum possible score = 13, maximum possible score = 65.
b Unadjusted mean change.
c Difference between treatment groups, adjusted for baseline value and cluster effect. A positive value indicates that the 5-week course results in a better change.

TABLE 16 Per-protocol analysis of change in EQ-5D scores

Outcome	Follow-up (months)	1-week course		5-week course		Model summary coefficient[b] (95% CI)
		n	Mean change[a] (95% CI)	*n*	Mean change[a] (95% CI)	
EQ-5D single index	6	61	0.47 (–3.20 to 4.14)	64	4.25 (–0.58 to 9.09)	2.59 (–3.51 to 8.69)
	12	61	–0.91 (–3.84 to 2.02)	69	3.26 (–0.60 to 7.12)	3.66 (–1.09 to 8.41)
State of health	6	62	5.26 (0.85 to 9.97)	71	5.08 (0.82 to 9.35)	0.33 (–4.90 to 5.56)
	12	62	4.40 (0.18 to 8.63)	74	6.20 (2.28 to 10.13)	2.64 (–1.75 to 7.02)

a Unadjusted mean change.
b Difference between treatment groups, adjusted for baseline value and cluster effect. A positive value indicates that the 5-week course results in a better change.

Qualitative substudy

In total, four 5-week courses were observed in their entirety. A total of 30 5-week course participants were recruited into the study from five out of seven participating centres. Details of these participants are provided in *Table 17*. A total of 20 1-week course participants were recruited into the 'booster' qualitative substudy from four centres. Their details are also provided in *Table 17*.

Objective 3: to understand and interpret any differences and similarities in biomedical and psychological outcomes in participants

Careful comparison of 5-week and 1-week course participants' interviews did not reveal any differences in their experiences and self-management practices post course and at 6 months (i.e. there were no differences in the kinds of adjustments patients made to their background insulin doses and mealtime ratios and whether these were done independently or with health professional input; patients' use of corrective doses; patients' approaches to hypoglycaemia management; patients' dietary changes; patients' use of blood glucose targets and the upwards slippage in these targets over time; and patients' expressed need for individualised and tailored input from health professionals and support from significant others, to help foster and maintain effective use of a flexible intensive insulin regimen in the long term). Positive experiences of the course and of converting to a flexible intensive insulin regimen were also reported by both groups of attendees. The only minor difference was that there was some indication, post course and at 6 months, that 5-week participants sometimes reflected on blood glucose readings collected over longer periods of time (although this increased reflection did not lead to patients being more likely to make independent adjustments to their background insulin doses and/or mealtime ratios). This finding was replicated in the results of the 12-month follow-up questionnaire. Of those patients who completed study procedures, 61/75 patients on the 1-week course and 76/85 patients on the 5-week course completed the 'Sustaining DAFNE Principles' questionnaire (developed for this trial – see *Appendix 2*) (86% ascertainment). Results showed that the proportion of participants self-reporting that they had reflected on blood glucose readings from the last 4 days or longer was 54% for the 5-week participants and 26% for the 1-week participants ($p = 0.002$). In both treatment arms the majority of patients were not using the recommended

TABLE 17 Characteristics of study participants (qualitative substudy)

Characteristic	5-week participants ($n = 30$)	1-week participants ($n = 20$)
Age (years), mean (range)	39 (21–72)	38.6 (21–61)
Gender male, *n* (%)	16 (53.3)	11 (55)
IFCC HbA_{1c} (mmol/l); HbA_{1c} (%), mean (SD), range	68 (16), 37–108; 8.4 (1.5), 5.5–12.0	73 (16), 43–108; 8.8 (1.5), 6.1–12.0

IFCC, International Federation of Clinical Chemistry and Laboratory Medicine (harmonising HbA_{1c} testing).

pre-meal and pre-bed blood glucose DAFNE targets but instead had revised them, usually in an upwards direction and to make them consistent across the day.

In summary, the data suggested that, in general, the experiences, self-management practices and need for health professional and other input to sustain use of a flexible intensive insulin regimen were the same for both patients who had attended the 1-week course and patients who had attended the 5-week course.

Objective 4: to ascertain patient preference for one format over the other

To address objective 4 we drew on the post-course accounts of patients who had attended a 1-week or a 5-week course as part of the 5 × 1-day trial. When asked whether they had had a preference for a 1-week or a 5-week course before randomisation, half of the sample (irrespective of their trial arm) claimed to have had no preference. Indeed, some patients suggested that, because they thought the course content would be the same in both trial arms, the format in which it was delivered would be incidental to their learning experience. When patients did convey a preference before randomisation they cited practical reasons and considerations, such as difficulties getting time off work to attend a 1-week course or wishing to attend a course spread over 5 weeks as this would make it easier to fulfil parenting and other caring responsibilities.[106]

After having completed their course all patients conveyed strong, and often well-articulated, views about why they now thought one type of course was preferable to the other and, hence, why that particular format should be used in the future. Furthermore, in virtually all cases, the course that patients reported now preferring was the one that they had just attended. In addition, whereas patients cited practical reasons to justify their preferences before randomisation, post course all patients made recourse to educational, clinical and behavioural benefits. As outlined below, the reasons given by the 5-week course participants for their post-course preferences were often diametrically opposed to those presented by 1-week participants.[106]

In terms of *educational* benefits, 5-week course participants talked about how their course's extended format had enhanced their learning by allowing them sufficient time between course dates to absorb and review course materials. In contrast, 1-week course participants talked about how their course's intensive focus promoted better learning – for 5 consecutive days they were constantly focused on the DAFNE curriculum. These patients also speculated that, had they been randomised to a 5-week course, they would have struggled to remember information between course dates.

In terms of *clinical* benefits, patients on the 5-week course talked very positively about how having a week between course dates had presented better opportunities to experiment with insulin dose adjustments; they also suggested that their course's extended format had meant that they had a larger body of clinical data to receive feedback on in their review sessions with course educators. In contrast, 1-week course participants talked about valuing the daily contact with the course educators and receiving prompt and timely clinical input from them in daily reviews sessions.

Finally, in terms of *behavioural* benefits, 5-week participants said that they favoured the 5-week course as its extended format allowed sufficient time to change old habits and to integrate new self-care practices, such as diary and record keeping, into their daily routines. In contrast, the 1-week course participants said that they favoured the 1-week format as they saw it as habituating DAFNE skills and practices by virtue of them focusing on DAFNE for 5 consecutive days.[106]

Results from the 12-month questionnaire reinforced these findings, showing that 85% of respondents thought that the format of course that they attended would be better than the alternative format and that 12% thought that neither format would be better; only 3% thought that the format that they did not undertake would be preferable.

Other relevant findings from the qualitative substudy

Observations of the 5-week courses did not reveal any unanticipated problems or issues arising from the conversion of the 1-week curriculum for use on a course with an extended format. Interactions between course attendees and peer support appeared to be the same on 5-week courses as on 1-week courses despite there being a week inbetween course dates on the former. In addition, when the 5-week curriculum was first put together, some concerns were expressed that patients would want, and need, to contact the educators between course dates, thereby adding to their overall workload. However, both patient and educator interviews highlighted that very few patients who attended the 5-week course either made contact with or felt that they needed to contact course educators between course dates.

Discussion and conclusions

The data in this trial show that participating in DAFNE structured training over 1 day per week for 5 consecutive weeks was as effective as attending a standard DAFNE course delivered over 5 consecutive days. Post course, participants and educators were enthusiastic about both types of format, irrespective of their initial reservations before the trial. The mean change in HbA_{1c} from baseline to 6 and 12 months was similar between groups, for all participants and for those with a baseline HbA_{1c} level of $\geq 7.5\%$. Across the whole cohort, the relative risk of severe hypoglycaemia was decreased by 82% following DAFNE training; this reduction occurred independently of treatment arm (5 weeks or 1 week). In the original DAFNE trial[7] no significant difference in the rate of severe hypoglycaemia was observed but a reduction has been reported in a later observational report of an evaluated roll-out.[14] There were some minor significant differences between participants in the 5-week arm and those in the 1-week arm. Those in the 5-week arm lost more weight than those in the 1-week arm (–1.61 kg vs. –0.07 kg), associated with larger reductions in BMI, diastolic blood pressure and triglyceride levels. However, the magnitude of these differences was not clinically relevant.

For the cohort as a whole the overall improvement in HbA_{1c} was modest for those with a baseline HbA_{1c} level of $\geq 7.5\%$, at –0.2% at 6 months ($p = 0.016$) and –0.18% at 12 months ($p = 0.055$), and of smaller magnitude than that achieved in the original DAFNE trial,[7] which reported values of –1.0% at 6 months and –0.5% at 12 months. Of course, restricting subjects to those with a baseline HbA_{1c} of $\geq 7.5\%$ risks regression to the mean and so is difficult to interpret. There are several possible explanations. First, the mean starting HbA_{1c} level was lower in our trial (9.0% vs. 9.4%) and so the improvement might be expected to be less. Second, the success of the DAFNE trial, over a decade ago, probably contributed to a change in culture so that more adults with type 1 diabetes are now encouraged to use a basal bolus regime even without formal DAFNE training. Whereas 25% of patients in the original trial were on a twice-daily mix of insulin before DAFNE training as opposed to basal-bolus regimes, in this cohort only 7% of patients were on a twice-daily mix before DAFNE training. In addition, more of the patients are likely to have undertaken CP counting education before the course, although this was probably less structured than that on a DAFNE course. Therefore, this cohort may already be more skilled in dose adjustment and CP counting. This may have reduced the potential for improvement in HbA_{1c} levels. It is noteworthy that another recent trial of the DAFNE intervention has also failed to show much improvement in HbA_{1c} levels.[85]

We also assessed psychosocial outcomes, which reinforce the findings of other DAFNE studies[12,14,74,85] in demonstrating marked improvements across a range of measures at 6 months and maintenance at 12 months, with no differences between participants in the two different arms.

Before the trial one of the reservations about a 5-week DAFNE course format was that the dropout rate during the course would be disproportionately higher than for a 1-week course, perhaps because of less strong peer support. However, analysis of the qualitative data showed that peer support was equally strong among participants attending both courses. Reassuringly, the number of participants not completing either course was low (only one participant in the 1-week arm and seven participants in the 5-week arm). The reasons for dropping out were generally life events, for example illness, bereavement,

illness of a relative or inclement weather, which are more likely to occur over a 5-week period than over a 1-week period.

We have undertaken a detailed health economic analysis to compare the cost-effectiveness of the two different delivery formats. This is described in detail in *Chapter 8* and indicates few differences. One concern before the trial was that participants attending the 5-week course would require more support between educational days than the 1-week participants; however, this was generally not the case and so did not add significantly to the cost of delivering a 5-week course.

We embedded a qualitative study within the RCT to help understand and interpret any differences and similarities in biomedical and psychological outcomes in participants. This qualitative substudy largely showed a lack of difference between 1-week and 5-week course participants' post-course experiences and self-management practices. This mirrors and supports the main clinical and psychosocial findings from the trial. Perhaps one relevant finding was that participants attending the 5-week course reflected on their blood glucose readings over a longer period of time than the 1-week participants. This increased reflection, an important aim of the DAFNE approach, was in part explained by the greater number of measurements that each individual brought to each training day as they had been recording these over a longer period of time. Interestingly, this did not result in better HbA_{1c} levels, possibly because patients still lacked confidence and numerical competence to spot patterns and determine complex insulin dose adjustments without professional help. As also argued in *Chapter 3*, enabling patients to gain this capability, and therefore self-manage more effectively, is an area that needs to be addressed in future work.

The other key objective of the qualitative research was to ascertain patient preference for one course format over the other. Before their course, half of the patients had no preference and those who did often cited practical reasons why one format would be better for them than the other. The number of participants failing to commence a course post randomisation was very similar across the two arms (18 for the 1-week course and 15 for the 5-week course). However, following their attendance participants usually cited educational, clinical and behavioural reasons to justify their course preferences. Overwhelmingly, patients preferred the format that they had received. This raises important questions about the potential limitations of patient consultation exercises, a subject that we have debated in a separate paper.[106] On the other hand, these findings also show very high levels of satisfaction with DAFNE courses, whatever the format in which they are delivered.

A strength of this trial is that it has not occurred in isolation but as one component of a NIHR 5-year programme grant, utilising the DAFNE programme as a research test-bed. Professionals from different disciplines have collaborated on other pieces of work within this grant and thus the development of the intervention and conduct of the trial have been informed and influenced by other facets of the research programme. By incorporating qualitative substudies within the programme grant (see *Chapter 3*) we were able to interpret the findings with a greater understanding and identify ways of modifying and improving the delivery of skills training, and it has also helped us to generate hypotheses for future studies.

In conclusion, we have demonstrated that there are no major differences in outcomes, biomedical, psychosocial or cost-effectiveness (see *Chapter 8*), between the 5-week DAFNE course and the 1-week course. As participants valued both course formats highly, and some find it easier to attend one type than the other, we are persuaded to provide both 5-week and 1-week courses in the future.

Chapter 5 A pilot/feasibility study developing a DAFNE course incorporating both DAFNE training and pump skills

Abstract

We conducted a pilot feasibility study to explore the potential of conducting a trial in which adults with type 1 diabetes were randomised to DAFNE training involving either MDI or subcutaneous insulin pumps. A group of experienced DAFNE educators developed a 5-day curriculum incorporating both DAFNE self-management principles and the skills necessary to use an insulin pump. Of 160 eligible individuals, 55 agreed to be randomised to either a pump course or a MDI course, of which 47 both completed the course and attended a 6-month follow-up apppointment. Improvements in HbA_{1c} were observed in those attending the pump course, which were comparable to those seen in the original DAFNE trial, and severe hypoglycaemia was reduced. We also observed improved psychosocial outcomes. Participants were happy to remain on their allocated therapy for the duration of the 6-month pilot.

This study demonstrated the feasibility of the proposed design for a full multicentre RCT and the improvements in biomedical outcomes also allowed us to carry out a robust power calculation for the primary end point. The success of the pilot work might have been an important reason why we were successful in applying to the Health Technology Assessment (HTA) programme for funding for a full trial.

Introduction

People with type 1 diabetes (around 250,000 individuals in the UK) have lost the ability to physcologically make insulin to control their blood glucose and energy needs. They need to take insulin by injection, 'estimating' doses in relation to eating and other activities. This may mean five or even six injections a day, but injecting the correct dose creates a high risk of hypoglycaemia, especially in those aiming for a blood glucose level close to normal. Insulin can now also be replaced using an infusion pump (the size of a mobile phone), which delivers insulin continuously under the skin through a small plastic tube (CSII). This approach is more expensive than multiple injections (£2500 for the pump and £1500 a year for running costs). It may produce more stable blood glucose levels[107] with a reduced risk of hypoglycaemia[108] and provide a more flexible lifestyle, although it also needs careful monitoring and attention from the user.[109] Up to now, evidence of such benefit comes largely from observations of patients started on insulin pumps. This evidence may overstate the benefits of pump therapy as those who participate are already committed to intensive self-management or have a particular clinical need.[110]

We hypothesise that many of the benefits of pumps may come from the retraining 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 decide not to switch to pumps after attending a DAFNE course as they 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 as, if not better than, those reported after pump therapy.[6,7,111]

No trials in adults have compared pump treatment with injections in which the same structured training in insulin adjustment has been given and so the added benefit of the pumps themselves is still unclear. There is an urgent need to establish this and identify patients who benefit the most from pump therapy. This will enable the Department of Health through NICE to work out what proportion of adults with type 1 diabetes would benefit from pump therapy to guide the commissioning bodies that are expected to provide funding. A RCT can assess these outcomes without bias. We are now conducting a multicentre RCT [Relative Effectiveness of Pumps Over MDI or Structured Education (REPOSE)] funded by the HTA programme thats aim is to establish for patients, professionals and those funding the service if there is an added benefit of using a pump during intensive insulin therapy (Current Controlled Trials ISRCTN 61215213).

However, to inform the conduct and design of this trial, as part of the work funded by this programme grant we piloted the DAFNE plus CSII course, taking into account the framework and guidance published by the Medical Research Council (MRC)[112] for those developing and evaluating complex interventions. In this chapter we describe the design and results of this pilot study.

Methods

The pilot work enabled (1) refinement of the curriculum in advance of the full study, (2) examination of the conduct of the recruitment and randomisation process, (3) ascertainment of how many patients are likely to agree to be randomised and (4) estimation of the change in the primary outcome, HbA_{1c}, and the secondary outcomes of QoL and reduction in severe hypoglycaemia.

The planned intervention: the DAFNE pump course

1. The standard DAFNE curriculum was adapted so that patients were taught to use insulin infusion pumps instead of MDI during the 1-week course. A team of six experienced DAFNE educators modified the original DAFNE curriculum to incorporate the need to teach the additional skills of CSII (pump course). The 5-day structure of the DAFNE course was maintained while incorporating the additional skills and learning outcomes of pump therapy. Thus, the principles of insulin dose adjustment taught on the standard course were unchanged. The additional components of the course were modelled informally during existing pump courses in the participating centres. The need to introduce 'pump skills' required the addition of a pre-course session, which was run during the week before the DAFNE course 'proper'. Each course was conducted over 5 consecutive days and delivered to groups of up to eight adults aged ≥ 18 years. The curriculum used a progressive modular-based structure to improve self-management in a variety of medical and social situations. Curriculum content was designed to deliver key learning topics at the appropriate time within the programme. As in the 5-day MDI course, knowledge and skills were built up throughout the week with active participant involvement and problem-solving as key methods of learning. The key modules were: what is diabetes; food and diabetes; insulin management; management of hypoglycaemia; sick day rules; and use of the insulin pump. Learning objectives for each day and each session were clearly identified and educators were provided with instructions on session preparation and teaching materials. Lesson plans gave guidance on timing and a student activity section served to give an idea of expected responses. Each meal and snack was used as an opportunity to practise carbohydrate estimation and insulin dose adjustment. All course materials were provided for both standard and modified curricula. Participating centre DAFNE educators were experienced in delivering DAFNE education and pump therapy, and received training in the use of the new curriculum.

2. Recruitment. We attempted to model a randomisation process to gauge the potential success (and recruitment rate) for a full trial. Three established DAFNE centres participated in the study. Each centre set dates for three courses but were not informed of the type of course (blinded) until the course had been filled. All courses were randomised so that each centre delivered at least one of each type of course, either the standard 5-day DAFNE course using MDI or a DAFNE course in which patients were taught to combine DAFNE skills with insulin delivered by pumps. Thus, those allocated to pump therapy attended a modified 5-day course with additional pump training. Patients awaiting DAFNE training were invited to participate and those consenting selected a course date, blind to the arm.
3. Participants completed questionnaires before the start of the course with a baseline evaluation of biomedical and psychosocial measures and a follow-up evaluation at 6 months post course.
4. The decliner survey. Those who were contacted but who declined to take part in the study were invited to complete a short survey indicating the reason(s) why they had declined and were also asked if they would be willing to be interviewed, designed to further explore the reasons for declining and therefore inform recruitment procedures for the main trial.

Primary outcome measure

The primary outcome measure was change in HbA_{1c} level from baseline to 6 months.

Secondary outcome measures

The secondary outcome measures were change in the number and severity of hypoglycaemic episodes, and change in psychological outcomes, specifically reduction in anxiety and depression scores on HADS.

Study duration

The total study duration was 12 months. We aimed to recruit patients and deliver courses over the first 6 months and assessed participants at 6 months following the intervention.

Design: randomised pilot study

Study courses were delivered in three DAFNE NHS centres (*Figure 4*), either standard DAFNE courses using MDI or modified DAFNE courses to deliver DAFNE education and pump skills to pump-naive patients. There were three study courses per centre. Nine courses were randomised so that each centre delivered at

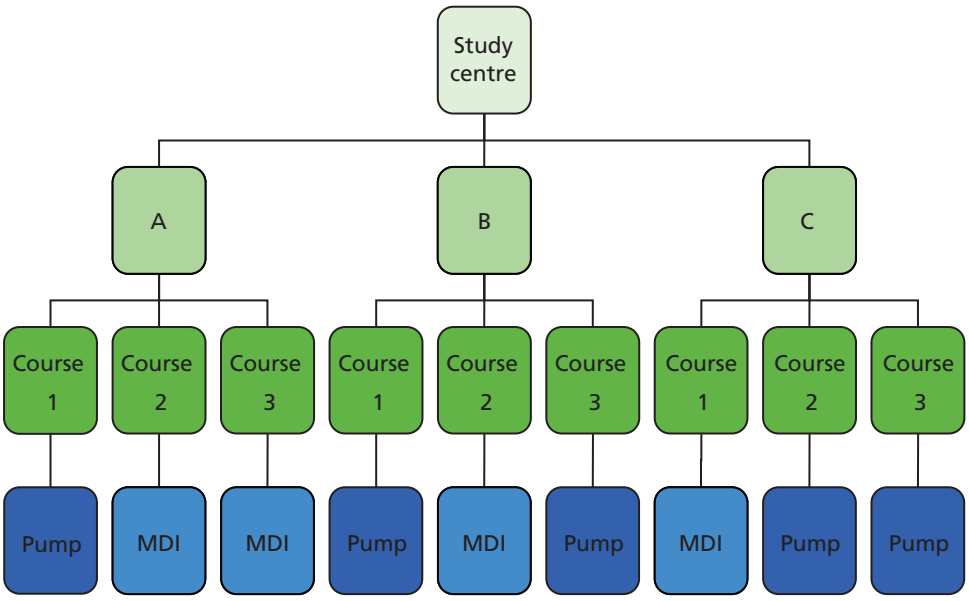

FIGURE 4 Randomised allocation of courses in the three centres (A, B and C).

least one course from each arm (using table devised by study statistician). Pump courses were run for up to six patients. MDI courses included six to eight patients as per standard DAFNE courses (course could be filled with non-study participants if not filled with recruits). The target was nine courses, five pump and four MDI courses, with 30 subjects in each arm.

Patients were recruited and self-selected a course date at their study DAFNE centre (double blind, i.e. both patient and centre were blinded to the course arm until course recruitment was completed).

Selection of subjects

Inclusion criteria

- Type 1 diabetes of at least 1 year's duration.
- Willingness to use an intensive insulin regimen either by MDI or pump.
- Currently on the DAFNE waiting list.
- HbA_{1c} level < 12%.

Exclusion criteria

- Factors preventing participation in group education, for example non-English-language speaking.
- Evidence of an eating disorder.
- Previous significant experience of pump therapy (> 6 months in the last 4 years).

Evaluation

Evaluation was conducted at 0 months (baseline, 1–2 weeks pre course) and 6 months (post course). Course evaluation forms were completed at the end of the 5-day course.

Biomedical

- HbA_{1c}.
- Weight, height, BMI and blood pressure.
- Frequency of hypoglycaemic events: self-report recall of both 'severe' hypoglycaemia (defined as needing help from a third party to recover) and 'moderate' hypoglycaemia (defined as being able to self-treat but in the patients' opinion needed to interrupt activities and requiring treatment to prevent a severe event).
- Hospital admissions for diabetic ketoacidosis (DKA).

Psychosocial measures

Measures of psychosocial outcomes, already being utilised in the standard DAFNE education programme linked to the NIHR DAFNE research database, collected at baseline and at 6 months included:

- QoL – this was assessed using both the DSQOLS[17] and the SF-12[19] and EQ-5D[113] generic measures of QoL
- emotional well-being – this was assessed using HADS[15] and PAID.[16]

Statistical analysis

As this was a small feasibility pilot study inferential statistics were not used, although means and SDs with *t*-test are reported here for information. The results allowed us to estimate the proportion of patients approached who might consent to take part in a full trial and also explore an upper bound of the ICC and CIs for the primary outcome of the main trial, namely HbA_{1c}, and for change in the number and severity of hypoglycaemic episodes. These helped inform the power calculation for the main RCT.

Ethics

Ethical approval was given by Sheffield Research Ethics Committee and research and development permissions were gained at the three NHS centres. The trial was registered as ISRCTN04179596.

Recruitment (Figure 5)

In total, 23 patients were allocated to the four MDI courses and 32 were allocated to the five pump courses. Twenty-two patients completed the MDI course and 30 completed the pump course; 17 MDI patients and all 30 pump patients provided 6-month follow-up data. Baseline demographics are shown in *Table 18*.

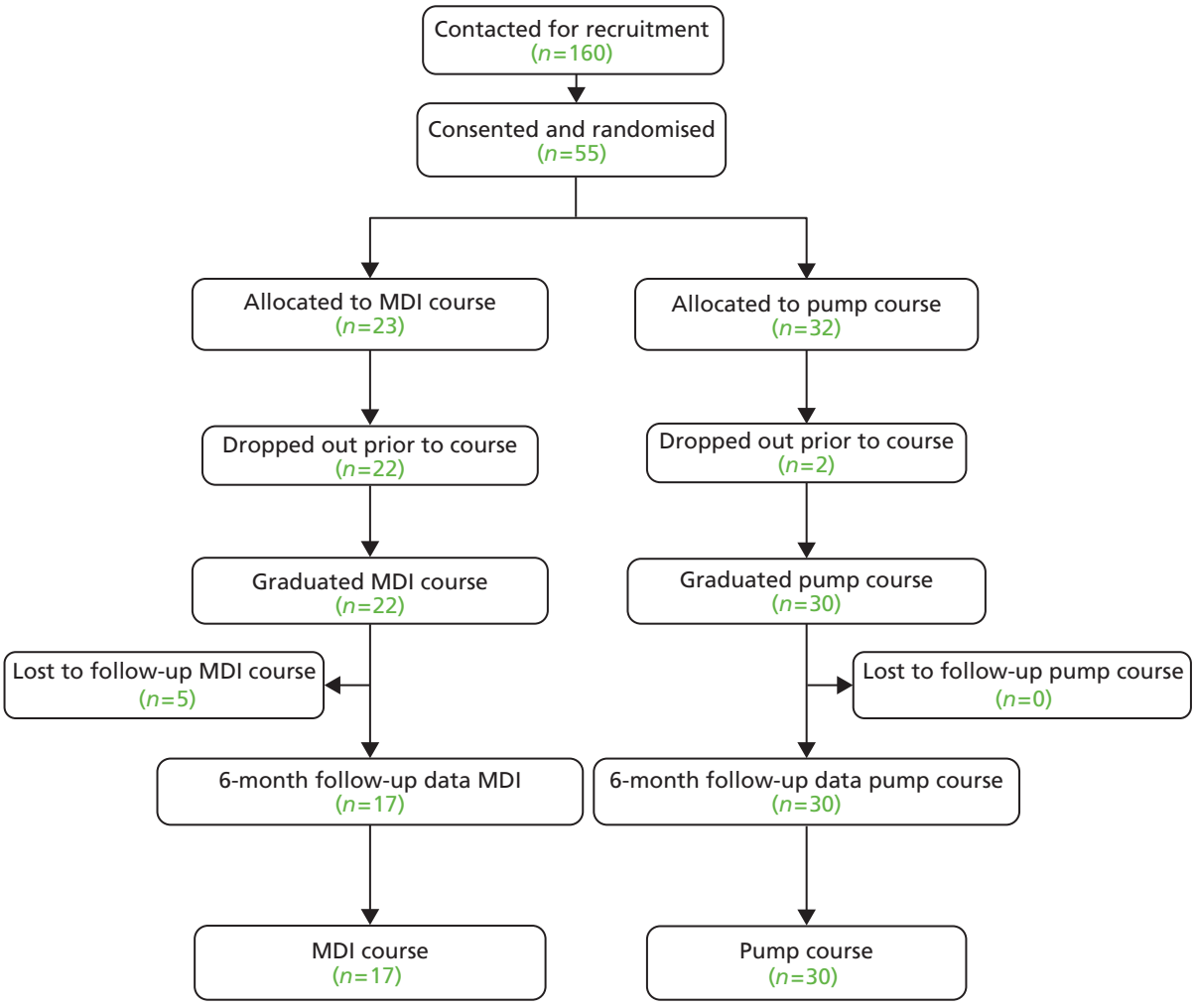

FIGURE 5 Consolidated Standards of Reporting Trials diagram: participant flow though the trial.

TABLE 18 Baseline demographics

Characteristic	MDI	Pump
Gender, female/male (%)	53/47	38/62
Age (years), mean (SD)	43.2 (16.4)	41.5 (13.2)
Duration of diabetes (years), mean (SD)	19.1 (13.6)	22.1 (13.7)
Ethnicity, white (%)	93	97
HbA_{1c} (%), mean (SD)	9.4 (1.7)	8.3 (1.3)

Results

To confirm the feasibility of making biomedical and psychosocial measurements over 6 months

Six-month data were collected for all 30 participants who completed the pump course and for 17 participants who completed the MDI course.

- Five MDI patients were lost to follow-up. Pump patients were easier to follow up as they had to return with their pumps at 6 months.
- All pump patients remained on pumps during the pilot.

To obtain data on change in the primary outcome measure to confirm power calculations for the main randomised controlled trial

- In the entire cohort, HbA_{1c} fell from a mean (SD) of 8.8% (1.7%) at baseline to 8.5% (1.7%) at 6 months ($p = 0.041$):
  - MDI group: 9.4% (1.7%) to 9.1% (1.8%) ($p = 0.20$)
  - pump group: 8.3% (1.3%) to 8.0% (1.2%) ($p = 0.12$).
- For those patients with a baseline HbA_{1c} level $< 7.5\%$ there was no deterioration in HbA_{1c}:
  - MDI group: no participants had a baseline HbA_{1c} level $< 7.5\%$
  - pump group: eight participants had a baseline HbA_{1c} level $< 7.5\%$; mean (SD) HbA_{1c} was 7.0% (0.5%) at baseline and 7.1% (0.6%) at 6 months ($p = 0.36$).
- For those patients with a baseline HbA_{1c} level $\geq 7.5\%$ HbA_{1c} improved between baseline and 6 months:
  - MDI group: 9.4% (1.7%) to 9.1% (1.8%) ($p = 0.20$)
  - pump group: 21 participants had a baseline HbA_{1c} level $\geq 7.5\%$; mean (SD) HbA_{1c} was 8.8% (1.1%) at baseline and fell to 8.3% (1.2%) at 6 months ($p = 0.05$).

To obtain data on the effect of DAFNE on hypoglycaemic events and diabetic ketoacidosis

- *Severe hypoglycaemia*. At baseline, severe hypoglycaemic episodes within the last year were reported in 10 out of 52 patients, of whom six had one episode, two had two episodes, one had 10 episodes and one had 20 episodes (these last two patients were randomised to insulin pump training). Within the 6-month post-course period, severe hypoglycaemic episodes occurred in only two out of 47 patients; these were the patients with high rates of hypoglycaemic episodes at baseline. For these two patients there was a reduction in rate of hypoglycaemic episodes, to four episodes in the patient who reported 20 episodes in the previous year and to one episode in the patient who reported 10 episodes in the previous year.

- *Hospital admissions for DKA*. In total, 17 admissions for DKA had been recorded in the past year for the entire cohort. No DKA admissions were reported within the 6-month post-course period.

To obtain data on the effect of DAFNE on quality of life

Scores on several measures of QoL (EQ-5D, HADS, PAID and SF-12) improved or there was no detriment in both arms of the study over the 6-month post-course period:

- *EQ-5D* (0 = worst imaginable health state, 100 = best imaginable health state). The mean (SD) baseline score was 71.2 (16.4) and the mean (SD) score at 6 months was 71.6 (17.4) ($p = 0.9$). There was no significant difference in either group with few people changing health states over the 6 months.
- *HADS* (maximum score of 21 for each scale; a score of ≥ 11 indicates a probable mood disorder). No participants in the MDI arm scored > 11 on the anxiety or depression scale. One participant on a pump was depressed at baseline and at 6 months. Four participants on pumps were anxious at baseline, two of whom remained so at 6 months, and one participant on a pump became anxious at 6 months.
- *PAID*. Diabetes-related distress was significantly reduced in the entire cohort, with mean scores of 29.3 at baseline and 16.4 at 6 months ($p = 0.0014$). The mean score was significantly reduced in those on pumps, from 30.5 to 17.4 ($p = 0.012$), and there was a trend to a reduction in mean score in the MDI arm (from 23.1 to 14.5, $p = 0.06$).
- *SF-12* (norm = 50). There was no change in the physical component score of the SF-12 but there was an improvement in the mental component score across the entire cohort, from 45.1 to 49.8 ($p = 0.015$). The greatest change was seen in the pump group (pump: 42.5 to 49.6, $p = 0.0015$; MDI: 51.8 to 50.2, $p = 0.65$).

To assess the proportion of patients on DAFNE waiting lists who agree to participate in a randomised controlled trial and be randomised to either pump or multiple injection therapy

A decliner survey was undertaken by an experienced qualitative investigator. In total, 40 patients who were approached for recruitment to the main study but who declined consented to return a screening questionnaire on reasons for declining. Of these, 18 consented to be approached for an interview to discuss their non-participation. The aim was to explore any possible barriers to recruitment. In total, eight were selected for in-depth interview. The findings were used to inform recruitment for the main RCT. A brief report of the findings has been published.[114]

Eight participants were interviewed, along with another five who had given 'other' reasons for non-participation. All respondents completed the full interview and answered all questions when prompted. All participants were using MDI therapy and had a duration of diabetes of a minimum of 10 years.

Overall, there was poor understanding of insulin pump therapy, with three-quarters of participants reporting very little knowledge of either how the pump worked or what it looked like. Myths and misinformation about insulin pumps were prevalent, for example one participant believed that the pump delivered only basal insulin and that bolus injections were still required. Lack of knowledge about the appearance or functions of pump therapy clearly put some people off. Despite insulin pump therapy being increasingly available as a therapy choice, patient knowledge of what the therapy looks like or understanding of the device and treatment regimen remains limited. Having an insulin pump available in clinic for potential participants to see could improve understanding and remove some potential anxieties such as those around cannula insertion.

The suggestions put forward for how the research team could make it easier to take part were varied and contradictory, perhaps reflecting personal preference and lifestyle commitments. More information was preferred to less information; the range of approaches requested was wide and included face-to-face contact as well as the availability of professionals to discuss the research project in more detail. This will be

limited by resources and the availability of health-care professionals and so compromises will be required to strike a balance. A common theme that was apparent, however, was that potential participants would find it helpful to be able to talk to someone in person (or by e-mail in the case of one participant) who could explain in more detail exactly what was required before signing up to the trial. This preference for personal contact is consistent with that seen in the literature.

The potential to offer participants incentives to respond to questionnaires (baseline and follow-up) was not raised in this brief study; however, it may be useful when considering how to maximise recruitment and retention to the REPOSE trial. A recent Cochrane review[115] reported that 'researchers may be able to double the odds of response by offering participants payment for completion of questionnaires' (p.12). This is something that should be explored in greater detail. Similarly, offering alternatives to completing large questionnaire booklets such as telephone interviewing may be appealing to individuals who might be put off by the number of written questions. Maintaining participation throughout the 2-year follow-up of the REPOSE trial is imperative to ensure robust statistical analysis. A better explanation of pumps and their potential advantages/disadvantages may help both to recruit potential participants and to ensure that they remain in the trial.

Discussion and conclusions

In this pilot study a team of DAFNE educators, specialist nurses and dietitians adapted the DAFNE curriculum to train adults with type 1 diabetes to use both a DAFNE intensive insulin approach and an insulin pump during a 5-day course. We confirmed that such training could be delivered successfully and was acceptable to participants. We also tested the feasibility of other components that would be required in a full RCT. We showed that it was possible to deliver both DAFNE and pump training, that HbA_{1c} levels improved to levels seen with MDI courses and that we could recruit sufficient numbers of participants to confirm that running a much larger trial in other centres was viable.

An additional set of learning objectives were selected and incorporated into the curriculum which covered the skills needed to ensure that participants randomised to the pump arm were able to use the pump safely and effectively. Experienced educators constructed the curriculum and delivered it successfully in the five pilot courses specified in the pilot trial protocol. The pump pilot courses went well; apparent from the positive feedback, with similar patient responses to those expressed after standard DAFNE courses.

We tested a recruitment model that we intended to use in the main trial and supplemented this with a small qualitative study exploring the views of patients on the DAFNE waiting list who declined an invitation to participate. Of 160 patients who were invited to participate around 55 consented to join the pilot study, that is, one-third of those who were approached. As we were intending to randomise 280 patients in the main trial this provided clear guidance that we would need to identify around 800 potential recruits in the seven centres that would be involved in the main trial.

The qualitative trial also provided important and useful information on the reasons why individuals declined an invitation to participate in the trial. This work indicated that the main reason why individuals chose not to join the study was a lack of information about the technology involved and a lack of understanding of how an insulin pump worked. Many of those who chose not to participate had never seen a pump before and were unclear about the potential benefits. This information was extremely useful as the professional preconception was that the main difficulty with recruitment would be that most potential recruits would be determined to join the insulin pump arm. It was clear that we would need to provide some detailed information for potential participants. As a result, we made an information video that explained, in detail, how an insulin pump worked. We also ensured that at any recruitment meeting (which we arranged in groups) we would have a real pump available for patients to see and hold. We also decided to offer a small financial incentive (subject to ethical approval) to maximise the likelihood of participants continuing to attend for data collection during follow-up.

Another positive result was that patients who were randomised to both arms were prepared to remain in the trial for the duration of the 6-month follow-up. Although this is only a rough guide to the conduct of those participating in a trial in which the follow-up lasts for 2 years, it at least suggested that the proposed study design of the full trial was feasible. Furthermore, the results of the trial prompted us to modify the protocol for the main trial. In this pilot, the baseline HbA_{1c} levels in the two groups were very different and all of the participants with a HbA_{1c} level of $< 7.5\%$ were randomised to the pump arm. As it was important that we included similar numbers of participants with high HbA_{1c} levels in each group (as an improved HbA_{1c} level is the primary end point), we decided in the main trial to use a randomisation technique including minimisation (based on the most recent HbA_{1c} level before randomisation). In this way we hope to maximise our chances of achieving equivalent numbers of patients with a HbA_{1c} level $< 7.5\%$ in both arms.

In conclusion, the pump pilot study fulfilled all of the main aims. The work of developing the curriculum and the demonstration of the feasibility of the study design, the improvement in HbA_{1c} levels and the reduction in severe hypoglycaemia were all important outcomes that contributed to our success in securing funding from the HTA programme to conduct a full multicentre trial across Scotland and England.

Chapter 6 A pilot intervention to improve outcomes in people experiencing problems with hypoglycaemia after DAFNE training: DAFNE-HART

Abstract

Hypoglycaemia remains a clinical problem for people with type 1 diabetes. DAFNE reduces severe hypoglycaemia and improves hypoglycaemia awareness but not for everyone. Reduced motivation for regimen change to avoid hypoglycaemia may contribute to sustained intractable hypoglycaemia avoidance. In a collaboration between King's College Hospital and Sheffield Teaching Hospitals NHS Foundation Trust, two centres with experience in the management of hypoglycaemia, we designed and piloted a 6-week intervention that revised principles of hypoglycaemia avoidance and addressed unhelpful beliefs concerning hypoglycaemia unawareness, incorporating motivational enhancement and cognitive–behavioural approaches. A total of 24 people with type 1 diabetes and impaired hypoglycaemia awareness (Gold score ≥ 4) attended a pilot course and were reviewed 3 months later. One was lost to follow-up. In the remaining 23, the Gold score improved [from a mean of 5.5 (SD 1.8) to a mean of 4.4 (SD 2.2); $p < 0.001$]. The annualised rate of severe hypoglycaemia fell from a median (range) of 3.5 (0–70) to 0 (0–40) ($p = 0.14$), with a fall in episodes of moderate hypoglycaemia from 14 (0–100) to 1 (0–11) per 6 weeks. Depression scores (HADS) improved from a mean of 5.4 (SD 4.9) to a mean of 4.6 (SD 4.3) ($p = 0.04$) and behaviour around hypoglycaemia and worry about hyperglycaemia also improved. HbA_{1c} remained stable. Patients described the detrimental impact of hypoglycaemia on their lives, and family members also described restrictions and fears. We conclude that an intervention based on changing motivations and cognitions around hypoglycaemia was able to engage patients with otherwise intractable impaired hypoglycaemia awareness and recurrent severe hypoglycaemia, and produce significant improvement in the short term in problematic hypoglycaemia that persisted following DAFNE education. Using qualitative data from patient interviews we can now adjust the curriculum ready for a roll-out as a fully powered RCT.

Background

From the inception of the DAFNE intervention it has been recognised that the benefit that people obtain from attending a DAFNE course, and the duration of that benefit, will vary widely. In the original DAFNE trial[7] there was evidence for a waning of the improved blood glucose control over time, with a mean fall of 1% from baseline to 6 months, which regressed to an overall fall of 0.5% at 1 year, with a small but significant further loss of improvement (–0.36%) at 44 months. Most notably, neither the initial benefit, nor any subsequent deterioration, was universal, with one-quarter of subjects being able to maintain a fall in HbA_{1c} of at least 1.5% over 12 months and just over one-tenth of patients exhibiting a rise of $\geq 1.5\%$.[7] Clinical experience later confirmed that not all patients benefit equally from DAFNE education and some achieve immediate benefit that they are unable to maintain. Our programme therefore included the intention to develop and pilot a new intervention to improve diabetes control in DAFNE 'graduates' who either failed to achieve or were unable to sustain sufficient glycaemic benefit after attending a conventional DAFNE course.

The initial intention had been to design a course to improve HbA_{1c} outcomes. However, during the qualitative research undertaken as part of the psychosocial study reported in *Chapter 3*, it was found that people who took part in DAFNE training talked as much about their fear of hypoglycaemia as they did about their fear of hyperglycaemia (although both were relevant).[71] Specifically, some patients described

adjusting their targets to a higher glucose concentration, which could mitigate against achieving optimal HbA_{1c}, to avoid hypoglycaemia,[79] and others reported difficulties in either remembering or adhering to the relatively conservative treatment strategies for episodes of hypoglycaemia taught during the course.[78]

The German programme on which DAFNE was based had earlier reported its ability to achieve a fall in the severe hypoglycaemia rate in parallel with the fall in HbA_{1c},[6] and indeed went on to publish observational data that broke the axiomatic link between lower HbA_{1c} and severe hypoglycaemia risk.[77] Although the original DAFNE trial failed to show a reduction in the severe hypoglycaemia rate, there was no increase despite the 1% fall in HbA_{1c}.[7] This may have been because rates of severe hypoglycaemia were low at entry to the trial. A later clinical audit of the UK DAFNE programme showed a significant impact on severe hypoglycaemia rates.[14] The audit also found a high rate of people being referred into the DAFNE programme with impaired hypoglycaemia awareness (40% vs. the near 20% reported previously in the literature[116]). Uniquely, the audit also reported that, of those people entering the DAFNE programme with impaired awareness, although 43% had regained awareness at 1 year, 57% had a persistent problem. Most of the residual severe hypoglycaemia in the DAFNE graduates in the audit was then experienced by these people.[14]

Meanwhile, working simultaneously on a different NIHR programme grant, the research group attached to the King's College Hospital DAFNE centre had continued to investigate the pathophysiology of impaired hypoglycaemia awareness and problematic hypoglycaemia resistant to intervention. Bingham *et al.*[117] and Dunn *et al.*[118] had formulated a model of hypoglycaemia unawareness based on unexpected neuroimaging data that showed a different activation pattern in the brain's centres for hedonic perception and reward in response to acute hypoglycaemia, as well as in the central stress and interoceptive pathways. The response of the brain to hypoglycaemia in people with impaired subjective awareness of their hypoglycaemia (and reduced counter-regulatory stress responses to hypoglycaemia experimentally induced) was compatible with a potential lack of motivation to avoid hypoglycaemia. Examining adherence to therapeutic decisions made during one clinic visit at subsequent clinic visits they found that hypoglycaemia-unaware patients were significantly less likely to be maintaining regimens presumably agreed to reduce hypoglycaemia risk than patients without problematic hypoglycaemia, in whom treatment strategies were presumably focused around other aspects of glycaemic control.[119] Semistructured interviews with people with hypoglycaemia unawareness found that most had unhelpful attitudes and cognitions that were likely to inhibit hypoglycaemia avoidance.[120] The group were planning an intervention to explicitly tackle motivation to change behaviour with the intention of reducing hypoglycaemia and improving awareness. It was decided to devise and pilot an intervention to improve outcomes for people experiencing persistent problematic hypoglycaemia after conventional DAFNE training. The intervention comprised a psychoeducational course that we called DAFNE-HART.

Aims

The main aim was to develop a pilot intervention for people with type 1 diabetes and hypoglycaemia unawareness to reduce the number of severe low blood sugar reactions (hypoglycaemic episodes) that they have.

Subsidiary aims

1. To determine if a pilot intervention can teach people with type 1 diabetes and hypoglycaemia unawareness to recognise that certain beliefs that they hold about hypoglycaemia unawareness are unhelpful.
2. To determine if this pilot intervention can help them change their behaviour.
3. To determine if this pilot intervention can improve their awareness of low blood glucose symptoms.
4. To determine if this pilot intervention can improve their QoL.

A qualitative substudy was also built into the pilot to:

1. understand and explore patients' experiences of living with problematic hypoglycaemia through impaired hypoglycaemia awareness and its impact on their everyday lives (better to understand patients' motivations for attending/not attending the pilot intervention)
2. establish patients' reasons for declining to take part in the pilot intervention
3. explore course attendees' reasons for attending, their likes and dislikes of the pilot intervention and their views about how the course might be improved.

When initial analysis of patient interviews highlighted that family members also appeared to play a central role in the detection and management of hypoglycaemia (see *Qualitative substudy*, *Family members*), and as the experiences and information and support needs of this group had not been explored in previous research, the qualitative substudy was also expanded to include an additional aim, namely to:

4. understand and explore the experiences of family members living with, and caring for, people with hypoglycaemia unawareness; the impact of hypoglycaemia unawareness on their own lives; and, family members' information and support needs.

Methods

Designing the intervention

Based on the findings of the interviews and knowledge of the evidence for psychological interventions in other clinical situations in which people persist in behaviours that are harmful to health (e.g. Vasilaki *et al*. [121] and Wariki *et al*. [122]), the clinical psychologist attached to the King's College Hospital NIHR programme (Professor Stephanie Amiel, RP-PG-0606-1142, Non-pharmacological approaches to improving diabetes outcomes) led on the design of a psychoeducational intervention to target the behaviours and cognitions supporting hypoglycaemia avoidance, which was refined collaboratively with the DAFNE-HART team, including input from members of the DUAG. The intervention was based on the principles of motivational interviewing and cognitive–behavioural therapy techniques. The curriculum would be delivered by DAFNE educators, who were trained and supervised by the clinical psychologist. The curriculum included review of the mechanisms of hypoglycaemia and hypoglycaemia unawareness and how best to avoid and treat it, recapitulating the original DAFNE curriculum. The literature was searched for evidence of existing programmes and three were found: Blood Glucose Awareness Training (BGAT),[123,124] Hypoglycaemia Anticipation, Awareness and Treatment Training (HAATT)[125] and HyPOS.[126] All aimed to foster improved symptom recognition and self-treatment practices and all were predicated on data showing that impaired hypoglycaemia awareness could be induced/reversed by hypoglycaemia exposure/avoidance[127–132] and increased the risk of severe hypoglycaemia sixfold.[133] Although all had led to some improvements, none had resulted in full restoration of awareness or obliteration of severe hypoglycaemia. Our curriculum built on the reported interventions tested in these studies but included psychological strategies to identify and address the specific unhelpful cognitions maintaining impaired hypoglycaemia awareness informed by our own qualitative research.

The draft curriculum was reviewed by a panel including clinical quantitative and qualitative researchers, DAFNE educators and doctors, and people with type 1 diabetes from the DUAG. In a 2-day workshop five DAFNE educators were provided with training in the curriculum and in the motivational interviewing and cognitive–behavioural therapy techniques necessary to deliver the 'thinking traps module' of the curriculum. Weekly supervision was provided by the clinical psychologist to the educators during each course that was delivered.

The pilot intervention

The intervention was tested in a pilot study in May 2012. Two courses were prepared in each centre, each serving six participants. Patients were recruited by the local teams at King's College Hospital and St George's University Hospital, London, and at Sheffield Teaching Hospitals NHS Foundation Trust by screening patients' diabetes notes, hospital diabetes databases and clinics for people with hypoglycaemia problems post DAFNE. Inclusion criteria were type 1 diabetes and persistent problematic hypoglycaemia post DAFNE, defined as a Gold score ≥ 4,[134] and one or more of the following: three or more episodes of blood glucose < 3 mmol/l in 2 weeks without symptoms; two or more episodes of severe hypoglycaemia (defined as requiring third-party assistance) since DAFNE and at least one in the last 2 years. People with type 1 diabetes and impaired hypoglycaemia awareness who had not attended the DAFNE course, people not fluent in spoken English and people with a severe mental disorder (schizophrenia, manic depression, depressive psychosis, active suicidal ideation, a learning disability, dementia, alcohol and substance dependence or a severe personality disorder) were excluded.

At baseline, data were collected by the DAFNE educators on demographics, current diabetes treatment, height, weight, BMI and blood pressure. Blood was taken for measurement of HbA_{1c}, creatinine, thyroid function, and cortisol and growth hormone if these data were not available from the notes. A booklet of self-report questionnaires was compiled (*Box 1*). The frequency of severe hypoglycaemia, defined as episodes in which the patient had required help from another person, as well as the degree of severity (requiring paramedic or emergency department attendance; associated with loss of consciousness), were documented for the year preceding the enrolment visit; the frequency of moderate hypoglycaemia,

BOX 1 Self-report questionnaires used in the DAFNE-HART study

Self-report questionnaires used in the DAFNE-HART study

Hypoglycaemia awareness status.[135,136]

HFS II.[a]

Hypo Cues Questionnaire.[b]

Hyperglycaemia Avoidance Scale.[a]

Attitudes to Awareness of Hypos (A2A).[120]

DAFNE self-management.

DSQOLS.[137]

PAID.[138]

HADS.[15]

SF-12.[139]

EQ-5D.[18]

Social networks/social support.

a Courtesy of Professors Dan Cox and Linda Gonder Frederick, University of Virginia, Charlottesville, VA, USA.
b www.ncl.ac.uk/nctu/assets/documents/hypoCOMPASS%20Protocol%20version%203.1%20-%2026%20Apr%202012.pdf.

defined as that which was self-treated but involved significant disruption to current activity, was documented for the 6 weeks before the assessment. Each patient's blood glucose meter was checked for calibration and quality control, and the most recent 2 weeks of data were downloaded and collected using Diasend® software (Diasend AB, Sweden, Datavägen 14A, SE-436 32 Askim; www.diasend.com). Each patient was fitted with a continuous glucose meter (Medtronic UK, Watford, UK), implanted into the subcutaneous tissue on the abdomen, instructed in its use and asked to keep it in place and calibrated for 7 days.

Qualitative substudy

All patients who declined to take part in the pilot intervention were invited to take part in an interview to explore their experiences of living with hypoglycaemia unawareness and their reasons for declining. The contact details of patients who opted in to the qualitative substudy were passed onto the qualitative research team and all were interviewed.

All patients who took part in the pilot intervention were invited to take part in a qualitative interview, timed to take place within 2 weeks of completing their course.

At the end of their interviews, patients (decliners and attenders) were asked if they could identify a partner or other adult family member who helped them detect and manage hypoglycaemia. Those who identified an eligible person were given a study information pack, which included an opt-in form. Family members who returned their opt-in forms were contacted to arrange an interview.

All interviews (with decliners, attenders and family members) were informed by topic guides to ensure that the discussion stayed relevant to the study aims while allowing participants to raise and discuss issues that they perceived as salient to them. The topic guides were devised to take account of previous research that has identified patients' concerns about hypoglycaemia unawareness[120] and findings from the psychosocial research reported in *Chapter 3*[71,78,79] and had input from the research team and other DAFNE educators; they were also revised in light of ongoing data analysis in line with the principles of grounded theory research.[103] Sampling was also revised in light of early data analysis, in this instance through the inclusion of family members within the qualitative substudy.

Interviews, which averaged 1 hour, were undertaken at a time that was convenient for participants. They were digitally recorded (with consent) and transcribed in full to permit in-depth analysis.

To maximise rigour, two experienced qualitative researchers (JL and DR) undertook data analysis. A thematic analytical approach was used in which transcripts were cross-compared[67] to identify issues and experiences that cut across different people's accounts and the underlying reasons for similarities and differences in their experiences and views. A coding framework was developed to capture key themes and each theme was subjected to further analysis. Throughout, JL and DR examined the data independently and wrote separate reports before meeting to compare interpretations and reach agreement on key findings. NVivo 9 (QSR International, Doncaster, Australia), a qualitative software package, was used to facilitate data coding/retrieval.

The curriculum

This was delivered over 6 weeks in four full-day group sessions, with two one-to-one telephone calls or face-to-face meetings. The main features of the curriculum are listed in *Box 2*.

Assessment and data analysis

A repeat of all of the baseline assessments was made at 3 months post course, apart from the semistructured interviews to determine views on the course and curriculum, which were conducted within 2 weeks of course completion. Demographic, biomedical and questionnaire data were entered into a spreadsheet and analysed using SPSS (version 4, IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA). CGM data were examined and excluded if the mean absolute error exceeded 28% or there were fewer than three valid calibrations per 24 hours. Data located between two valid calibration points were analysed

BOX 2 The curriculum

Week 1: full-day group programme – *how low can you go?*

- Introduction to the course and goal setting.
- Education topics: what is a hypo, consequences of severe hypos, model of hypo unawareness.
- Novel hypo awareness signs; teaching the body scan.[a]
- Complete individual severe hypo risk assessment.
- Modify goal setting based on education.

Homework: estimating blood glucose concentrations; doing a body scan and noting any novel hypo signs.

Week 2: full-day group programme – *the balancing act*

- Education topics: how to anticipate peaks/nadirs of insulin action; CP counting and matching; modifications for exercise/physical activity.
- Behavioural plan.

Homework: estimating blood glucose levels (as above) and noting insulin/diet/activity (biological factors); making insulin/food adjustments.

Week 3: full-day group programme – *thinking traps*

- Patients review answers to Attitudes to Awareness of Hypos (A2A) questionnaire.
- Education topics: concept of thinking traps; pros/cons of each one; how thinking traps interact with hypo management.
- Group discussion regarding more helpful thoughts.
- Strategies to support patients in their social context.
- Thinking traps plan.

Homework: estimating blood glucose levels (as above) and noting thoughts in response to blood glucose level (psychological factors).

Weeks 4 and 5: 1 hour per week individual appointments for face-to-face contact with a DAFNE educator to review patient progress/plans and provide troubleshooting support

Week 6: full-day group session – *keeping on track*

- Revise core education topics with group.
- Invitation to bring significant other and Q&A session.
- Group discussion on progress made.
- Group discussion on future challenges/relapse prevention.
- Opportunity for final troubleshooting.
- Individual relapse prevention plans.

Hypo, hypoglycaemic event; Q&A, question and answer.

a Teaching patients to scan their body for any subtle cues that may indicate being low.

from patients with at least 24 hours of valid data. A hypoglycaemic episode was defined as a period including a measurement of ≤ 3 mmol/l; its duration was measured from the time that the glucose level fell to < 3.5 mmol/l to the time that it rose above this value and had to be at least 20 minutes to be counted. Data are reported as mean and SD or median and range (insulin doses and hypoglycaemia rates) and are analysed using the Student's *t*-test or Wilcoxon's signed-rank test for non-parametric variables. When the data included many episodes with no incidence of hypoglycaemia or when only categorical variables were collected, a chi-squared test was performed. *p*-Values of < 0.05 were taken to be significant. As described above, NVivo software was used for the storage and analysis of interview data.

Ethics

Written informed consent was obtained from all participants. Ethics approval was obtained from the National Research Ethics Service Committee London – Dulwich (ref.: 12/LO/0083). The study was also approved by study centre research and development departments.

Results

The participants

In total, 24 (12 female) people with diabetes and problematic hypoglycaemia were recruited. The participants' baseline data are shown in *Table 19*. Sixteen patients were using MDIs with twice-daily background injections (one animal, four human NPH, 11 detemir) and pre-meal quick-acting insulin (one human, the rest analogue) and eight were using quick-acting insulin only (one human,

TABLE 19 Baseline demographic, biomedical, and anxiety and depression score data for participants in the DAFNE-HART pilot study (*n* = 24)

Characteristic	Value
Age (years), mean (SD)	54.3 (7.7)
Gender, male/female, *n*	12/12
BMI (kg/m_2), mean (SD)	25.7 (3.9)
Duration of diabetes (years), mean (SD)	30.1 (12.0)
Time since DAFNE course (years), mean (SD)	6.5 (4.1)
HbA_{1c} (%), mean (SD)	7.8 (1.2)
HbA_{1c} (mmol/mol), mean (SD)	61.8 (13.1)
Insulin dose/kg, median (range)	0.6 (0.3–1.8)
Episodes of severe hypoglycaemia in last year, median (range)	3.5 (0–70)
Episodes of moderate hypoglycaemia in last 6 weeks, median (range)	16 (0–100)
Gold score, mean (SD)	5.8 (1.1)
Clark score, mean (SD)	2.9 (0.3)
Ryan score, mean (SD)	924 (797)
No. of times glucose level < 3 mmo/l (CGM) per week	4.7 (3.1)
Duration of time spent at < 3 mmol/l (CGM) (minutes/week), mean (SD)	396 (375)
HADS-A score[a]	5.9 ± 4.5
HADS-D score[b]	5.3 ± 4.8
PAID score	30.3 ± 21.7

a HADS – anxiety.
b HADS – depression.

seven analogue) by CSII. Three of these were routinely using real-time CGM, which they continued during the study. One patient, a 64-year-old woman with a 10-year history of type 1 diabetes, using MDIs with a human background insulin and also taking aspirin, was lost to follow-up after the course. Her HbA_{1c} was 8.8% (73 mmol/mol) and she had had one severe and 42 moderate hypoglycaemic episodes in the 52 and 6 weeks preceding the course, respectively, and had a Gold score of 7 and so did not appear different from the rest of the group. Her data are included in the baseline analysis but not in the paired analyses of the follow-up data.

No patient had impaired renal function (eGFR $\geq$ 60 ml/minute) although one patient had had a renal transplant. Fourteen participants had retinopathy, of whom two had had proliferative retinopathy; four reported hypertension; one had had coronary revascularisation; two had had foot ulcerations; and three of the men reported erectile dysfunction. Sixteen were using lipid-lowering medication; 10 were using antiplatelet therapy; and five were taking antidepressants. One participant was taking 20 mg of temazepam in the evening to sleep through the pain of a frozen shoulder. All medications remained stable in type throughout the study, apart from one patient discontinuing an antiplatelet agent; one discontinued and one started antidepressant medication.

Baseline hypoglycaemia experience

In total, 21 of the 24 participants reported severe hypoglycaemia in the year before enrolment, with 14 out of 24 (58%) reporting unconsciousness (median of one episode per patient, range 0–30). Six out of 24 participants had had episodes requiring paramedical attendance, on one to 24 occasions. For three participants these had culminated in accident and emergency department attendance (one to 24 times); one patient had been admitted on two occasions. All but one participant reported moderate hypoglycaemia in the 6 weeks before the study. All participants ranked their awareness of hypoglycaemia with a Gold score of $\geq$ 4. No patients reported perceiving symptoms of hypoglycaemia with blood glucose concentrations of 3–3.5 mmol/l; 16 reported symptoms with blood glucose concentrations of < 3 mmol/l, with the remaining eight reporting no symptoms at all at any glucose concentration.

Quality of life and mental health data

Mean scores on the HADS and PAID questionnaires are provided in *Table 19*. Nine participants (39%) scored > 8 on the HADS-A (HADS – anxiety) and seven participants (30%) scored > 8 on the HADS-D (HADS – depression) questionnaires; five people scored > 40 on the PAID questionnaire.

*Three months after completion of DAFNE-HART (*Table 20*)*

At the 3-month follow-up, 15 out of 23 participants reported no severe hypoglycaemia, with one subject missing data. The annualised rate of severe hypoglycaemia had fallen from a median (range) of 3.5 (0–70) to 0 (0–40) ($p = 0.014$). The annualised rate of events requiring hospitalisation, paramedic call-out or complete loss of consciousness fell from a median (range) of 1(0–48) to 0 (0–40) ($p < 0.0001$). The rate of moderate hypoglycaemia also fell significantly. Although there were no differences in the frequency of hypoglycaemia on CGM, the mean duration of daytime episodes at a glucose concentration of < 3.0 mmol/l was significantly reduced, consistent with earlier treatment of episodes. Despite the fall in occurrence of hypoglycaemia, HbA_{1c} levels did not rise.

From the questionnaires, self-rated behaviours around hypoglycaemia changed, although worry about hypoglycaemia did not improve significantly. Worry about hyperglycaemia reduced significantly, although without significant measurable change in behaviours. Although anxiety, as assessed by the HADS-A questionnaire, did not alter, a significant fall in depression was measured using the HADS-D questionnaire. Although the mean PAID score fell slightly, and four rather than five people had PAID scores of > 40, this change did not reach significance. [Note added in revision: since we submitted the final report, 12-month data (beyond the scope of the work described in this chapter) have been reported.[140]]

TABLE 20 Demographic, biomedical, and anxiety and depression score data for participants in the DAFNE-HART pilot study: baseline and 3 months' follow-up

Characteristic	Baseline	3 months	*n* with paired data	*p*-value
HbA_{1c} (%), mean (SD)	7.8 (1.2)	7.7 (1.1)	23	0.699
HbA_{1c} (mmol/mol), mean (SD)	61.3 (13.1)	61.3 (12.2)	23	0.978
Episodes of severe hypoglycaemia in last year, median (range)	3.5 (0–70)	0 (0–40)	23	0.014
Episodes of moderate hypoglycaemia in last 6 weeks, median (range)	14 (0–100)	1 (0–11)	23	< 0.001
Gold score, mean (SD)	5.48 (1.8)	4.38 (2.16)	21	< 0.001
Clark score, mean (SD)	2.9 (0.3)	2.6 ± (0.8)	20	0.049
Ryan score, mean (SD)	948 (831)	372 (466)	20	< 0.001 (chi-squared)
CGM:[a] glucose < 3 mmo/l (episodes per week), day/night, mean (SD)	4.2 (5.4)/ 1.5 (1.6)	2.8 (3.6)/ 1.5 (2.0)	17	0.73/0.77
CGM:[a] mean duration of episodes < 3 mmol/l (minutes), day/night, mean (SD)	83 (59)/ 76 (106)	32 (43)/ 123 (159)	20	0.001/0.30
CGM:[a] total duration of episodes < 3mmol/l (minutes), day/night, mean (SD)	284 (295)/ 140 (207)	251 (409)/ 188 (288)	17	0.33/0.77
HADS-A score, mean (SD)	5.8 (4.6)	6.2 (5.0)	23	0.46
HADS-D score, mean (SD)	5.4 (4.9)	4.6 (4.3)	23	0.04
PAID score, mean (SD)	29.8 (21.7)	27.5 (20.4)	23	0.17
ALBGS score (behaviour), mean (SD)	39.5 (9.9)	32.3 (16.7)	23	0.029
ALBGS score (worry), mean (SD)	49.1 (15.9)	40.3 (20.8)	23	0.072
Hyperglycaemia avoidance score (behaviour), mean (SD)	30.3 (6.5)	28.3 (5.2)	21	0.192
Hyperglycaemia avoidance score (worry), mean (SD)	32.2 (8.9)	29.3 (8.9)	21	0.024

ALBGS, Adult Low Blood Glucose Survey.
a CGM: day 06.00 to 24.00; night 24.00 to 06.00.

Qualitative substudy

Decliners

A total of 17 patients who declined to take part in the pilot intervention were interviewed. Details of the decliner sample are provided in *Table 21*.

Attenders

Of the 24 patients who took part in the pilot intervention, 21 were interviewed. One patient was unavailable for an interview and the qualitative research team were unable to contact the two remaining patients. Details of the attender sample are provided in *Table 22*.

Family members

In total, 24 family members opted into the study and were interviewed, 12 of whom were related to a patient who had declined and 12 of whom were related to a patient who had participated in the study. The final sample comprised 18 partners (12 women, six men; mean (SD) age 51.4 (SD 11.2) years, range 26–72 years), three parents [all women; mean (SD) age 60.7 (SD 10.1) years, range 49–66 years] and three adult children [two women, one man; mean (SD) age 25.7 (SD 6.0) years, range 20–32 years].

Key findings from the qualitative substudy are structured under the four study aims

1. *Patients' experiences of living with hypoglycaemia unawareness and its impact on their everyday lives*. Both decliners and course attenders presented very similar accounts of their experiences of living with hypoglycaemia unawareness and the impact of hypoglycaemia unawareness on their everyday lives before being approached to take part in the pilot intervention. As well as highlighting some of the unhelpful psychological attitudes described by Rogers *et al.*[120] in their earlier qualitative study with patients with hypoglycaemia unawareness, patients in the current study talked in-depth about the various ways in which hypoglycaemia unawareness had had a detrimental impact on their lives.[141] In some cases this included having to give up work after experiencing severe hypoglycaemic episodes that had endangered their own safety and/or the safety of others in the workplace. Some patients also described restricting physical activity, curtailing travel and/or allowing elevated blood glucose levels to limit the impact of, and consequences arising from, hypoglycaemia unawareness. In extreme cases patients had become fearful of leaving their own home and/or worried when partners and other family members left them on their own.[141] Patients also described a heavy reliance on family members to help them detect and treat hypoglycaemia because of their own inability to recognise that their blood glucose levels were becoming low. Although the support of family was often appreciated,

TABLE 21 Demographic characteristics of the 17 patients who declined to take part in DAFNE-HART but who agreed to participate in an interview to discuss their reasons for declining

Characteristic	Value
Age (years), mean (SD), range	46.5 (11.9), 26–63
Gender, female, *n* (%)	11 (64.7)
Diabetes duration at recruitment (years), mean (SD), range	30.4 (10.3), 16–47

TABLE 22 Demographic characteristics of the 21 patients who took part in DAFNE-HART and were interviewed

Characteristic	Value
Age (years), mean (SD), range	54 (8.3), 40–73
Gender, female, *n* (%)	10 (47.6)
Diabetes duration at recruitment (years), mean (SD), range	30.3 (12.4), 6–50

some resented their dependency on others, and others described behaving in irrational, argumentative and sometimes violent ways when family members attempted to help them detect and treat hypoglycaemia. Some patients also indicated that they worried less about having hypoglycaemia unawareness and made less stringent efforts to detect/pre-empt hypoglycaemia when family members were present to act as a 'safety net'.[141] As indicated earlier, patients' accounts of the involvement of family members prompted a decision to expand sampling in the qualitative substudy so that the perspectives and views of family members could be considered directly. This decision was also made because patients' accounts suggested that family members might have unrecognised information and support needs that could be taken into account in the development or refinement of future psychoeducational interventions.

2. *Patients' reasons for declining to take part in the pilot intervention*. The majority of decliners indicated that they would have liked to have attended the pilot intervention but had been unable to do so for practical and logistical reasons. Most typically, patients described difficulties with having time off work or having time away away from caring/family responsibilities to participate in what was seen as a lengthy course requiring a considerable time commitment. Other logistical barriers included course dates conflicting with other commitments, such as having to attend elective surgery; already taking part in another research study; and difficulties travelling to the course. It is noteworthy that travel was highlighted as a particular problem by patients who, by virtue of having become hypoglycaemia unaware, had lost confidence in leaving their own home. Other psychological barriers were also apparent in some patients' accounts, including a belief that hypoglycaemia unawareness was an inevitable side effect of insulin treatment and/or of having had diabetes for a long time (and hence a condition that could not be reversed); some patients also conveyed anxieties that attending the course would require them to elevate their blood glucose levels and thereby increase their risk of long-term complications. In sum, although logistical issues and considerations featured heavily in these patients' accounts, there was some indication that they were sometimes underlined by more complex psychological issues.
3. *Course attendees' reasons for attendance, likes and dislikes of the pilot intervention and views about how the course might be improved*. Most attenders regarded themselves as likely to benefit from the intervention, although, in advance of the course, most had limited expectations of what the course would actually achieve. In some cases this was because of a belief, also conveyed by decliners, that hypoglycaemia unawareness was an inevitable consequence of ageing/insulin treatment; other patients also reported unsuccessful attempts to address their hypoglycaemia unawareness in the past.[141] Indeed, some indicated that their primary motivation for attending the course was to support and please their health-care providers. Irrespective of their initial motivations, having attended the pilot intervention, all patients highlighted 'modest' and 'gentle' behavioural and emotional changes and benefits. Key among these were heightened/renewed use of SMBG to detect hypoglycaemia (and an increased confidence arising from knowing what their blood glucose levels were); increased/new recognition of cues and signs that could signal that blood glucose levels were becoming low; and an increased recognition of the importance of attending to hypoglycaemia, if detected promptly. Patients also highlighted subsidiary benefits from taking part in the pilot intervention, most typically how attending a diabetes-related course had resulted in a renewed focus on their disease; educational top-ups, such as retraining in CP counting, were also appreciated by some, especially among those for whom several years had elapsed since they had attended a DAFNE course. Although in general patients were very positive about the course and said that they would recommend it to others, they made various recommendations for fine-turning the format and content of the course. These data will be further analysed and used by the DAFNE-HART team to inform possible revisions to the course curriculum before its use in a future RCT.

4. *Family members' experiences of living with, and caring for, people with hypoglycaemia unawareness, the impact of hypoglycaemia unawareness on their own lives and their information and support needs*. All family members had restricted their own lives as they saw patients as being reliant on them to help them detect and help treat hypoglycaemia, especially before attending the pilot intervention.[142] Family members described themselves as being in a constant state of alert so that they could pick up on cues that their relative's blood glucose levels were dropping. Many also described being fearful for their relative's safety if he or she was left alone, these concerns having often been precipitated by distressing events such as returning home and finding the person with hypoglycaemia unawareness collapsed on the floor. As patients could act in argumentative, irrational and sometimes violent ways when hypoglycaemic, family members also worried about their own safety and the safety of their children and grandchildren.[142] Argumentative and aggressive behaviour could also make family members' attempts to help with treatment administration very difficult. Over time, caring for a person with hypoglycaemia unawareness was described as having had a detrimental impact on family members' own lives; some, for instance, reported exhaustion arising from constantly worrying about the person with hypoglycaemia unawareness and/or very poor, interrupted sleep because of their worries that the person with hypoglycaemia unawareness would slip into a coma or exhibit violent behaviour towards them during the night. Others described neglecting their own health and careers to fulfil their monitoring and caring responsibilities. Anger and resentment was common in family members' accounts, sometimes accompanied by a sense of guilt arising from the recognition that, when experiencing hypoglycaemia, patients could not be held responsible for their mood and behavioural changes.[142] Very few family members reported having ever been asked by a health professional how they were coping and if they needed information and support. All indicated a need for emotional support from people in similar situations to themselves and advice on how to help administer treatment when patients were hypoglycaemic and acting in argumentative ways,[142] and all were supportive of an intervention that could help patients address hypoglycaemia unawareness. Family members of patients who attended the pilot intervention highlighted similar behavioural and emotional changes to those noted by patients. Some concerns were raised, however, that patients would find it difficult to sustain these changes over time.

Discussion and conclusions

In this collaborative study we have developed a new intervention to address recalcitrant, problematic hypoglycaemia in people with type 1 diabetes who are already trained in self-adjustment of insulin doses around a flexible lifestyle. We present here the methodology and the results of the pilot study of the intervention. Although this is a pilot/feasibility study and we obtained outcome data only 3 months after completion of the study, we believe we can support the following assertions:

1. We can successfully identify a group of people with type 1 diabetes who have persistent and apparently intractable problems with hypoglycaemia despite completing structured education in flexible insulin therapy, using a course that is documented to improve hypoglycaemia awareness and reduce severe hypoglycaemia. Our patient group showed several characteristic features associated with impaired hypoglycaemia awareness.[4,143] Compared with people undertaking DAFNE education for the first time in the UK, they were older and had a longer duration of diabetes. They also had a much higher background rate of severe hypoglycaemia (*Figure 6*).
2. We have described a methodology that allowed us to document our subjects' hypoglycaemia experience quantitatively in a robust way that allows for data collection in multiple centres and allows us to measure the impact of an intervention targeting reducing hypoglycaemia problems.
3. Our intervention was acceptable to the target patient group. We have not yet completed an analysis of participants' reflections on the course, collected at 2 weeks, but there were no dropouts once the courses had begun.

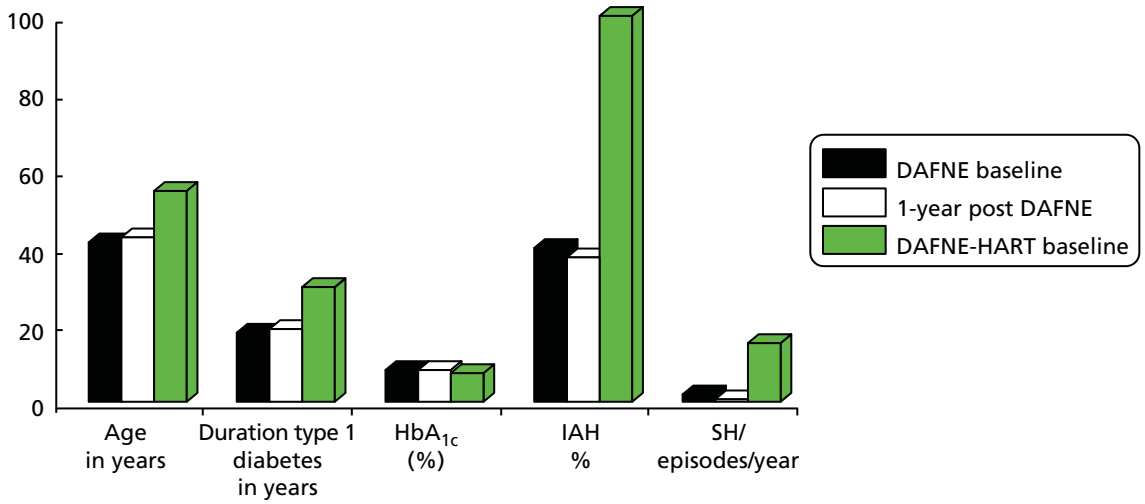

FIGURE 6 Comparison of the DAFNE-HART population with the UK DAFNE population. Baseline characteristics of the DAFNE-HART cohort (green) compared with data from 639 people with type 1 diabetes before (black) and 1 year after (white) conventional DAFNE training in 29 UK centres. The DAFNE-HART cohort are older and have a longer duration of diabetes. Their HbA_{1c} levels are not dissimilar from those in the 1-year post-DAFNE group but, in conjunction with 100% impaired awareness of hypoglycaemia (IAH), they have a much higher rate of severe hypoglycaemia (SH), similar to the data reported by Hopkins *et al.*[14]

4. Our intervention was deliverable by diabetes educators, admittedly already experienced in delivering the conventional DAFNE teaching programme (and all experienced in the management of adults who have problematic hypoglycaemia) in a small group setting, supported by a clinical psychologist.
5. The analysis of the 3 month post-course data indicates a significant degree of success of the course, with statistically significant reductions in moderate hypoglycaemic events over a 6-week period and the annualised rate of severe hypoglycaemia and improvements in ratings of hypoglycaemia awareness, and without any indication of a deterioration in mean blood glucose concentrations.
6. We have collected rich data on patients' recommendations for making (modest) improvements to the course, which, together with input from the educators who delivered the course, will allow us to refine it before it is taken forward in a future full-scale RCT.

Our data adds to the growing evidence for cognitive barriers to the successful management of significantly impaired hypoglycaemia awareness in type 1 diabetes. There is some evidence in the literature that people with this problem may be less perturbed by their condition,[120] and certainly less able to reverse it,[119] than the health-care professionals supporting them. Mühlhauser *et al.*[144] first described this in relation to severe hypoglycaemia risk in a seminal prospective study of hypoglycaemia. Our new qualitative data suggest that, in many cases, the issue may be a belief that the condition of hypoglycaemia unawareness is inevitable and irreversible or it may involve making choices that the hypoglycaemia-unaware person is unwilling to make (such as maintaining a high glucose level). We also detected more distress about their condition in the hypoglycaemia-unaware people than these earlier studies. Nevertheless, all of the qualitative work supported the development of an intervention focused on enhancing motivation and providing psychological support for behaviour change. The small but significant reduction in worry about hyperglycaemia (often quoted as a barrier to hypoglycaemia prevention) and in behaviours, such as not treating hypoglycaemic episodes appropriately or giving too much insulin, suggests that our course was beginning to address some significant barriers to hypoglycaemia avoidance in our patients. It is worth noting, however, that, despite the earlier literature describing that people with impaired awareness were not overtly worried by their condition, in our data the scores on the anxiety and depression questionnaires were higher than we would expect. For comparison, in a published audit of conventional DAFNE education from the UK DAFNE database, the scores for people 1 year after DAFNE were 4.2 for HADS-D, 4.6 for HADS-A and 16.7 for PAID compared with scores for DAFNE-HART patients pre course of 5.9, 5.3 and 30.3 respectively.[14] These data suggest significant anxiety, depressed mood and diabetes-related stress in our DAFNE-HART patients, which was addressed at least in part by participation in the pilot.

Parenthetically, it is worth considering that patients' views that treating hypoglycaemia unawareness is likely to be difficult may be reinforced not just by their own experiences but also by health-care professionals sharing those beliefs, and the DAFNE-HART pilot study notably addressed this in the educator training.

The third part of a triangle of people affected by hypoglycaemia unawareness are the relatives of the patients. Our interviews with relatives make an even more powerful case for interventions such as DAFNE-HART to be taken forward, as our study has powerfully demonstrated how hypoglycaemia unawareness not only affects the lives of patients with the condition but also has a major impact on the lives, health and well-being of their families. Addressing hypoglycaemia unawareness through interventions such as DAFNE-HART is likely to have clinical and psychosocial benefits (and ultimately provide savings for the NHS) that extend beyond the patient. Our findings thus also suggest that, when evaluating DAFNE-HART in a future RCT, it may be prudent and beneficial to include an assessment of family members' QoL among the outcome measures – and to consider the needs of the patients' families in the intervention.

We cannot yet be sure which parts of the DAFNE-HART course were most beneficial. We have collected data on self-management behaviours related to blood glucose control and also conducted semistructured interviews with patients after completion of the study. These data will be enhanced by further data collection at 1 year (ethical application pending). Additional data will be available from an ongoing analysis of semistructured interviews with the participants within 2 weeks of completion of the study, which specifically asked for their thoughts on the intervention, and from a post-course debriefing meeting with educators to collect their feedback on what worked well and what could be improved in the curriculum. It will be important to consider this input in converting the pilot into a finalised curriculum for a RCT.

Our study has some obvious limitations. It was a pilot study and was therefore not powered to detect all relevant factors. As we did not include a control group who did not undergo the intervention we cannot check the attribution of benefit to the intervention itself. However, we feel that the intervention has developed sufficiently to create a final draft curriculum and present it for ethical approval for a fully powered RCT. We will use the data from the qualitative studies and debriefings to refine the intervention. At the same time we have also identified a need for a support package for the families of our patients.

Chapter 7 An evaluation of user involvement in the DAFNE research programme

Abstract

The DAFNE research programme is committed to the principles of user involvement in research. DAFNE graduates were represented on the steering group of the various workstreams by way of the DUAG. A longitudinal evaluation of the impact of DUAG members on the work of the DAFNE research programme was undertaken, and this included an evaluation of the training that was provided to DUAG members at the start of their involvement. The evaluation used a mixed-methods approach that included (1) semistructured in-depth interviews with key informants and (2) non-participant observation at DAFNE meetings at which DUAG members were present. Discussion centres around six broad topic areas: (1) set-up of DUAG and the characteristics of DUAG members; (2) a lack of user involvement in the development of the grant application; (3) the induction and training event for DUAG members; (4) support for DUAG members attending research meetings; (5) practicalities of DUAG attendance at research meetings; and (6) the impact of DUAG involvement on specific work packages and the DAFNE research programme as a whole.

Background

The DAFNE grant application to the NIHR outlined a clear commitment to active and meaningful patient and public involvement (PPI) as part of the research, with plans for two DAFNE graduates to attend each workstream's steering group meetings, to provide lay input into the conduct of the research. When the grant was funded, PPI was a relatively new initiative, having recently been recognised as a priority for NIHR-funded research. As such, there was little or no involvement of relevant patients (i.e. DAFNE graduates) within the development and design of the study.

The DAFNE programme itself benefited from a large number of active DAFNE graduates who had formed a DUG. Members of the DUG were interested in being involved, as patient representatives, in the DAFNE research study. A decision was made to invite DAFNE graduates to apply for this opportunity, with a series of national adverts being placed to attract participants. A total of 21 applications were received and all of the applicants were interviewed, with 15 originally selected to form the DUAG. The purpose of the DUAG is to promote and support the continuing development of the DAFNE programme. The DUAG acts as a critical friend to the National DAFNE Executive Group and the Central DAFNE team.

Recognising the need to provide training and support to DAFNE graduates to facilitate their involvement in the work of the research programme,[145] a 2-day event was arranged for all new DUAG members. This included a training programme on the research being undertaken and the research methods being utilised and giving participants the option of selecting the workstreams of the research programme that interested them most.

To contribute to the growing body of literature examining the impact of service users on research processes and outcomes,[146–149] and to provide learning points to guide user involvement in future NIHR-funded programme grants, the chief investigator of the DAFNE research programme commissioned a research team at the University of Sheffield to undertake a longitudinal qualitative evaluation of the impact of DUAG members on the work of the DAFNE research programme, and of the training that DUAG members received to facilitate their involvement.

Methodology for the evaluation

Guided by a recent evaluation of user involvement in the UK Clinical Research Collaboration,[150] the evaluation employed a longitudinal, mixed-methods design. The evaluation was informed by a number of conceptual frameworks in the user involvement literature including:

- The consensus-derived principles and indicators of successful service user involvement in NHS research.[151,152]
- A study that evaluated training packages for users and proposed good practice guidance.[145]
- Recent literature reviews on the impact of user involvement in health research,[148,149] which proposed multidimensional frameworks for describing the impact of users on research.
- Recent reviews of user involvement in the design of health research[153] and the involvement of users in the design and conduct of clinical trials.[154] Both of these studies highlighted the specific contributions that users can make to the design and conduct of research, and the tensions and facilitating strategies that have been identified in the literature.

The evaluation employed two main methods:

- semistructured in-depth interviews[155] with key informants, including DUAG members, DAFNE researchers, chairs of the various DAFNE committees, the facilitators of the training programme delivered to DUAG members and the programme manager
- non-participant observation[156] at DAFNE meetings at which DUAG members were present.

With regard to the interviews, a constructivist methodology was adopted,[157] with the intention of creating a joint understanding, shared by the researcher and the participant, of each participant's experiences. Within constructivist research, interviewing is a creative process in which the interactions and conversations between the interviewer and the respondent produce statements and formulations that draw on the knowledge and experience of both participants. Data analysis is inductive and emergent findings are fed into subsequent interviews to identify points of consensus and divergence.

Ethical approval

A favourable ethical opinion was obtained from the research ethics committee of ScHARR, University of Sheffield. Written informed consent was obtained from all of the participants in the user involvement evaluation.

Data collection

In total, 25 semistructured interviews were undertaken with key informants at three time points: at baseline ($n = 11$), at follow-up, approximately half-way through the evaluation period ($n = 5$), and at the end of the research programme ($n = 9$) (*Table 23*). An interview schedule was developed for each interview cycle and permission was sought from each participant for his/her interview to be tape-recorded. Each interview was transcribed verbatim and a copy sent to participants for information.

A total of eleven DAFNE research programme meetings, at which at least one DUAG member was present, were observed, along with a teleconference (see *Table 23*). At these meetings, contributions made by DUAG members, and their verbal interactions with researchers, were noted by a member of the evaluation team. Immediately after each meeting, the observer's field notes of the meeting were written up and a copy sent to each DUAG member to check for accuracy.

The characteristics of the DUAG members are provided in *Table 24*.

TABLE 23 Data collection points for the evaluation of user involvement

Interviews with key stakeholder groups			Non-participant observation
Baseline interviews ($n = 11$)	**Follow-up interviews ($n = 5$)**	**Final interviews ($n = 9$)**	**DAFNE meetings with at least one DUAG member**
Chair of the Research Group	Chair of the Research Group	Chair of the Research Group	Research Group meetings:
Chair of the Database Group	Chair of the Database Group	Programme Manager	10 June 2010 – one DUAG member
Chair of the DAFNE-HART Group	One DUAG member	Four DUAG members	9 June 2011 – two DUAG members
Three DUAG members (who sit on the Research Group, the Database Group and the DAFNE-HART Group)	Health professional on the Research Group	Researcher on the Database Group	5 October 2011 – one DUAG member
Health professional on the Research Group	Researcher on the Database Group	Chair of the DAFNE-HART Group	22 February 2012 – two DUAG members
Researcher on the Database Group		Health professional on the Research Group	21 June 2012 – two DUAG members
Programme Manager			2 November 2012 – two DUAG members
Two DUAG training facilitators			Database Group meetings:
			2 June 2011 – one DUAG member
			22 February 2012 – two DUAG members
			DAFNE-HART meetings:
			14 January 2011 – two DUAG members
			11 May 2011 – one DUAG member
			5 October 2011 – one DUAG member
			Teleconference 15 April 2011 – two DUAG members

TABLE 24 Information on characteristics of DUAG members

DUAG member	Gender	Date attended DAFNE course	Prepared to participate in		Type of diabetes	Background
			DAFNE Executive	User Research Group		
DM1	Male	2007	Yes	Yes	1	Company director
DM2	Female	2008	Yes	Yes	–	Administrator
DM3	Male	2003	Yes	Yes	1	Educator
DM4	Male	2004	Yes	Yes	2	Solicitor
DM5	Male	2008	Yes	No	–	Information technology
DM6	Male	2008	Yes	Yes	2	Company director
DM7	Female	2008	No	Yes	–	Retired journalist
DM8	Male	2008	Yes	Yes	1	Company vice-president
DM9	Male	2007	Yes	Yes	1	Company director
DM10	Male	2007	Yes	No	1	Director
DM11	Male	2007	Yes	Yes	1	Programme manager
DM12	Male	2007	Yes	Yes	1	Retired service manager
DM13	Female	2006	Yes	Yes	1	Student
DM14	Female	2008	Yes	Yes	1	Retired civil servant
DM15	Female	2008	Yes	Yes	1	Retired nurse
DM16	Male	Not known	Yes	Yes	1	Director
DM17	Male	Not known	Yes	Yes	1	Retired

DM, DUAG member.

Data analysis method

Two researchers were involved in the analysis of the evaluation data, to strengthen the credibility and trustworthiness of the findings.

The 'framework' method was employed to guide the analysis of the in-depth interviews and the field notes from the non-participant observation of DAFNE research meetings.[158] The framework method is an analytical approach to applied policy research that is consistent with a range of qualitative approaches, including constructivism.[155] Although an iterative dynamic process, the framework method has the following key stages:[158] familiarisation with the data, identifying a thematic framework, indexing and charting of the data using the thematic framework and mapping an interpretation.

Findings

The findings section is divided into six main topic areas. Throughout this section, quotes from interviewees are presented to illustrate key points. Each quote is accompanied by a code, describing the role played in the research programme by the interviewee. The codes are as follows: DM – DUAG member; PM – programme manager; CRG – Chair of the DAFNE Research Group; CDG – Chair of the Database Group; TF – training facilitator; MRG – member of the Research Group.

Set up of the DAFNE Users Action Group and the characteristics of DAFNE Users Action Group members

The process of selecting members from the existing DUG was extremely efficient and well received by those who went on to form the DUAG. However, the formal process utilised to select representatives appeared to attract members who were largely from a professional background and who were comfortable with the concept of applying for posts and participating in subsequent interviews (see *Table 24*). Of these 17 DUAG members, four (DM6, DM8, DM16 and DM17) were actively involved in the work of the DAFNE research programme and were interviewed as part of the evaluation of their impact.

One DUAG member agreed that DUAG members were not representative of typical DAFNE graduates:

> *I agree entirely that we are atypical, and you know it is sort of self-selecting, isn't it? You wouldn't have a committee of highly trained professionals and a DUAG member who was not educated or sufficiently intelligent, with the right perspective, and who would probably not be able to contribute effectively in that environment. So you have got the dilemma that the DAFNE graduates that you have got and the DUAG members are not going to be typical.*
>
> *DM16*

This dilemma presented a challenge for the research team in that the DUAG members actively involved in the research were those who had largely benefitted from the DAFNE programme and who were successfully managing their diabetes, whereas the focus of the DAFNE research programme was primarily on DAFNE graduates who were struggling to manage their condition. The following quote from a DUAG member illustrates this point very clearly:

> *But what shocked me from that meeting we went to the other day in Sheffield, was that basically 50% of type 1 diabetics can't cope with the numbers, and actually managing their diabetes. And how you deal with that half [of type 1 diabetics] would seriously improve the figures. Well I mean, you have to count your carbohydrate, it is a fairly straightforward mathematics, but it doesn't say much for the numerical literacy of our population.*
>
> *DM8*

A lack of user involvement in the development of the grant application

Although the grant application set out a strong commitment, on the part of the research team, to user involvement, DAFNE graduates were not involved in the development of the grant application itself, nor were they involved in the design of most of the workstreams. This lack of involvement at the outset of grant development was seen as a disadvantage:

> *I think it would probably have added weight to the grant application if as well as it being based purely on [the work of] academics and medical people, there were some lay people on it as well.*
>
> *DM6*

A key issue that DUAG members were not able to influence during the grant-writing stage was the choice of outcomes on which the impact of the various quantitative components of the study (DAFNE 5 × 1-day and DAFNE-HART trials) would be evaluated. For DUAG members, the key outcome on which the DAFNE programme should be evaluated is QoL, whereas the main outcome for the quantitative workstreams was HbA_{1c}:

> *For us, quality of life is the key aspect. HbA_{1c} is an abstract figure that doesn't tell me how I feel and where I am in my life and in itself it is a fairly meaningless figure.*
>
> *DM8*

The induction and training event for DAFNE Users Action Group members

The rationale for the 2-day training event for DUAG members was clearly articulated:

> *It was clear that in order to enable those users not to be at too great a disadvantage during the meetings, and that they would understand the process and would understand a little more about what goes on in a research project, it was clear that we would need to offer some training to them in research methods and the projects themselves.*
>
> *PM*

However, the 2-day event was seen in retrospect as being hugely ambitious with unrealistic expectations of those attending. There was no recognition that the DUAG members required time to get to know each other and to establish roles and objectives. The training programme focused ultimately only on information about DAFNE and what was expected of the group. As a result, the event failed to deliver on the initial objectives of providing an overview of the research and of research methodology:

> *I think that the members were critical about the amount of [research-related] information that was being given and they felt they weren't ready at that level at the time. I do think actually we did ask DUAG what they wanted in the training, but they didn't know. I think that was the problem. They didn't know what they wanted in the training because there were very few of them if any had ever had an experience of this. So that is one of the difficulties is that they might not know themselves what they actually need.*
>
> *PM*

Describing the complexity of a Programme Grant for Applied Research to those outside the study team was a major challenge, as participants failed to grasp how each work package was linked and, more importantly, what was expected of them:

> *Well to be honest, even though I am not involved in research, I found it quite interesting. So to me, it wasn't a problem. Other members of the group, I think a few of them, it flew over the top to be quite blunt.*
>
> *DM6*

> *I haven't got a map of how the projects fit together and how the organisations work together, how each part is funded and so on and so forth.*
>
> *DM16*

The facilitators adapted the planned programme of training to enable a greater amount of time for members to familiarise themselves with the research and each other. At the end of day 2, roles for the group were established, although some expressed uncertainty as to what they were expected to do. When feasible, two DUAG members were selected to attend research meetings of the various workstreams together (however, observation at research meetings revealed that there were few occasions when more than one DUAG member was present at a meeting):

> *I think the [training] programme was too ambitious and expected too much of them . . . It was designed as an intensive 2-day, everything you need to know about DAFNE, set the group up, workstreams, who is going to be sitting on the different groups, who is going to be accountable, who is going to be reporting to who and you will also know everything about research that you will need to know to be a service user, in 2 days. And it just wasn't realistic.*
>
> *TF*

It was interesting to note that the DUAG members had issues or ideas that they wanted to discuss that were outside the remit of DUAG; thus, from the researchers' perspective, this was interpreted as DUAG members bringing their own agendas to the event. This resulted in a certain degree of frustration among the DAFNE research team, who felt that 'this wasn't what the group was meant to be doing', but perhaps this was an inevitable consequence of the involvement of a highly professional group who bring their own life experiences to such an event.

Support for DAFNE Users Action Group members attending research meetings

A particularly positive aspect of the DAFNE programme, from the DUAG members' perspective, was the high level of support provided to those attending the research meetings. A lot of effort was made by the research team to ensure that DUAG members had pre- and post-meeting briefings, were introduced at all meetings and were actively involved in discussions:

> *I must admit that I had quite a lot of briefings. I had spoken to [the programme manager] who had briefed me quite well, and before the meetings, I met with the chairman and we both introduced ourselves, so I think as far as me joining the group, it was well organised and I was as well briefed as I could have been.*
>
> *DM6*

Practicalities of DAFNE Users Action Group attendance at research meetings

The DUAG members were geographically dispersed, which impacted on their ability to attend research meetings, which were generally held in the north of England:

> *There is one [DUAG member] up north, one in Ireland, and there is one in London and the rest are based in the Home Counties. So yes, I would say it might be a slight leaning towards the Home Counties.*
>
> *DM6*

The DUAG members were not paid for their time for attendance and, despite agreeing to this at early DUAG meetings, it was clearly a barrier for some who had to miss work to attend:

> *I get the feeling that if you were paid for time it would make it a more attractive thing. I actually take unpaid leave from work in order to reduce my time. So that would make it an easier pill to swallow, it would make it more attractive, and other parts of the government have paid in the past for my time, professionally. It would be more attractive than giving my own time at the moment.*
>
> *DM16*

> *The majority of [DUAG members] have other jobs and in the current climate, it is quite difficult sometimes to say to your employer, 'I am going to take a day off'.*
>
> *DM17*

Impact of DAFNE Users Action Group involvement on specific work packages and the DAFNE research programme as a whole

As discussed earlier, the DAFNE research programme was designed and developed without user involvement and user input was delayed, with the DUAG being set up 12 months into the grant. This was seen to have reduced the overall impact that DUAG members were able to have on the work of the DAFNE research programme as a whole:

> *I don't think [DUAG members] contributed as much as I would have hoped, but that may be the processes and structures that we set up.*
>
> *CRG*

> *It takes you a bit of time to actually understand and get a feel for what the various people are talking about. I have never had a problem of not participating in a meeting, but I must admit the first one I went to, I deliberately decided not to say a great deal, but to be there and to listen.*
>
> *DM6*

The first two work packages of the research programme (the psychosocial study and the database) were already under way by the time that DUAG was established, and for some of these early work streams the ability of DUAG to influence their direction was limited. This was particularly evident in the database study, which was a highly technical workstream; as such, it was difficult to engage DUAG members in a meaningful way. The Chair of the Database Group questioned the value of DUAG involvement in the early technical work with which the database workstream was engaged:

> *I just think this particular committee, which has a narrow, technical [remit], I am not sure that it is the best use of their time. I just feel it is not really where patient involvement is going to be all that helpful. I think when it comes to getting data out of the database, then I can see them as having more of a role.*
>
> *CDG*

The psychosocial study was the first workstream to commence and was underway for about 1 year before DUAG members became involved in the work of the DAFNE research programme. As such, there was no user involvement in the design or conduct of this workstream. One DAFNE researcher reflected that the psychosocial study could have benefited from user involvement at the design stage:

> *Because we were trying to look at the treatment mechanisms, we could have got people involved in a brainstorming session at the design stage, and to say 'are there particular things that you think we should be measuring with our questionnaires or asking people about in the interviews?' Helping us to select questionnaire tools and looking at the interview topic guides as well. I think actually advising us on what they thought we should be including would have been really helpful.*
>
> *MRG*

Two workstreams commenced after the establishment of DUAG (the DAFNE 5 × 1-day trial and DAFNE-HART). DUAG members were involved at the start of the DAFNE 5 × 1-day trial and this workstream did benefit from DUAG input before the beginning of data collection. Although DUAG members did not have any influence on the development of the curriculum, one DUAG member interviewed did recall influencing the wording of the information sheet for the DAFNE 5 × 1-day trial by reminding the research team to include a mention of expenses on the information sheet:

> *With regard to the 'five times one' trial, I was on the work group. And there were certain things that, when you are doing research, that a patient can give input. For example, a lot of people were expected to go on these courses and they are going to have to travel there, so there was no mention for example about expenses in the information sheet, and obviously it is quite hard to get people to do research, so that was included, which the researchers had forgotten about, because they were more concerned with the more complex parts of the research aspect.*
>
> *DM8*

From non-participant observation at meetings, it was notable that DUAG members had a significant input into the overall design of the DAFNE-HART workstream. Field notes from observation at DAFNE-HART research meetings revealed that DUAG members had input into (1) the mode of delivery of the curriculum, (2) the inclusion criteria regarding the number of hypoglycaemia episodes that a DAFNE graduate needs to have had to be offered the intervention and (3) the wording of guidance notes to assist those completing data collection instruments.

Other research team members interviewed, when asked to reflect on the research programme as a whole, felt that the input from DUAG members did not meet their expectations, as contributions were often limited to personal experiences and therefore did not reflect the larger DAFNE graduate population. It was felt that DUAG members appeared unable or unwilling to engage with the extended group of DAFNE graduates, through their own networks (such as the DUG or through DAFNE online), and, in addition, a lack of continuity in DUAG attendance at DAFNE research meetings was seen as problematic:

> *One of my big difficulties in reality is that, with the exception of [named DUAG member], who has come along more than once and who actually has made a really good contribution, the other people who participated have been fleeting, which makes it difficult for them and for us.*
>
> *CRG*

Although all those interviewed were generally positive about user involvement and saw it as a 'good thing', it was not seen as being without difficulties. A number of tensions were reported and were also observed at meetings. A particular example of this was the case of a DUAG member suggesting changes to research methodology, which were considered scientifically unfeasible by the research team:

> *[The DUAG member] has commented on some of the practical difficulties of some of the research. He has suggested that certain of the questionnaires seemed significant and he has made some actually quite useful suggestions about how that burden could be alleviated, although interestingly for technical reasons, the social scientists have pointed out that what he wanted probably couldn't happen.*
>
> *CRG*

Discussion

This evaluation contributes to the growing literature on the impact of user involvement on research processes and outcomes[148,149] and is one of the very few longitudinal evaluations of public involvement in a research study so far reported.[147,159]

Commitment to the principles of user involvement

All interviewees expressed strong support for the principles of user involvement. Researchers interviewed early on in the evaluation discussed the positive, practical impacts that they expected DUAG members could have on the research, such as ensuring that research participants are not overburdened and improving the wording of participant information material. These expected positive impacts are referred to in the literature as 'consequentialist' arguments in favour of user involvement.[154] The consequentialist argument states that user involvement has the potential to improve the quality, relevance and impact of health research while also improving the transparency of the process and the accountability to the wider community of the researchers themselves.[154] Most researchers interviewed expected that DUAG involvement would have such positive consequentialist impacts on the DAFNE research programme.

DAFNE Users Action Group members' motivations for getting involved and their experiential knowledge

The DAFNE members who were interviewed at the start of the evaluation stated that they were actively involved in the DAFNE research programme as a way of giving something back, after the support and help that they had received to manage their diabetes through the DAFNE programme. 'Giving something back' resonates with the reasons given for active involvement in a recent study of the motivations of lay people for their active involvement in research.[160]

Through observation at DAFNE research meetings, it was noted that DUAG members concentrated their input at these meetings on issues mainly relating to their lived experience as a diabetic and a DAFNE graduate, and how the research might impact on other DAFNE graduates. This appreciation by DUAG members of their own 'experiential knowledge', and how this might add value to the DAFNE research programme, resonates with one of the main rationales for user involvement in research, which is the

'epistemological argument'. The epistemological argument states that service users have direct knowledge of their own illness, disease or health condition that can be of benefit to researchers, who may not have first-hand experience themselves of the illness, disease or health condition that they are researching.[161] DUAG members were therefore expecting that their experiential knowledge would add value to the DAFNE research programme. Although this personal experiential knowledge was seen to be important by the researchers interviewed in this evaluation, there were concerns expressed that the DUAG members actively involved in the research programme were not representative of the wider community of DAFNE graduates and that more should have been done to enable DUAG members to engage with their wider community either through the DUG or through DAFNE online.

Reflections on the impact of DAFNE Users Action Group involvement

The actual impact of DUAG involvement was seen to vary across the different workstreams of the DAFNE research programme. For example, the Chair of the Database Group queried the value of DUAG involvement in the early stages of the workstream. This contrasted with the more tangible input of DUAG members into the work of DAFNE-HART and the DAFNE 5 × 1-day trial, as discussed earlier. The specific contributions made by DUAG members to the DAFNE-HART and DAFNE 5 × 1-day workstreams (in terms of helping to word participant information material and contributing to discussions about inclusion and exclusion criteria) resonate strongly with recent literature reviews that have synthesised, from published case examples, the key contributions that service users can make to the design and delivery of research, including clinical trials.[153,154]

Interviewees did not identify any serious negative impacts of actively involving DUAG members in the work of the DAFNE research programme. However, an interviewee did highlight a tension that occurred at one research meeting when a suggested word change to a validated questionnaire, made by the DUAG member, was not endorsed by the researchers, who thought that this suggestion would compromise the scientific validity of the questionnaire. This finding mirrors an account in the user involvement literature of an outcome identified by service users as being important during the development of a grant application for a clinical trial, which caused difficulty for the research team because no validated measures existed at that time to assess the particular outcome that the service users had identified.[162]

Despite some positive impacts being reported in two of the workstreams, the evaluation revealed that the impact of DUAG members across the whole of the DAFNE research programme was not maximised. First, this was because DAFNE graduates were not involved at the beginning of the research process during the initial stage of grant writing. DUAG members expressed dismay at this, as they were not able to influence the choice of main outcome measures for the quantitative workstreams in the research programme. INVOLVE, the body that promotes PPI in research in England, recommends that researchers involve the public at an early stage in the research cycle, as early involvement enables the public to develop a greater sense of shared ownership of the research (see www.invo.org.uk/involve-people-as-early-as-possible/; accessed 2 October 2014). This issue has been fed back to the chief investigator as part of the evaluation process and has been taken onboard. For example, a further grant to develop the work of the DAFNE research programme is currently being planned and the grant-writing process will fully involve DUAG members. Second, it was noted that there were continuity problems whereby it proved difficult for at least two DUAG members to attend every DAFNE research meeting. The issue of continuity problems with regard to users attending research meetings has recently been highlighted in reviews of the literature on user involvement in clinical trials[154] and user involvement in systematic reviews.[161]

Reflections on the training and support provided to DAFNE Users Action Group members

Reflecting best practice guidance on user involvement,[145,151] DUAG members were offered training to facilitate their involvement in the DAFNE research process. Although largely appreciated by the DUAG members interviewed, the training that was offered was criticised as being too intensive and too ambitious. Any future training offered to DUAG members (e.g. if funding is obtained for a further programme grant) will be informed by new guidance on training and support provided by INVOLVE[163]

and the generic training package on user involvement and research currently being piloted by the NIHR Cancer Research Network and Macmillan Cancer Support (see http://learnzone.org.uk/downloads/Building%20Research%20Partnerships%20-%202013%20Report%20-%20Macmillan%20NIHR%20CRN.pdf; accessed 2 October 2014).

The DAFNE Group members were strongly supportive of the other forms of support and guidance provided by the DAFNE research programme's project office. For example, they were appreciative of the offer of pre- and post-meeting briefings and the offer of overnight accommodation. However, disagreement was noted among the DUAG members interviewed with regard to whether or not they wish to receive payment for time over and above expenses. INVOLVE's position is that users who are actively involved in research should be paid, as this helps to build more equal power relationships within the research process.[164] If a further grant is to be developed to take forward the work of the DAFNE research programme, thought should be given to whether or not payment for DUAG members' time should be costed into the grant.

Discussion and conclusions

The findings of this evaluation have a number of implications for the delivery of user involvement within NIHR programme grants. NIHR programme grants are complex research projects that involve a number of different workstreams. Not every workstream is necessarily going to benefit from user involvement and the present evaluation found that users had a greater impact on some workstreams than others. Research groups submitting programme grant applications need to therefore consider very carefully which workstreams will benefit most from the active involvement of service users and the experiential knowledge that they bring to the research process. Users should not be involved in workstreams within NIHR programme grants that they have no tangible impact on – as this can be seen as tokenistic and, ultimately, unethical.

It was found that user involvement in the DAFNE research programme was not maximised because DAFNE graduates were not involved at the very beginning of the research cycle, at the grant-writing stage. Research teams planning programme grants should ensure that they involve relevant service users in the design and development of their grant application. Advice and support for involving users in research design are available to researchers in England through the 10 regional NIHR Research Design Services.[165]

Most NIHR funding streams, including programme grants, expect applicants to detail the extent of training and support that will be provided by the research team to service users. Findings from this evaluation suggest that, if a panel of service users is to be established for a programme grant, with different users assigned to different workstreams within the programme, it is preferable to bring the group together first and to deliver training on research methods later, on a separate occasion. This allows time for the group of users to bond and time for the research team to establish the training needs of the users.

One important component of support for user involvement in research is payment for time. In the DAFNE research programme it was reported that users were not paid for their time; they received out-of-pocket expenses only. This decision was reached to maintain consistency with the payment policy for users involved in the DAFNE Executive, by agreement and at the request of DUAG. One user interviewed in this evaluation suggested that a lack of payment for time might explain why users were not able to attend all DAFNE research meetings. Investigators planning future programme grants are encouraged, therefore, to ensure that they include costs for users' time as well as their out-of-pocket expenses.

Chapter 8 Health economics of the DAFNE programme

Abstract

Health economics was a cross-cutting workstream of the DAFNE research programme and consisted of five linked substudies: analysis of health-related QoL data collected in the DAFNE research database, development of a health economic model of type 1 diabetes, the re-estimation of the cost-effectiveness of DAFNE education compared with no DAFNE education using the new model, estimation of the cost-effectiveness of 5-week DAFNE education compared with 1-week DAFNE education using the new model and integration of individual psychological and behavioural characteristics into the health economic model. This chapter draws together these five substudies, describing their methods and results in turn. The key messages from the health economics study were that DAFNE education is a cost-effective intervention compared with no structured education, even with limited observed HbA_{1c} benefit, and that the 1-week and 5-week versions of the course have similar cost-effectiveness. Other results include a set of health-related QoL values for people with type 1 diabetes with varying degrees of diabetes-related complications and that predicting HbA_{1c} response to DAFNE education from individuals' psychosocial characteristics and restricting access to training based on these predictions would not be cost-effective. The health economic workstream has produced a flexible patient-level simulation model, the Sheffield Type 1 Diabetes Policy Model, that can be used to answer a multitude of policy questions relating to the treatment and self-management of type 1 diabetes.

Introduction

The DAFNE RCT data[7] have previously been used as part of a cost-effectiveness analysis of structured treatment and teaching programmes for type 1 diabetes.[166] This study suggested that DAFNE was cost-effective over a 10-year time horizon and would pay for itself within 4 years. However, the analysis relied on limited data, did not include macrovascular complications of type 1 diabetes and did not consider costs and effects beyond the 10-year time horizon. The cost-effectiveness of DAFNE education in the UK therefore remains unclear. Updated evidence from the literature and data from the NIHR DAFNE research programme now calls for a more thorough and comprehensive cost-effectiveness analysis of the DAFNE programme. The health economics workstream of the DAFNE NIHR programme grant was devised to update and expand the earlier cost-effectiveness analysis of DAFNE.[166] Further economic evaluation was deemed necessary to address the limitations of this analysis[166] to provide an updated robust estimate of the cost-effectiveness of the original DAFNE programme and to evaluate alternative versions of the programme (e.g. 5-week DAFNE; see *Chapter 4*).

The DAFNE RCT[7] used the Audit of Diabetes-Dependent Quality of Life questionnaire[167] to measure QoL before and after DAFNE education and found that DAFNE education significantly reduced the negative impact that diabetes has on QoL. However, for economic evaluations, NICE[168] recommends that a generic preference-based utility measure is used to measure QoL and the DAFNE RCT did not include such a measure. The current NIHR research programme collected utilities data using the EQ-5D[113] and SF-12 measures [to convert to Short Form questionnaire-6 Dimensions (SF-6D) utilities[169]] in order to estimate the effects of DAFNE on utility-based QoL.

The health economics workstream was divided into three main components: an analysis of utilities (health-related QoL), an economic evaluation alongside the 5-week compared with 1-week DAFNE education RCT and long-term cost-effectiveness modelling to update the previous economic evaluation[166]

and extrapolate results from the 5-week compared with 1-week DAFNE education RCT beyond the time horizon of the trial. The three components of the economic evaluation combined data from the NIHR DAFNE research database, the psychological study and trial-based studies with supporting evidence from published literature to calculate the cost-effectiveness of the developing DAFNE programme and to provide evidence, techniques and infrastructure to evaluate related interventions in the future. The long-term cost-effectiveness modelling was further split into three components: estimating the cost-effectiveness of DAFNE education compared with no DAFNE education, estimating the cost-effectiveness of 5-week compared with 1-week DAFNE education and exploring methods to incorporate patient psychology and behaviour into the economic model.

The current study addressed two RQs: 'What is the cost-effectiveness of the DAFNE programme for the management of type 1 diabetes?' and 'How does DAFNE education affect health-related QoL as measured by utility-based instruments?'

The specific study aims were to:

- estimate the impact of diabetes-related complications on utility-based measures of QoL in adults with type 1 diabetes
- estimate the change in utility after DAFNE education
- explore predictors of change in utility after DAFNE education
- develop a cost-effectiveness model to be used in the current study and to evaluate related interventions in the future
- re-estimate the cost-effectiveness of DAFNE education compared with no DAFNE education
- estimate the cost-effectiveness of 5-week DAFNE education compared with 1-week DAFNE education
- explore methods for modelling patient psychology and behaviour alongside economic outcomes in order to account for psychosocial factors when estimating the cost-effectiveness of DAFNE education.

As there were several components of work involved in the health economics workstream, this chapter is organised by component rather than in the traditional format of 'Introduction', 'Methods', 'Results' and 'Conclusions'. The next section of this chapter will outline the analysis of the utilities data, *Development of the Sheffield Type 1 Diabetes Policy Model* will describe the development of the cost-effectiveness model used to estimate the long-term cost-effectiveness of the DAFNE programme, *Cost-effectiveness of DAFNE education compared with no DAFNE education* and *Cost-effectiveness of 5-week compared with 1-week DAFNE* education will present the results of the cost-effectiveness analyses of DAFNE education compared with no DAFNE education and of the 5 × 1-day DAFNE RCT, respectively, and *Modelling patient psychology and behaviour alongside economic outcomes* will report on the integration of patient behaviour modelling alongside health economic modelling.

Utilities analysis: the impact of diabetes-related complications on utility-based measures of quality of life in adults with type 1 diabetes

Introduction

This substudy sought to provide information that may help populate economic models that consider the cost-effectiveness of interventions for type 1 diabetes. Full details of all the analyses conducted are reported elsewhere.[170] The impact of diabetes-related health states on utility was derived from a baseline and 1- and 2-year follow-up surveys of patients with type 1 diabetes attending the DAFNE structured education programme.

The first aim of this substudy was to consider whether or not existing utility values derived from research on type 2 diabetes patients can be appropriately used within economic models for type 1 patients. We compared the estimated impact of complications in patients with type 1 diabetes from the baseline DAFNE data with three sets of published estimates of the impact of complications on utility values for type 2 diabetes.

The second aim was to explore in more detail the impact of diabetes-related complications, comorbidities and clinical indicators on the utility scores of patients with type 1 diabetes in the UK, making full use of the extensive data available within the DAFNE research database.

Methods

Questionnaire data from the DAFNE research database (see *Chapter 2*) were used for all analyses. A questionnaire was given to DAFNE entrants prior to their training, and 1 and 2 years after training. This survey collected demographic, behavioural and clinical variables, and history of relevant clinical events, especially diabetes-related complications. In addition, various standard instruments were used to collect health-related QoL, including the EQ-5D and European Quality Visual Analogue Scale (EQ VAS)[18] and the SF-12[19] [in the grant application it was originally planned to use the SF-36[171] but the SF-12 was selected as the final instrument as it is shorter and therefore reduced responder burden].

The first set of models compared decrements for complications from type 1 diabetes with those from published literature for type 2 diabetes. For comparison against previously published estimates we attempted to replicate the methods used in these studies as far as possible.

For the final utility analyses for use in the health economic decision model, we have undertaken longitudinal random-effects modelling using a Tobit model. The preferred model used individual-level random effects analysis, which allowed for correlation in the error term at the individual level between the three time periods.

Results

Comparison of DAFNE-derived utilities with utilities in existing literature

Table 25 shows the comparison of the impact of comorbidities on the EQ-5D between patients with type 2 diabetes in the studies by Clarke *et al.*[172] (re-estimated in Pullenayegum *et al.*[173]) and Alva *et al.*,[174] and patients with type 1 diabetes in the pooled (three waves) DAFNE data. The marginal effects on the EQ-5D models are remarkably close, suggesting that the use of utility decrements derived from type 2 patients within type 1 economic models may not introduce significant bias. *Table 25* also shows that cross-section analysis tends to give greater decrements than the methods that take advantage of panel data.

The comparison with ordinary least square (OLS) utility decrements from European data from Bagust and Beale[175] (*Table 26*) gives a slightly more mixed picture. Bagust and Beale[175] show a fairly similar decrement to that in the DAFNE database for depression (–0.20 vs. –0.22), which is classified as a history of depression in Bagust and Beale[175] or as a current user of medication for depression in the DAFNE database. Bagust and Beale[175] found the duration of diabetes to be a significant predictor for utilities of patients with type 2 diabetes; however, this was not found for patients with type 1 diabetes in the DAFNE research database when conditioning on similar controls. A negative impact of duration of diabetes on type 1 patients was not found by Coffey *et al.*[176] or Hart *et al.*[177] but it was found by Ahola *et al.*[178] in a larger sample. Having had a transplant or being on dialysis was associated with a substantial decrement in the Bagust and Beale model,[175] but not in the DAFNE data. This may be because the DAFNE data include few cases that are only undergong dialysis ($n = 3$) and we would expect those who have had a transplant to have a higher utility value than those undergoing dialysis (see Ahola *et al.*[178]). The impact of a high BMI on EQ-5D is about one-third of the size in the DAFNE data as in the Bagust and Beale[175] data. This smaller decrement is apparent both in the DAFNE data and in the study by Ahola *et al.*[178] This may be because of the smaller variation in BMI in patients with type 1 diabetes than in patients with type 2 diabetes and also because a higher BMI contributes directly to the development and progression of type 2 diabetes itself. Although the EQ-5D decrement for foot ulcers (–0.17) is the same in both data sets, there are differences in the decrements for amputation (–0.27 vs –0.17) (although the EQ VAS decrement is about –9 in both cases) and differences in the impact of neuropathy; the most severe neuropathy in the Bagust and Beale[175]

TABLE 25 Comparison of the impact of diabetes complications on utilities between data on type 2 diabetes from Clarke *et al.*[172] and Alva *et al.*[174] and DAFNE baseline data on type 1 diabetes. Data are presented as EQ-5D coefficients (standard error)

	Type 2 diabetes			Type 1 diabetes	
Complication	Clarke *et al.*[172] (re-estimated in Pullenayegum *et al.*[173]) (UKPDS)	Alva *et al.*[174] (UKPDS)		DAFNE	DAFNE
Model used	Tobit	Pooled OLS	Fixed effects	Tobit (pooled)	OLS (pooled)
MI	–0.061			–0.067 (0.034)	–0.067 (0.051)
MI (year before)		–0.086 (0.036)[a]	–0.065 (0.030)[a]		
MI (previous history)		–0.019 (0.018)	0.008 (0.024)		
Ischaemic heart disease	–0.105	–0.067 (0.017)[b]	–0.028 (0.022)		
Coronary revascularisation or hospital admission for ischaemic heart disease				–0.049 (0.045)	–0.078 (0.067)
Stroke	–0.201	–0.179 (0.030)[b]	–0.165 (0.035)[b]	–0.135 (0.041)[b]	–0.177(0.066)[b]
Heart failure[c]	–0.127	–0.168 (0.032)[b]	–0.101 (0.032)[b]		
Amputation	–0.368	–0.180 (0.040)[b]	–0.172 (0.045)[b]	–0.153 (0024)[b]	–0.191(0.039)[b]
Blind in one eye	–0.085	–0.050 (0.022)[a]	0.033 (0.027)		
Blind or partially sighted				–0.051 (0.045)	–0.066 (0.055)
Constant		0.845 (0.031)[b]	0.807 (0.005)[b]		0.924 (0.013)
Observations	3192	11,614	11,614	3849	3849
Number of patients	3192	3380	3380	2382	2382

MI, myocardial infarction; UKPDS, UK Prospective Diabetes Study.

a $p < 0.05$.

b $p < 0.01$.

c DAFNE does not have direct self-report data on heart failure; however, the baseline participants reported no hospital admissions in the last 12 months with heart failure as the primary reason for admission.

Notes

Controlling for fixed time effects in panel data, gender in the Clarke *et al.*[172] data and age in the Alva *et al.*[174] data, and age and gender in the DAFNE data. Standard errors are clustered at the individual level for the pooled models.

TABLE 26 Comparison of the impact of diabetes complications on utilities between data on type 2 diabetes from Bagust and Beale[175] and DAFNE baseline data on type 1 diabetes: OLS models

	Bagust and Beale:[175] OLS model for type 2 diabetes[a]		DAFNE baseline data: OLS pooled model for type 1 diabetes	
	EQ-5D coefficient (SE)	EQ VAS coefficient (SE)	EQ-5D coefficient (SE)	EQ VAS coefficient (SE)
Constant	1.027 (0.027)[b]	81.44 (1.95)[b]	0.9649 (0.013)[b]	69.5277 (1.230)[b]
Patient characteristics				
Age (per 10 years)	–0.0235 (0.000)[b]	–0.94 (0.28)[b]	–0.0124 (0.003)[b]	1.8251 (0.296)[b]
Female	–0.094 (0.009)[b]	–3.54 (0.58)[b]	–0.0224 (0.008)[b]	–2.4895 (0.744)[b]
Duration (per 10 years)	–0.0163 (0.001)[b]	–2.06 (0.39)[b]	–0.0058 (0.004)	–0.4053 (0.332)
Complications				
CHD	–0.028 (0.10)[b]	–3.60 (0.071)[b]		
Coronary revascularisation or MI			–0.1165 (0.045)[b]	–9.9543 (2.735)[b]
Stroke	–0.115 (0.017)[b]	–5.95 (1.17)[b]	–0.0516 (0.046)	–3.6498 (3.905)
Nephropathy				
Proteinuria	–0.048 (0.022)[b]	–3.18 (1.53)[b]	–0.0666 (0.033)[c]	–4.9644 (2.955)
Dialysis or transplant	–0.175 (0.028)[b]	–13.90 (1.93)[b]	0.0257 (0.037)	0.9945 (2.989)
Lower extremity disease				
Neuropathy	–0.0484 (0.014)[b]	–3.58 (0.097)[b]		
PVD	–0.061 (0.015)[b]	–4.10 (1.05)[b]		
Neuropathy and PVD	–0.085 (0.018)[b]	–5.09 (1.26)[b]		
Painful neuropathy			–0.2853 (0.033)[b]	–13.9992 (2.094)[b]
Foot ulcers (not amputation)	–0.170 (0.019)[b]	7.95 (1.27)[b]	–0.1659 (0.050)[b]	–16.1442 (3.906)[b]
Amputation	–0.272 (0.029)[b]	–8.66 (1.99)[b]	–0.1739 (0.046)[b]	–8.9447 (4.990)
Retinopathy				
Proliferative retinopathy		–2.27 (1.10)[c]	–0.0497 (0.027)	–1.7004 (1.914)
Blindness	–0.057 (0.022)	–2.72 (1.53)		
Blind/partially sighted			–0.0017 (0.058)	–4.6335 (3.461)
Obesity (per 1 unit of BMI > 25 kg/m^2)	–0.0061 (0.001)[b]	–0.29 (0.64)[b]	–0.0027 (0.001)[c]	–0.4748 (0.105)[b]
Depression (clinical history)	–0.202 (0.014)[b]	–9.00 (0.94)[b]		
Depression (current medication)			–0.2195 (0.021)[b]	–12.5654 (1.434)[b]
Number of patients	4183	4206	3288	3232
Adjusted R^2	0.214	0.162	0.204	0.104

CHD, coronary heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; SE, standard error.
a Bagust and Beale[175] also control for taking tablets or insulin.
b $p < 0.01$.
c $p < 0.05$.
Note
SEs are clustered to allow for correlation across multiple observations in the same individual.

data has a decrement of 0.085 whereas the decrement for painful neuropathy in the DAFNE data is 0.285. This may be a result of how individuals were classified in the two studies or may be due a different degree of severity or experience of neuropathy between patients with type 1 diabetes and those with type 2 diabetes. Solli *et al.*[179] also find that neuropathy results in the greatest decrement on the EQ-5D for a sample of type 1 patients in Norway. This indicates that there are potential problems with using utility decrements for painful neuropathy from patients with type 2 diabetes in cost-effectiveness models of type 1 diabetes. The DAFNE cohort is considerably younger than that in the study by Bagust and Beale[175] (mean age 39 years at baseline vs. 67 years) and hence contains many more individuals of working age; consequently, painful neuropathy may have had more impact on their daily lives. Similarly, it might be expected that the impact of other complications such as retinopathy or foot ulceration would be higher. However, because of the small numbers of these events within our cohort, we have not observed any significant differences. Interestingly, we see the coefficient for having had a stroke reduces in size and loses significance when the additional controls are included compared with the more parsimonious model in *Table 25*.

Final analyses using longitudinal methods: utilities for use in the health economic modelling

The average marginal effects for the random-effects Tobit models for the EQ 5D, EQ VAS and SF-6D are shown in *Table 27*. For the EQ-5D, the first column (1) shows the simplest model with key comorbidity states and basic controls for age and gender only as required for the economic model. The second column (2) includes additional controls (smoking status, BMI, if the participant was born in the UK and four additional diabetes-related health states). The third column (3) includes HbA_{1c} and whether or not the patient is taking medication for depression.

The greatest utility decrement for the EQ-5D is for experiencing painful neuropathy (–0.168 in the most complete model) and taking antidepressants (–0.128), with the impact of these slightly smaller for the SF-6D and EQ VAS. The negative impacts of having experienced a stroke, coronary revascularisation, microalbuminuria, proteinuria, having had dialysis or a transplant and the presence of hypertension were limited in magnitude, which may be because the sample sizes for these comorbidities are relatively small. It is interesting that the decrement for stroke becomes insignificant when more health states are controlled for. For vision problems, retinopathy has a decrement of around 0.02 in the full model for the EQ-5D and EQ VAS; proliferative retinopathy and being blind or partially sighted have a similar magnitude of decrement but were not significant. Again, this may be because of the small number of individuals at baseline (1%) who experience partial or full blindness, resulting in imprecise estimates. This is broadly in line with findings from Hart *et al.*,[177] who found that new cases of retinopathy result in a decrease in the EQ-5D of 0.048. Having experienced amputation results in a reduction of 0.146 in the EQ-5D in the first model with limited controls, falling to a reduction of 0.0796 in the full model. For the EQ VAS and SF-6D this is lower still, at –0.0488 for the EQ VAS and –0.0566 for the SF-6D. This may again be driven by the small number of amputees (< 1%). In the complete models, having a foot ulcer impacts most strongly on the EQ VAS score (–0.1260), by almost twice as much as on the SF-6D score (–0.0695). Undergoing severe hypoglycaemic episodes has a negative impact but this is not significant for any of the measures. DKA events are significantly negative for the EQ-VAS and SF-6D (lowering utility by 0.012) but are no longer significant for the EQ-5D once additional controls are included. HbA_{1c} levels have a significantly negative association with all measures, although the models found no evidence of non-linearity (squared terms were not significant and reduced model performance). Controlling for other variables, a one-unit increase (increase by 1%) in HbA_{1c} lowers the EQ-5D score by –0.018. This decrement remained virtually unchanged when the controls for weight and frequency of hypoglycaemic episodes were removed.

TABLE 27 Average marginal effects for the longitudinal analysis of utility decrements using random-effects Tobit models

	EQ-5D coefficient (SE)			EQ VAS coefficient (SE)	SF-6D coefficient (SE)
Patient characteristic	1	2	3	4	5
Age (years) (/10)[a]	–0.0205[b] (0.003)	–0.0209[b] (0.003)	–0.0215[b] (0.003)	0.0082[c] (0.003)	–0.0003 (0.002)
Female	–0.0307[b] (0.008)	–0.0376[b] (0.0080)	–0.0290[b] (0.008)	–0.0250[b] (0.007)	–0.0337[b] (0.005)
Smoker		–0.0539[b] (0.010)	–0.0359[b] (0.010)	–0.0478[b] (0.009)	–0.0329[b] (0.007)
BMI		–0.0015 (0.001)	–0.0016[c] (0.001)	–0.0013 (0.008)	0.0010 (0.006)
Born in the UK		–0.0294[b] (0.010)	–0.0218[c] (0.009)	0.0082[c] (0.003)	–0.0003 (0.002)
MI	–0.0498 (0.033)	–0.0445 (0.038)	–0.0686 (0.036)	–0.0850 (0.036)	–0.0391 (0.027)
Stroke	–0.0613 (0.036)	–0.0402 (0.037)	–0.0114 (0.035)	–0.0377 (0.034)	–0.0051 (0.025)
Microvasular complications	–0.0011 (0.022)	0.0083 (0.023)	0.0228 (0.022)	–0.0204 (0.020)	0.0184 (0.015)
Proteinuria	–0.0591[c] (0.026)	–0.0420 (0.026)	–0.0386 (0.025)	–0.0426 (0.024)	–0.0231 (0.017)
Transplant or dialysis	–0.0239 (0.043)	–0.0174 (0.045)	–0.0064 (0.044)	–0.0122 (0.041)	0.0045 (0.031)
Retinopathy	–0.0368[b] (0.009)	–0.0309[b] (0.010)	–0.0243[c] (0.009)	–0.0186[c] (0.009)	–0.0103 (0.006)
Proliferative retinopathy	–0.0531[c] (0.018)	–0.0395 (0.019)	–0.0271 (0.018)	–0.0154 (0.017)	–0.0221 (0.013)
Blind or partially sighted	–0.0191 (0.041)	–0.0410 (0.043)	–0.0223 (0.042)	–0.0469 (0.037)	0.0224 (0.028)
Painful neuropathy	–0.1951[b] (0.018)	–0.1843[b] (0.018)	–0.1681[b] (0.018)	–0.0877[b] (0.018)	–0.0953[b] (0.013)
Foot ulcer	–0.1351[b] (0.027)	–0.1227[b] (0.029)	–0.0974[b] (0.028)	–0.1260[b] (0.028)	–0.0695[b] (0.021)
Amputation (any)	–0.1460[b] (0.039)	–0.1058[c] (0.043)	–0.0796 (0.047)	–0.0488 (0.046)	–0.0566 (0.035)
Erectile dysfunction		–0.0253 (0.019)	–0.0294 (0.018)	–0.0096 (0.017)	–0.0189 (0.013)
Coronary revascularisation		–0.0220 (0.044)	0.0111 (0.042)	0.0112 (0.039)	0.0028 (0.030)
Revascularisation of peripheral arteries		0.0196 (0.052)	0.0011 (0.052)	0.0087 (0.056)	0.0025 (0.043)
Hypertension		–0.0215 (0.012)	–0.0227 (0.012)	–0.0176 (0.011)	–0.0170[c] (0.008)
Severe hypoglycaemia last year	–0.0012 (0.001)	–0.0015 (0.001)	–0.0011 (0.001)	–0.0005 (0.001)	–0.0011 (0.001)
DKA last year	–0.0164[c] (0.005)	–0.0138[c] (0.005)	–0.0085 (0.005)	–0.0223[c] (0.007)	–0.0120[c] (0.004)
HbA_{1c}			–0.0176[b] (0.002)	–0.0174[b] (0.002)	–0.0086[b] (0.002)
Medication for depression			–0.1281[b] (0.012)	–0.0816[b] (0.011)	–0.0847[b] (0.009)
Wave 2	0.0147[c] (0.006)	0.0150[c] (0.006)	0.0128 (0.007)	0.0232[b] (0.006)	0.0170[b] (0.004)
Wave 3	0.0063 (0.008)	0.0074 (0.009)	0.0128 (0.010)	0.0234 (0.009)	0.0209[c] (0.007)
Observations	3615	3211	2927	3033	2916
Sigma_u[d]	0.130	0.130	0.130	0.288	0.0946
Sigma_e[d]	0.0847	0.0847	0.0847	0.209	0.0871
Rho[d]	0.701	0.701	0.701	0.655	0.541

MI, myocardial infarction; SE, standard error.

a (/10) indicates that individual-level values in the age variable were divided by 10 in order to limit the impact of the outliers.

b $p < 0.01$.

c $p < 0.05$.

d Sigma_u represents the individual-level variable and sigma_e the overall variance and rho shows the proportion of total variance arising at the individual level.

Discussion

There are some important issues to consider when interpreting the estimates of utility decrements. We find a considerable decrement in QoL in the DAFNE cohort arising from the use of depression medication. At baseline, 8.4% of the sample were taking antidepressants; however, there might be other cases in the sample with diagnosed or non-diagnosed depression who are not currently on medication. Furthermore, we do not know whether or not the depression in these cases has arisen as a result of the diabetes. A decrement in QoL for depression has also been shown for type 2 patients.[175] The largest decrement from the random-effects Tobit models arises from painful neuropathy. The best estimate can be taken from the full random-effects model, which finds a decrement in the EQ-5D score of 0.168 but in the SF-6D score of only 0.095. The large decrement arising from painful neuropathy supports the findings of Currie *et al.*,[180] who found a close association between the EQ-5D score and the Neuropathic Total Symptom Score. Because of the small sample sizes it is difficult to see robust significant decrements for some long-term complications. Aggregating categories such as partially sighted and blindness is problematic as we would anticipate a different impact for these two categories. Indeed, the division should arguably be much finer, taking into consideration the deterioration in each eye. The number of severe hypoglycaemic events was not identified as having a significant impact on QoL. For the EQ VAS and SF-6D, there is a significant negative relationship with the number of DKA episodes during the previous year, but for the EQ-5D this relationship is no longer significant in the full model. All models identified an independent impact on utility of HbA_{1c} level, which is greater for the EQ-5D and EQ-VAS than for the SF-6D. The impact on EQ-5D score is around –0.017 per 1% increase in HbA_{1c}. This is greater than the decrement identified for type 1 patients by Ahola *et al.*[178] using the 15D© (see www.15d-instrument.net/15d; accessed 2 October 2014), who find a 1% increase to result in a 0.006 decline in utility using cross-sectional data. Hart *et al.*[177] did not find HbA_{1c} level to be a significant predictor of EQ-5D score (or of subsequent changes in EQ-5D scores) in their data from the Netherlands, although their sample size is small ($n = 234$). However, there is reason to be concerned about potential endogeneity given that HbA_{1c} level does not have an obvious direct impact on QoL. HbA_{1c} level may be correlated with time-variant unobservables, for example an individual may experience a new stressful event that both results in a decline in their ability to control blood glucose levels and increases their probability of responding at level 2 or 3 to the anxiety/depression item on the EQ-5D. Furthermore, the direction of causality is a little unclear. Poor overall health (as picked up by the utility measures) may be contributing to high HbA_{1c} levels.

The comparison between the EQ VAS, SF-6D and EQ-5D does not reveal anything very systematic. We anticipated that the SF-6D would be more sensitive to mild changes in health whereas the EQ-5D may show a greater decrement for more severe health states.[169] Indeed, the minimum value for the EQ-5D is –0.594, with a minimum value in this data set of –0.239, whereas the minimum value for the SF-6D is only 0.29, with a minimum value in this data set of 0.345.[181,182] However, no such pattern emerges.

If we had a larger sample size and longer follow-up times, other methods of analysis could be used. Although the random-effects Tobit model is the most suitable approach in this case, this still rests on the assumption that the unobserved individual effect is not correlated with any of the covariates. If more waves of data were available, fully controlling for individual heterogeneity using fixed-effects Tobit models would be preferred.

Conclusions

The analysis of the DAFNE research database provides utility estimates based on panel data on diabetes-related health states to populate economic models exploring the cost-effectiveness of interventions for patients with type 1 diabetes. The preferred random-effects Tobit model improves on existing available estimates together with the large sample size available across three time periods. Even with the large data set available, it is still difficult to identify robust estimates for many complications because of the small number of patients who experience some complications.

Comparing the decrements in EQ-5D score for comorbidities, complications and diabetes-related events in type 1 and type 2 diabetes suggests that the use of estimates from type 2 patient data in health economic models of type 1 diabetes is reasonable, with the possible exception of estimates for BMI and neuropathy. This is important as the small numbers of individuals experiencing some complications [such as stroke, myocardial infarction (MI), dialysis, transplant and blindness] in the DAFNE data set makes it difficult to generate robust estimates of the utility decrement for these states.

Development of the Sheffield Type 1 Diabetes Policy Model

Introduction

The aim of this section is to describe the conceptual modelling, model implementation and model validation phases of the Sheffield Type 1 Diabetes Policy Model development process. The model is highly flexible and has broad potential application to evaluate the DAFNE programme, other diabetes structured education programmes and other interventions for type 1 diabetes.

Conceptual modelling

The conceptual modelling phase included two workshops with clinical and social science experts in diabetes, a systematic review of published models of type 1 diabetes and structured decision-making by researchers at the University of Sheffield. An initial workshop (workshop 1) was held in June 2009 with invited clinical diabetes specialists (including a nurse specialist) and the University of Sheffield DAFNE health economics team to understand the natural history of type 1 diabetes. The next stage of the conceptual modelling process was a systematic review of previously published cost-effectiveness models of type 1 diabetes. A total of 65 papers, relating to 32 individual cost-effectiveness models, were selected for inclusion in the review (details available from the authors on request). A draft model structure including all potential diabetes-related complications was then developed based on the systematic review of previous cost-effectiveness models. In July 2010, the University of Sheffield DAFNE health economics team conducted a second workshop (workshop 2) with clinical experts to discuss the results of the review and the proposed conceptual model. The final conceptual model was developed after discussions in the workshop and is shown in *Figure 7*.

Model description

The Sheffield Type 1 Diabetes Policy Model is a flexible and comprehensive long-term simulated patient-level Markov model incorporating up-to-date methodologies [such as capturing parameter uncertainty and the time profile of patient characteristics (i.e. updating the time-dependent characteristics at the beginning of each annual cycle) and including patient behaviour] to allow a number of cost-effectiveness evaluations.

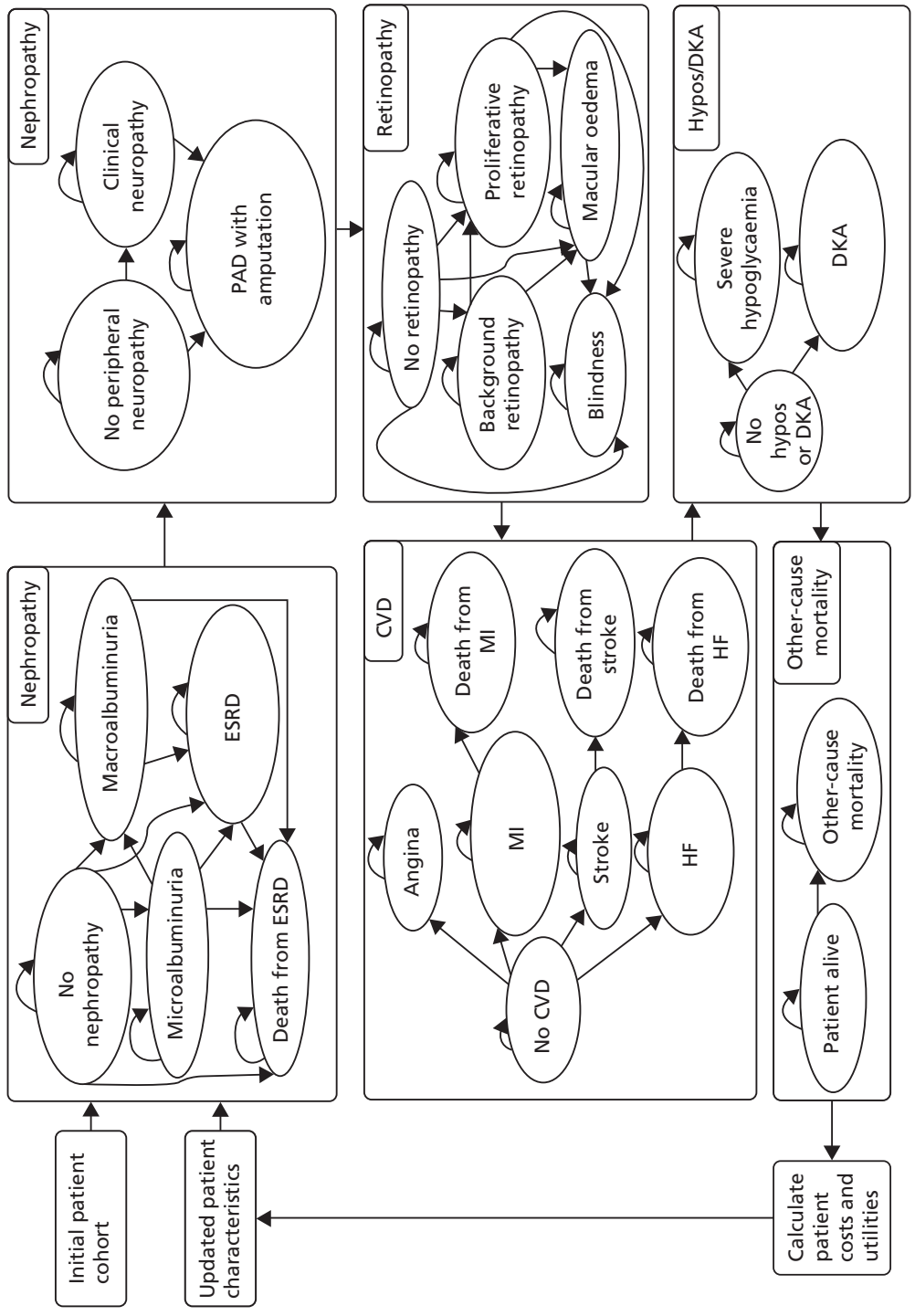

FIGURE 7 Structure of the Sheffield Type 1 Diabetes Policy Model (from Thokala *et al.* 2013[183] with permission). ESRD, end-stage renal disease; HF, heart failure; hypos, hypoglycaemic attack; PAD, peripheral arterial disease.

The Sheffield Type 1 Diabetes Policy Model consists of a series of submodels simulating the progression of each of the diabetes-related complications, acute complications and mortality in a given population with type 1 diabetes, dependent on their characteristics, by using annual cycles. The individual patient characteristics include demographics (age, gender and duration of diabetes), clinical variables (HbA_{1c}, smoking status, blood pressure, HDL and total cholesterol), existing diabetes-related complications and treatment status. The complications included in the model are nephropathy, retinopathy, neuropathy, severe hypoglycaemia, MI, stroke, heart failure and angina whereas the adverse events included are severe hypoglycaemia and DKA, as shown in *Figure 7*. Each health state is associated with an annual cost and a utility value, which is combined with the number of annual time cycles that the patient spends in that health state to estimate costs and quality-adjusted life-years (QALYs). Costs and QALYs are summed across time and patients for use in cost-effectiveness analyses. *Table 28* provides a comparison between the two models widely used in the cost-effectiveness analysis of type 1 diabetes [CORE[184] and Economic Assessment of Glycemic Control and Long-Term Effects of diabetes (EAGLE)[185]] and the Sheffield Type 1 Diabetes Policy Model.

TABLE 28 Comparison of the Sheffield Type 1 Diabetes Policy Model, the IMS CORE model and the EAGLE model

Feature	Sheffield model	CORE model[184]	EAGLE model[185]
Scope	Type 1 diabetes	Type 1 and type 2 diabetes	Type 1 and type 2 diabetes
Model type	Patient-level simulation with Markov submodels	Patient-level simulation with Markov submodels	Patient-level simulation with Markov submodels
Diabetes-related complications included	Retinopathy, nephropathy, neuropathy, macular oedema, MI, stroke, angina, heart failure, severe hypoglycaemia, ketoacidosis	Retinopathy, nephropathy, neuropathy, macular oedema, cataract, MI, stroke, angina, heart failure, severe hypoglycaemia, ketoacidosis	Retinopathy, nephropathy, neuropathy, macular oedema, cataract, MI, stroke, angina, heart failure, severe hypoglycaemia, ketoacidosis
Risk engine for microvascular complications	Developed own transition probabilities from published data	Developed own transition probabilities from published data	UKPDS,[186] WESDR XXII,[187] DCCT[188]
Risk engine for macrovascular complications	Type 1-specific transition probabilities based on DCCT[189] and Cederholm *et al.*[190]	UKPDS[186] (type 2 diabetes) and Framingham (general population) risk equations[191]	UKPDS,[186] WESDR XXII,[187] DCCT,[188] ARIC,[192] EURODIAB[193]
Dynamic nature of HbA_{1c}	HbA_{1c} included in risk engines as a continuous variable updated over time (e.g. based on long-term effects of structured education)	HbA_{1c} levels are controlled solely by exogenous insulin	HbA_{1c} is simulated over time with regard to predefined target HbA_{1c} values for each individual patient and updated annually according to user input
Inclusion of psychosocial factors	Can incorporate psychological and behavioural predictors of treatment response, e.g. self-efficacy/self-care behaviours	Not included	Not included

ARIC, Atherosclerosis Risk in Communities; EURODIAB, Childhood Diabetes in Europe; UKPDS, UK Prospective Diabetes Study; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Microvascular complications

For each microvascular complication (retinopathy, neuropathy and nephropathy), patients progress to the more severe health states within each annual time cycle according to the probabilities reported in *Table 29*. These probabilities of transitioning between states within a particular complication were estimated by combining data from multiple sources (full details of these methods are reported elsewhere[183,196]). The probabilities were estimated at the reference HbA_{1c} level of 10% and the method of Eastman *et al.*[197]

TABLE 29 Annual probability of microvascular events

Annual transition probabilities for microvascular complications		
Parameter	**Base-case value**	**Source(s)**
Neuropathy		
Healthy to clinically confirmed neuropathy[a]	0.0354	DCCT,[188] Moss *et al.*[194] (WESDR)
Healthy to PAD with amputation	0.0003	
Clinically confirmed neuropathy to PAD with amputation	0.0154	
Nephropathy		
Healthy to microalbuminuria[b]	0.0436	DCCT,[188] Wong *et al.*[195] (WESDR), UKPDS 33[186]
Healthy to macroalbuminuria[c]	0.0037	
Healthy to ESRD	0.0002	
Healthy to death from ESRD	3.3e-6	
Microalbuminuria to macroalbuminuria[c]	0.1565	
Microalbuminuria to ESRD	0.0133	
Microalbuminuria to death from ESRD	0.0004	
Macroalbuminuria to ESRD	0.1579	
Macroalbuminuria to death from ESRD	0.0070	
ESRD to death from ESRD	0.0884	
Retinopathy and macular oedema		
Healthy to background retinopathy[d]	0.0454	Klein *et al.*[187] (WESDR XXII)
Healthy to proliferative retinopathy[e]	0.0013	
Healthy to macular oedema[f]	0.0012	
Healthy to blindness	1.9e-6	
Background retinopathy to proliferative retinopathy[e]	0.0595	
Background retinopathy to macular oedema[f]	0.0512	
Background retinopathy to blindness	0.0001	
Proliferative retinopathy to blindness	0.0038	
Macular oedema to blindness	0.0016	

ESRD, end-stage renal disease; PAD, peripheral arterial disease; UKPDS, UK Prospective Diabetes Study; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.
a β-coefficient for neuropathy = 5.30.
b β-coefficient for microalbuminuria = 3.25.
c β-coefficient for macroalbuminuria = 7.95.
d β-coefficient for background retinopathy = 10.10.
e β-coefficient for proliferative retinopathy = 6.30.
f β-coefficient for macular oedema = 1.20.

was used to adjust the risk of background retinopathy, macular oedema, proliferative retinopathy, microalbuminuria, macroalbuminuria and neuropathy for patients with different HbA_{1c} levels (P_{HbA1c}) using the formula:

$$P_{HbA1c} = P_{HbA1c=10}(HbA_{1c}/10)\hat{}\beta \quad (1)$$

where the baseline probabilities ($P_{HbA1c=10}$) are as shown in *Table 29* and the β coefficients are as shown in the footnote of *Table 29*. The rest of the transition probabilities are assumed to be independent of HbA_{1c} level.

The rationale and the procedure followed to choose the sources is provided in *Conceptual modelling*. The baseline values are obtained from three main source papers.

For neuropathy, the DCCT[188] is a multicentre RCT involving 29 US and Canadian clinical centres and includes 1441 patients aged 13–39 years, of whom 726 had had type 1 diabetes mellitus for 1–5 years and had no retinopathy at baseline (primary prevention cohort), and 715 had had diabetes for 1–15 years and had minimal to moderate non-proliferative retinopathy at baseline.

For retinopathy, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR XXII)[187] is a population-based study that examined the 25-year cumulative progression and regression of diabetic retinopathy and its relation to various risk factors, based on a total of 955 insulin-taking patients living in an 11-county area in southern Wisconsin with type 1 diabetes diagnosed before the age of 30 years.

For nephropathy, a mix of evidence from the DCCT,[188] WESDR[195] and UK Prospective Diabetes Study (UKPDS)[186] was utilised. The UKPDS compared, in a RCT, intensive blood glucose control with either sulphonylurea or insulin with conventional treatment with regard to the risk of microvascular and macrovascular complications in 3867 newly diagnosed patients with type 2 diabetes (median age 54 years).

Macrovascular complications

The risks of fatal and non-fatal macrovascular complications (MI, stroke, heart failure and angina) are modelled in three stages. First, the annual probability of experiencing any cardiovascular event, P_CVD, is estimated based on patient characteristics, as per the 5-year cardiovascular risk model of Cederholm *et al.*:[190]

$$P\_CVD = 1 - \exp(-(-(\ln(1 - 5\ year\_CVD\_risk))/5) \times 1), \quad (2)$$

where 5 year_CVD_risk is given by the equation:

$$5\ year\_CVD\_risk = 1 - 0.97136^{\exp[H]}, \quad (3)$$

where

$$\begin{aligned} H = [&0.08426 \times (duration - 28.014) + 0.04742 \times (age - duration - 16.601) + 0.80050 \\ &\times (\log(total\ cholesterol{:}HDL) - 1.1470) + 1.27275 \times (\log(HbA_{1c}(DCCT)) - 2.0605) + 1.20050 \\ &\times (\log(systolic\ blood\ pressure) - 4.8598) + 0.56688 \times (smoker - 0.1483) + 0.41995 \\ &\times (macroalbuminuria - 0.1237) + 1.25506 \times (previous\ CVD - 0.0612)]. \end{aligned} \quad (4)$$

The risk equations for macrovascular complications are obtained from Cederholm *et al.*[190] and Palmer's 2012 thesis.[198] Cederholm *et al.*[190] assessed the association between risk factors and CVD in an observational study with a derivation sample of 3661 patients (aged 30–65 years) with type 1 diabetes from the Swedish National Diabetes Register; they used a separate validation data set of 4484 patients. The study by Cederholm *et al.*[190] was chosen because it is a recent large European study of the risk of macrovascular complications in type 1 diabetes patients from the Swedish National Diabetes Register. Palmer[198] developed a microsimulation model consisting of a series of Markov health states that could

predict both CVD and end-stage renal disease (ESRD) based on data from the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study.[189]

Second, if the patient is deemed to experience a cardiovascular event, the type of event (MI, stroke, heart failure or angina) is determined using methods outlined in Palmer,[198] based on data from the DCCT/EDIC study.[189] Given a cardiovascular event, there is a 53% chance that it is a MI, a 28% chance that it is angina, a 12% chance that it is heart failure and a 7% chance that it is stroke, as shown in *Table 30*. These values were obtained from Nathan *et al.*,[189] who studied whether the use of intensive therapy compared with conventional therapy during the DCCT affected the long-term incidence of CVD.

Third is the issue of fatality. If the event experienced is a MI, stroke or heart failure, it is determined whether the event is fatal using methods outlined in Palmer[198] and as shown in *Table 31*. The values in *Table 31* are obtained from a number of source papers including Sonke *et al.*[199] and Malmberg *et al.*[200] Sonke *et al.*[199] investigated if the reported higher case fatality in hospital after an acute cardiac event in women can be explained by sex differences in mortality before admission and baseline risk factors, by analysing data from a community-based coronary heart disease register in the Auckland region, New Zealand, with 5106 patients (aged 25–64 years) with an acute cardiac event leading to coronary death or definite MI within 28 days of onset, occurring between 1986 and 1992. Malmberg *et al.*[200] investigated how insulin–glucose infusion followed by MDI treatment in diabetic patients with acute MI affected mortality during the subsequent 12 months of follow-up by studying 620 patients admitted to the coronary care units of 19 Swedish hospitals in the Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study.

TABLE 30 Probability of different cardiovascular events

		Gamma distribution		
Parameter	Base-case value	Alpha	Beta	Source
MI	0.53	1	0.0053	Nathan *et al.*[189] (DCCT/EDIC)
Stroke	0.07	1	0.0007	
Angina	0.28	1	0.0028	
Heart failure	0.12	1	0.00126	

TABLE 31 Probability of dying from cardiovascular events

		Gamma distribution		
Parameter	Base-case value	Alpha	Beta	Source
MI death in hospital: men	0.3930	1	0.00393	Sonke *et al.*[199]
MI death in hospital: women	0.3640	1	0.00364	Sonke *et al.*[199]
MI death within 1 year: aged < 65 years	0.1522	1	0.00152	Malmberg *et al.* (DIGAMI)[200]
MI death within 1 year: aged 65–75 years	0.1860	1	0.00186	Malmberg *et al.* (DIGAMI)[200]
MI death within 1 year: aged > 75 years	0.2508	1	0.00250	Malmberg *et al.* (DIGAMI)[200]
Stroke death within 30 days	0.1240	1	0.00124	Eriksson *et al.*[201]
Stroke death within 1 year	0.1063	1	0.00106	Nathan *et al.* (DCCT/EDIC)[189]
Heart failure death within 1 year	0.0570	1	0.00057	Anselmino *et al.*[202]

Acute complications

Two acute complications are simulated in the Sheffield Type 1 Diabetes Policy Model: severe hypoglycaemia (defined as a hypoglycaemic event that the person with type 1 diabetes is unable to treat themselves) and DKA. The model parameters for the incidence of these two events were estimated from the DAFNE research database and the original DAFNE education compared with no DAFNE education RCT data set (DAFNE NIHR Research Group, Central DAFNE Administration Office, North Tyneside General Hospital, North Shields, Tyne and Wear, 2006, personal communication). Negative binomial models were developed to predict the annual rates of hypoglycaemia and DKA, and the results of the models are presented in *Table 32*. Full details of these methods are available from the authors on request.

Mortality

Patients can also die from other causes (than ESRD and CVD) and this other-cause mortality is modelled based on UK interim life tables from 2008 to 2010.[203] The model allows for other life tables to be selected, for example there is an option to select US mortality data used in the CORE model[184] or mortality rates from the EAGLE model.[185]

Treatment effectiveness in terms of change in glycated haemoglobin

Treatment effect is measured in terms of change in HbA_{1c} from baseline over time.

The specific details of the evidence used for the various analyses undertaken in this research programme are outlined in the final three sections of this chapter. These evidence sources include the different components of the DAFNE programme, that is, the original RCT of DAFNE education compared with no DAFNE education, the RCT of 5-week compared with 1-week courses, the psychosocial study and the general database. In most cases the analysis of the individual-level data is carried out using a statistical regression. For example, to quantify the impact of DAFNE education after 12 months in the 5 × 1-day RCT we undertake a regression with:

$$12\text{month}HbA_{1c} = \text{constant} + \text{Coeff}1 \times \text{Baseline}HbA_{1c} + \text{Coeff}2 \times \text{Treatment}. \quad (5)$$

Change in HbA_{1c}, as a result of an intervention, has an impact on the risk of developing several microvascular complications and this effect is modelled based on Eastman *et al.*'s[197] method of adjusting the risk for changes in HbA_{1c} levels. For macrovascular complications the coefficients for HbA_{1c}, HDL, smoking status, blood pressure and total cholesterol used in Cederholm *et al.*[190] were used to adjust the probability of any cardiovascular event.

TABLE 32 Negative binomial models of the annual number of severe hypoglycaemic and DKA episodes

Covariates	Coefficient	Standard error	95% CI
Total number of hypoglycaemic episodes that you were unable to treat yourself (in the last year)			
Intercept B_{1H}	0.928	0.553	–0.155 to 2.012
Before/after DAFNE education	–1.291	0.142	–1.569 to –1.013
HbA_{1c} B_{2H}	–0.113	0.064	–0.259 to –0.006
Total number of episodes of DKA requiring admission (in the last year)			
Intercept B_{1K}	–8.108	1.097	–10.259 to –5.958
Before/after DAFNE education	–0.965	0.351	–1.653 to –0.277
HbA_{1c} B_{2K}	0.617	0.115	0.392 to 0.842

The negative binomial model is log(number of events) = intercept $B_1 + (B_2 \times HbA_{1c}) +$ error.

Utilities

The model calculates lifetime QALYs for each patient based on his or her life expectancy and corresponding annual utility given the health states experienced. Each health state is associated with a disutility value (negative) as reported in *Table 33* and these decrements are added to the baseline utility to estimate the absolute utility in the given health state. In case of multiple complications, the utility is estimated by aggregating the disutilities of the multiple complications with the baseline utility. As all three source papers[170,174,176] used to assign the utility decrements are based on statistical regression models that are essentially assuming an additive model within the regression, it would be incorrect to use another structure for multiple complication utilities. The parameters themselves are estimated in an additive form. The model has the flexibility to use alternative utility values as inputted by the model user.

The base-case utility parameters reported in *Table 33* are based on four main source papers.[170,172,174,176] To decide which estimates to use we considered both the merits of the evidence (size of the sample and appropriateness to a UK type 1 diabetic population) and the utility measure used (favouring the EQ-5D in line with NICE reference case guidance[168]) and also compared utilities across the studies and between the health states within a comorbidity, favouring estimates that were similar to those in other studies and did not look to be outliers.

Alva *et al.*[174] estimated the impact on QoL of six diabetes-related complications (MI, ischaemic heart disease, stroke, heart failure, amputation and visual acuity) using longitudinal data (seven rounds) from EQ-5D questionnaires administered to 3380 individuals with type 2 diabetes in the UKPDS (11,684 questionnaires, a mean of 3.4 questionnaires completed per patient) between 1997 and 2007. This study both provides a very large sample of UK patients who experienced diabetes complications, including a long follow-up period compared with that used in other studies, and uses a fixed-effects longitudinal data analysis model that, as far as possible, estimates the change in EQ-5D utility in individuals who actually experienced changes in health state over time. We used this source whenever possible, including for CVD health states and amputation. Alva *et al.*[174] did not report utilities for several of our health states and other sources were also needed. We utilised UKPDS cross-sectional analyses from Clarke *et al.*[172] for angina.

Our own analysis of DAFNE utilities data is used as one of the key sources of evidence (see *Utilities analysis: the impact of diabetes-related complications on utility-based measures of quality of life in adults with type 1 diabetes* for details as well as Peasgood *et al.*[170]). The analysis showed broadly similar results to those of Alva *et al.*[174] when comparisons were able to be made. We used data from Peasgood *et al.*[170] for EQ-5D utility decrements related to hypoglycaemia, DKA, background retinopathy and proliferative retinopathy.

For other health states we used the only other source of type 1 diabetes utility evidence we could find. Coffey *et al.*[176] described the health utilities associated with diabetes and its treatments, complications and comorbidities based on data collected using the Quality of Well-Being Scale – Self-Administered from 784 individuals with type 1 diabetes registered at the Michigan Diabetes Research and Training Center, USA. This is a US-based study and the measure used is also not a preference-based measure. We used these data for macroalbuminuria and ESRD in type 1 diabetics as well as for the three milder neuropathy health states.

Costs

The model calculates long-term costs by using health state cost values from the literature, as presented in *Table 34*. Each health state is associated with an annual cost. In case of multiple complications, the cost is estimated by aggregating the annual costs of the different complications. Some disease progression events are also associated with a one-off transition cost that is incurred in the transition year. All costs have been inflated to 2010/11 prices using Personal Social Services Research Unit inflation indices.[209] The model has the flexibility to use alternative cost profiles as inputted by the model user.

TABLE 33 Base-case utility parameters

Health state or event	Utility	SE	Beta distribution		Source
			Alpha	Beta	
Baseline utility value					
Male with type 1 diabetes and no complications	0.888	0.006	2452.36	309.3067	Peasgood *et al.*[170]
	Disutility decrement	**SE**	**Gamma distribution**		**Source**
			Alpha	**Beta**	
Complications or covariates					
Female with type 1 diabetes and no complications	–0.030	0.008	14.0625	0.002133	Peasgood *et al.*[170] (table 4)
Nephropathy					
Microalbuminuria	0.000				Assumption
Macroalbuminuria	–0.017	0.01	2.89	0.005882	Coffey *et al.*[176] (table 2)
ESRD	–0.078	0.026	9.0000	0.008700	Coffey *et al.*[176] (table 2, type 2 diabetes)
Neuropathy					
Clinical neuropathy	–0.055	0.01	30.25	0.001818	Coffey *et al.*[176] (table 2)
Clinically confirmed neuropathy	–0.055	0.01	30.25	0.001818	Coffey *et al.*[176] (table 2)
Diabetic foot syndrome	–0.076	0.016	22.5625	0.003368	Coffey *et al.*[176] (table 2, sores)
PAD with amputation	–0.172	0.045	14.6094	0.011773	Alva *et al.*[174] (table IV)
Retinopathy					
Background retinopathy	–0.0368	0.009	16.9012	0.002189	Peasgood *et al.*[170] (table 4)
Proliferative retinopathy	–0.0531	0.018	8.3457	0.006231	Peasgood *et al.*[170] (table 4)
Blindness	–0.208	0.013	256	0.000813	Coffey *et al.*[176] (table 2)
Cardiovascular					
MI (first year)	–0.065	0.03	4.6944	0.013846	Alva *et al.*[174] (table IV)
MI (subsequent years)	–0.057	0.03	3.6100	0.015789	Alva *et al.*[174] (table IV)
Heart failure	–0.101	0.032	9.9619	0.010139	Alva *et al.*[174] (table IV)
Stroke	–0.165	0.035	22.2245	0.007424	Alva *et al.*[174] (table IV)
Angina	–0.090	0.018	24.0091	0.003749	Clarke *et al.*[172] (table 4, ischaemic heart disease)
Hypoglycaemia episode unable to treat yourself	–0.0012	0.001	1.4400	0.000833	Peasgood *et al.*[170] (table 4)
DKA	–0.0165	0.005	10.8900	0.001515	Peasgood *et al.*[170] (table 4)

PAD, peripheral arterial disease; SE, standard error.

TABLE 34 Base-case health state and transition costs

Health state	Mean cost (£)	Gamma distribution		Source
		Alpha	Beta	
Microalbuminuria (ongoing)	34	100	0.34	BNF,[204] McEwan *et al.*[205]
Macroalbuminuria (ongoing)	34	100	0.34	
ESRD (ongoing)	23,275	100	232.75	NHS Reference Costs[206] (activity-weighted average of LD01A, LD02A, LD03A, LD04A, LD05A, LD06A, LD07A, LD08A, LD09A, LD010A and LD011A and LD012A)
Clinically confirmed neuropathy	258	100	2.58	Currie *et al.*[207]
Clinical neuropathy	258	100	2.58	Assumed to be equivalent to clinically confirmed neuropathy
Diabetic foot syndrome	2713	100	27.13	NHS Reference Cost[206] [activity-weighted average of 'Non-Elective Inpatient (Long Stay)', 'Non-Elective Inpatient (Long Stay) Excess Bed-day' and 'Non-Elective Inpatient (Short Stay)' for currency code QZ17B]
PAD with amputation (year 1)	6878	100	68.78	NHS Reference Costs[206] [activity-weighted average of 'Non-Elective Inpatient (Long Stay)', 'Non-Elective Inpatient (Long Stay) Excess Bed-day' and 'Non-Elective Inpatient (Short Stay)' for currency codes QZ12Z and QZ11B]
PAD with amputation (ongoing)	418	100	4.18	McEwan *et al.*[205]
Background retinopathy	138	100	1.38	McEwan *et al.*[205]
Proliferative retinopathy	630	100	6.30	
Macular oedema	630	100	6.30	Assumed to be equivalent to proliferative retinopathy
Blindness (year 1)	1509	100	15.09	Clarke *et al.*[208] (UKPDS 65)
Blindness (ongoing)	494	100	4.94	
First MI (year 1)	6465	100	64.65	
Second MI	6465	100	64.65	
Final MI	6465	100	64.65	
MI (ongoing)	861	100	8.61	
Fatal MI	2001	100	20.01	
First stroke (year 1)	4154	100	41.54	
Second stroke	4154	100	41.54	
First stroke (ongoing)	532	100	5.32	
Fatal stroke	5414	100	54.14	
Heart failure (year 1)	3637	100	36.37	Clarke *et al.*[208] (UKPDS 65)
Heart failure (ongoing)	1117	100	11.17	
Fatal heart failure	3637	100	36.37	
Angina (year 1)	3236	100	32.36	
Angina (ongoing)	906	100	9.06	

TABLE 34 Base-case health state and transition costs (*continued*)

Health state	Mean cost (£)	Gamma distribution		Source
		Alpha	Beta	
Hypoglycaemia	178	100	1.78	Authors' calculation (weighted average of the following HRG codes, with activities obtained from the hypoglycaemia rates observed before and after DAFNE: KB02D, KB02E, KB02F. KB02D, KB02E, KB02F, KB01B, KB01B, KB01A, KB01A, PS13A, PS13B, PS13C, VB09Z, VB09Z)
DKA with hospitalisation	1333	100	13.33	NHS Reference Costs[207] [activity-weighted average of 'Non-Elective Inpatient (Long Stay)', 'Non-Elective Inpatient (Long Stay) Excess Bed-day' and 'Non-Elective Inpatient (Short Stay)' for currency codes KB01B and PA67Z respectively]
Cost of a diabetic patient with no complications	4212	100	42.12	Clarke *et al.*[208] (UKPDS 65)

BNF, *British National Formulary*; HRG, Healthcare Resource Group; PAD, peripheral arterial disease.

In addition to sources such as the *British National Formulary*[204] and NHS Reference Costs,[206] two main source papers that informed the mean costs reported in *Table 32* were those by McEwan *et al.*[205] and Clarke *et al.*[208] McEwan *et al.*[205] used a discrete simulation model to forecast the cost and health outcomes of a cohort of 10,000 individuals with type 1 diabetes over a time horizon of 40 years, with the unit costs of each event obtained from a number of sources including Clarke *et al.*[208] and McEwan *et al.*[210] Clarke *et al.*[208] used data from 5102 patients with type 2 diabetes (mean age 52.4 years at diagnosis) who participated in the UKPDS to develop a multiple regression model for estimating the immediate and long-term health-care costs associated with seven diabetes-related complications (MI, stroke, angina or ischaemic heart disease, heart failure, blindness in one eye, amputation and cataract extraction).

Perspective, discounting and other model functionality

The model was developed in line with Modelling Good Research Practice guidelines,[211] recommendations from the American Diabetes Association[212] and published checklists for economic evaluation.[213,214] The model uses an annual discount rate of 3.5% as default (for both costs and QALYs, as recommended by NICE[168]). The model takes a health service perspective and uses a lifetime horizon (i.e. until all simulated patients have died) as the default but the perspective and time horizon are flexible and can be set by the model user. The model is capable of performing probabilistic sensitivity analysis (PSA), allowing the effects of parameter uncertainty to be captured and the likelihood that interventions are cost-effective to be reported.

Model outputs

The model allows tracking of the history of each patient every year, which enables easy verification and validation of the model. This includes patient characteristics (e.g. HbA_{1c}, blood pressure, HDL), the incidence of acute complications (e.g. severe hypoglycaemia and DKA), and microvascular and macrovascular complication status (i.e. disease progression) for each year that the patient is alive. The aggregated numbers of patients in different health states are output each year and the total numbers of each event are also output at the end of the lifetime horizon. The costs and utility values, including the split of costs and disutilities by complication, are output for each patient for every year that they are alive (and also at the end of the lifetime horizon).

Model flexibility

The model, programmed in Simul8 software (version 17; Simul8 Corporation, Boston, MA, USA), was developed in a flexible manner that allows the use of alternative sets of input data. The user can select whether to perform a deterministic analysis or conduct PSA whereby model parameters are sampled from probability distributions. The model also has several option dialogues that allow the user to change the time horizon, discount rates for costs and QALYs, patient cohort characteristics, cohort size, treatment effects and cost, and utility sources.

Model verification

Internal verification of the model code (visual logic in Simul8) was conducted throughout the model implementation process. Patient characteristics and complication statuses were checked to ensure that they were changing as expected and that patients were following expected routes. The costs and utility value outputs each year were checked against the patient status outputs for face validity. The aggregated outputs were also cross-checked against the sum of individual patient outputs. Second-order validation was also conducted whereby the risk model was validated against the data from which it was estimated.

Results framework

The model outputs include a series of simulated clinical event rates over the lifetime of the simulated patients. These include microalbuminuria, macroalbuminuria, ESRD, death from ESRD, background retinopathy, proliferative retinopathy, macular oedema, blindness, clinical neuropathy, amputation, non-fatal MI, fatal MI, non-fatal stroke, fatal stroke, non-fatal heart failure, fatal heart failure, angina, severe hypoglycaemia and DKA. The total numbers of patient-years and life-years per patient are also reported.

For cost-effectiveness, the model reports the intervention cost, that is, the DAFNE education programme costs, discounted insulin costs, the discounted cost of long-term complications, the discounted cost of adverse events and the combined total average discounted cost. On the benefits side we report the mean discounted QALYs lived if no complications, discounted QALYs lost because of long-term complications, discounted QALYs lost because of adverse events and the combined total average discounted QALYs. From these measures we can then compute incremental cost-effectiveness ratios (ICERs) and net monetary benefit at a threshold of £20,000 per QALY and examine uncertainty using PSA to compute the percentage probability that an intervention is more cost-effective than its comparator at different willingness-to-pay thresholds.

Validation exercises

The results of second-order validation, which compared the model results with the data from the studies used to build the model, are shown in *Table 35*. For microvascular complications, the normalised differences between the model results and the published data ranged between 0% and 15%, except for deaths from ESRD (for which the difference is > 50%, attributed to low event rates) and neuropathy events (difference of approximately 25%), with most differences < 10%. For macrovascular complications, the normalised differences between model results and the published data ranged between 0% and 10%, with most differences < 5%. More details on these validation exercises can be found in the published paper.[183]

Discussion and conclusions

The Sheffield Type 1 Diabetes Policy Model has several key strengths. First, the model is based on a structured conceptual modelling process that included input from multidisciplinary experts in the fields of clinical diabetes, psychology, diabetes education and simulation modelling. Second, the model is highly flexible, allowing users to specify the characteristics of simulated patients, the time horizon, cohort size, how treatment effects are accounted for, what outcomes are tracked by the model and whether to run the model deterministically or probabilistically. Third, the model is a patient-level simulation that offers the advantage of being able to account for individual differences between patients. Fourth, the model allows for patients' psychological and behavioural characteristics and their impact on treatment effectiveness to be incorporated into analyses. Finally, the model is structured to facilitate PSA, which accounts for uncertainty in the model parameters and is recommended by several HTA agencies including NICE.[168]

TABLE 35 Results of second-order validation against source data for event rates

Microvascular complication	Source	Observed incidence (%)	Modelled incidence (%)
Nephropathy			
Microalbuminuria	DCCT[215]	20	17
Macroalbuminuria	Wong *et al.*[195] (WESDR)	33	27
ESRD	Wong *et al.*[195] (WESDR)	20	18
Death from ESRD	UKPDS 33[186]	0.26	0.11
Retinopathy			
Background retinopathy	Klein *et al.*[187] (WESDR XXII)	80	64
Proliferative retinopathy	Klein *et al.*[187] (WESDR XXII)	39	40
Macular oedema	Klein *et al.*[187] (WESDR XXII)	26	18
Blindness	Klein *et al.*[187] (WESDR XXII)	2.3	2.3
Neuropathy			
Neuropathy	DCCT[188]	9.3	11.9
Amputation	Moss *et al.*[194] (WESDR)	9.6	9.5
Macrovascular complication	**Source**	**Observed % of total events**	**Modelled % of total events**
MI	Cederholm *et al.*,[190] Palmer[198]	53	52
Stroke	Cederholm *et al.*,[190] Palmer[198]	7	7
Heart failure	Cederholm *et al.*,[190] Palmer[198]	12	13
Angina	Cederholm *et al.*,[190] Palmer[198]	28	29
All CVD	Cederholm *et al.*[190]	5.41	5.61

Despite its many advantages, the Sheffield Type 1 Diabetes Policy Model also has some limitations. The model used published data from non-UK settings to define the risk of long-term complications, some of which are now very old. The risk of long-term macrovascular complications is dependent mainly on HbA_{1c} levels and the effect of other risk factors is not captured, which might cause bias when evaluating interventions that affect risk factors other than HbA_{1c}. Although the uncertainty in most of the parameters is incorporated into the model, uncertainty in some parameters (e.g. coefficients of the risk equations) is not captured.

Model summary and list of versions

In summary, the Sheffield Type 1 Diabetes Policy Model offers a new whole-disease model of type 1 diabetes and its associated complications. The model development process was evidence based and was carried out in consultation with multidisciplinary experts. The model is highly flexible and has broad potential application to evaluate the DAFNE programme, other diabetes structured education programmes and other interventions for type 1 diabetes. *Table 36* provides an overview of the development of the model and key features of each version of the model.

TABLE 36 List of model versions and key changes

Version	Key aspects	Use in published work and this report	References
1.0	First version of the model structure developed	Structure described in this section of the chapter	Thokala *et al.*[183]
1.1	Version used for analysis of the DAFNE programme during 2012, incorporating evidence from the DAFNE research database, the original trial and the psychosocial study	(a) Initial analyses of DAFNE education vs. no DAFNE education, i.e. revision of the analyses of Shearer *et al.*[166]	Kruger *et al.*[216]
		(b) Analysis of the incorporation of psychological predictors of treatment response to DAFNE education (see final section of this chapter)	Kruger *et al.*,[217,218] *Modelling patient psychology and behaviour alongside economic outcomes*
1.2	Version used for analysis of the DAFNE programme in late 2013 and 2014. Key developments from version 1.1 include revision of utilities incorporating evidence from Peasgood *et al.*[170] and Alva *et al.*[174] and revision of estimates of the effects of changes in hypoglycaemia and DKA rates as a result of DAFNE education based on analysis of the research database and incorporation of revised costs and utilities for these	(a) Further revised analyses of DAFNE education vs. no DAFNE education, updating Kruger *et al.*[216] from version 1.1 to version 1.2 of the model (see *Cost-effectiveness of DAFNE education compared with no DAFNE education*) and examining cost-effectiveness in the original trial population and in a wider population based on DAFNE participants from the research database	*Cost-effectiveness of DAFNE education compared with no DAFNE education*
		(b) Analysis of the 1-week DAFNE vs. 5-week DAFNE course using evidence from the 5 × 1-day RCT	*Cost-effectiveness of 5-week compared with 1-week DAFNE education*

Cost-effectiveness of DAFNE education compared with no DAFNE education

Introduction

Alongside clinical effectiveness, cost-effectiveness is a key factor that health policy decision-makers take into consideration when deciding what health technologies to commission. The cost-effectiveness of an intervention can be estimated by comparing the outcomes and costs associated with the intervention with those of the next most effective alternative.[219] If these outcomes are estimated as QALYs, as recommended by NICE,[168] the ICER, or incremental cost per QALY, can be calculated and compared with those for alternative uses of health-care funding. NICE[168] typically recommends funding interventions with an ICER below a threshold of £20,000 per QALY.

In 2004, Shearer *et al.*[166] published an economic evaluation of DAFNE modelled on the RCT data,[7] which suggested that the programme was cost-effective over a 10-year time horizon when compared with no DAFNE education. However, this analysis had four key limitations. First, the evaluation used a short time horizon whereas the costs and benefits of DAFNE may extend throughout the lifetime of the person with diabetes. Second, the economic model used to estimate the cost-effectiveness of DAFNE education included only microvascular diabetes-related complications and did not include the potential impact of DAFNE education on the risk of cardiovascular complications. Third, the evaluation did not include PSA to fully account for uncertainty regarding the model parameters. Finally, Shearer *et al.*[166] modelled a fixed 10-mmol/mol (0.9%) HbA_{1c} reduction 12 months after DAFNE education for all patients, whereas more recently published evidence suggests that patients display a heterogeneous and more limited HbA_{1c} response following DAFNE training.[12] New evidence on the DAFNE programme is now available from the NIHR research programme[23,101] and therefore an updated estimate of the cost-effectiveness of DAFNE education is required.

The aim of the current study was to use a new economic model of type 1 diabetes that addresses some of the limitations of the previous economic evaluation[166] to re-estimate the incremental cost per QALY of DAFNE education compared with no training for adults with type 1 diabetes. Full details of all analyses conducted have been reported elsewhere.[216]

Methods

Model structure

The Sheffield Type 1 Diabetes Policy Model version 1.2, a patient-level simulation model of type 1 diabetes, was used to conduct the economic evaluation. The model is described in the previous section.

Data sources

Most of the Sheffield Type 1 Diabetes Policy Model data sources are outlined in the previous section.

In addition, an individual-level data set providing demographic and biomedical data (baseline and 6-month, 12-month and approximately 44-month follow-up data) from participants in the DAFNE RCT[12] ($n = 141$) was used to define the characteristics of simulated individuals and the effect of the DAFNE intervention on HbA_{1c}.

The NIHR DAFNE research database[23] was used to define the risk equations for adverse events in a sensitivity analysis (*see Development of the Sheffield Type 1 Diabetes Policy Model*).

Table 37 provides the breakdown of the cost of the DAFNE programme, with the per-patient cost corresponding to £359 in the current scheme; further details can be found on DAFNE *Fact Sheet Six*.[220] The annual cost of insulin delivery was assumed to be slightly higher in the DAFNE training arm (£609) than in the no DAFNE training arm (£559) based on data from the DAFNE RCT[7] suggesting that, after DAFNE training, people use slightly more insulin and inject insulin more times per day.

TABLE 37 Breakdown of the cost of the DAFNE programme

	Cost of original DAFNE course (£)			Cost of 5-week DAFNE course (£)		
	Number of courses per year			Number of courses per year		
Items included in costing	6	12	15	6	12	15
Educator backfill at 10 days per course based on Agenda for Change top band 7 including 22.3% on-costs	11,333.40	22,666.80	28,333.50	11,333.40	22,666.80	28,333.50
Administration and clerical backfill at 3 days per course based on Agenda for Change top band 3 including 22% on-costs	1611.36	3222.72	4028.40	1611.36	3222.72	4028.40
Patient resources	231.36	462.72	578.40	750.24	1500.48	1875.60
Training two educators and one doctor 10% depletion of staff per year	300.00	300.00	300.00	300.00	300.00	300.00
5-week training for two educators, 10% depletion of staff per year	0.00	0.00	0.00	33.00	33.00	33.00
DAFNE programme set-up costs, 10% depletion per year	110.70	110.70	110.70	110.70	110.70	110.70
Central administration contribution	3650.00	3650.00	3650.00	3650.00	3650.00	3650.00
Total	17,236.82	30,412.94	37,001.00	17,788.70	31,483.70	38,331.20
Number of patients	48	96	120	48	96	120
Cost per patient	359.10	316.80	308.34	370.60	327.96	319.43

Treatment effectiveness

In the base-case analysis the change in HbA_{1c} level after DAFNE training was based on analysis of the longer-term follow-up data from the DAFNE RCT.[12] For the DAFNE training arm an OLS regression model was used to predict the 12-month HbA_{1c} level from the baseline HbA_{1c} level (*Table 38*). A similar regression model was constructed to predict the 44-month HbA_{1c} level from the baseline and 12-month HbA_{1c} levels (*Table 39*). It was assumed that the HbA_{1c} level returns to the baseline value at year 5. In the control arm the HbA_{1c} level was assumed to remain unchanged from baseline (as observed up to 6 months in the RCT[7]). Sensitivity analysis was carried out using data on 6-month HbA_{1c} levels for both arms in the trial (*Table 40*) instead of the 12-month data. Further sensitivity analysis used the treatment effect on HbA_{1c} estimated from the research database rather than from the original RCT (*Table 41*).

TABLE 38 Regression for the 12-month HbA_{1c} treatment effect from the original RCT:[12] DAFNE training arm only

	Coefficient	Standard error	95% CI
Intercept	2.3398	1.5628	–0.8614 to 5.5410
Baseline HbA_{1c}	0.6976	0.1710	0.3473 to 1.0478

Regression model: 12-month HbA_{1c} = Intercept + coeff × baseline HbA_{1c} + error.

TABLE 39 Regression for the 44-month HbA_{1c} treatment effect controlling for baseline and 12-month HbA_{1c} from the original RCT:[12] DAFNE training arm only

	Coefficient	Standard error	95% CI
Intercept	1.8164	1.5039	–1.3025 to 4.9352
Baseline HbA_{1c}	–0.0302	0.1562	–0.3542 to 0.2938
12-month HbA_{1c}	0.8552	0.1229	0.6003 to 1.1101

Regression model: 44-month HbA_{1c} = Intercept + coeff × baseline HbA_{1c} + coeff × 12 month HbA_{1c} + error.

TABLE 40 Regression for the 6-month HbA_{1c} treatment effect from the original RCT:[7] DAFNE training and no DAFNE training arms

	Coefficient	Standard error	95% CI
Intercept	0.9879	0.7843	–0.5833 to 2.5591
Treatment arm	1.0780	0.1776	0.7221 to 1.4338
Baseline HbA_{1c}	0.7859	0.0811	0.6235 to 0.9484

Regression model: New_HbA_{1c} = Intercept + coeff × treatment arm + coeff × baseline HbA_{1c} + error (note: within the cost-effectiveness model we assume that new_HbA_{1c} = 12-month HbA_{1c} from DAFNE and new_HbA_{1c} = 6-month HbA_{1c} from delayed DAFNE).

Note

DAFNE refers to participants in the original RCT who received the DAFNE intervention at the beginning of the trial. 'delayed DAFNE' identifies participants in the control arm, who received the intervention 6-months after the initiation of the trial.

TABLE 41 Regression for the 12-month HbA_{1c} treatment effect from the research database

	Coefficient	Standard error	95% CI
Intercept	2.7618	0.2089	2.3396 to 3.1840
Baseline HbA_{1c}	0.6526	0.0254	0.0601 to 0.0704

Regression model: 12-month HbA_{1c} = Intercept + coeff × baseline HbA_{1c} + error.

The modelling for the probability of occurrence of hypoglycaemia and DKA is based on the statistical analyses reported in *Table 32*.

Economic evaluation

Essentially, we address two RQs in this section:

1. What is the cost-effectiveness of DAFNE education compared with no DAFNE education in the original RCT population?
2. What is the cost-effectiveness of DAFNE education compared with no DAFNE education in the DAFNE research database population? (Given that the original RCT had higher average HbA_{1c} levels than the average for current recipients of DAFNE in the research database, this might make a difference).

The model was used to simulate 5000 individuals under two treatment conditions: DAFNE training and no DAFNE training. The 5000 simulated individuals were representative of the participants in the DAFNE trial;[7] *Table 42* presents a summary of the baseline characteristics of the simulated patients. Costs and QALYs were estimated over a lifetime horizon from a NHS perspective and were discounted at a rate of 3.5% as recommended by NICE.[168]

Sensitivity analyses

Probabilistic sensitivity analyses[219] were conducted to explore uncertainty in the model results. Sensitivity analyses were also conducted by simulating plausible alternative assumptions about treatment effectiveness.

TABLE 42 Baseline characteristics of the simulated patients ($n = 5000$) based on the original DAFNE RCT participants and the research database DAFNE participants

Characteristic	Original DAFNE RCT participants, mean (SD) or % in category	Research database DAFNE participants, mean (SD) or % in category
Age (years)	40 (9)	41 (13)
Diabetes duration (years)	16 (10)	17 (13)
Systolic blood pressure (mmHg)	130 (18)	128 (17)
LDL (mmol/l)	3.2 (0.9)	2.5 (0.8)
HDL (mmol/l)	1.5 (0.5)	1.6 (0.5)
Triglycerides (mmol/l)	1.5 (0.9)	1.2 (0.9)
Total cholesterol (mmol/l)	5.1 (0.9)	4.6 (1.0)
HbA_{1c} (mmol/mol)	79 (12)	71 (17)
HbA_{1c} (%)	9.4 (1.1)	8.7 (1.5)
Gender		
Male	45	51
Female	55	49
Smoking status		
Current smoker	23	19
Former smoker	22	25
Non-smoker	55	57

continued

TABLE 42 Baseline characteristics of the simulated patients ($n = 5000$) based on the original DAFNE RCT participants and the research database DAFNE participants (*continued*)

Characteristic	Original DAFNE RCT participants, mean (SD) or % in category	Research database DAFNE participants, mean (SD) or % in category
Physical activity status		
Medium	100	100
Race		
White	100	90
Nephropathy status		
No nephropathy	94	90
Microalbuminuria	5	8
Macroalbuminuria	1	4
Dialysis/transplantation		2
Neuropathy status		
No neuropathy	94	89
Clinical neuropathy	6	8
Foot ulcer		3
Retinopathy status		
No retinopathy	61	47
Background retinopathy	29	41
Proliferative retinopathy	10	10
Partially sighted/blind		2
MI status		
No history of MI	100	100
Stroke status		
No history of stroke	100	100
Heart failure status		
No history of heart failure	100	100
Angina status		
No history of angina	100	100

Results

Results for DAFNE education compared with no DAFNE education in the original trial population

Table 43 presents the results of the base-case cost-effectiveness analysis along with the corresponding 10-year results (when reported) from the previous economic evaluation of the DAFNE programme.[12]

Clinical results

The survival gain for DAFNE education compared with no DAFNE education was 407 patient-years across the whole cohort, equivalent to an expected gain in life expectancy of 30 days per patient. DAFNE education resulted in a lower incidence of nephropathy and neuropathy but a slightly higher incidence of retinopathy, some cardiovascular events and adverse events. These increases were primarily due to the increase in number of life-years lived across the whole cohort as the rates per patient-year were very similar between the arms.

TABLE 43 Economic evaluation of DAFNE education vs. no DAFNE education in the original trial population[7] using evidence of effect from the RCT

Diabetes-related complications	Control: no DAFNE education ($n = 5000$)	Intervention: DAFNE education ($n = 5000$)	Increment	Incremental 10-year result from Shearer *et al.*[166]
Clinical results (total incidence in whole cohort over a lifetime horizon)				
Microalbuminuria	3214	3205	–9	–
Macroalbuminuria	2831	2822	–9	–
ESRD	2432	2418	–14	–
Death from ESRD	1380	1367	–13	–
Background retinopathy	1613	1648	35	–
Proliferative retinopathy	1255	1266	11	–
Macular oedema	1251	1266	15	–
Blindness	150	151	1	–
Clinical neuropathy	2345	2342	–3	–
Amputation	673	670	–3	–
Non-fatal MI	1769	1773	4	–
Fatal MI	1732	1740	8	–
Non-fatal stroke	357	359	2	–
Fatal stroke	100	101	1	–
Non-fatal heart failure	761	761	0	–
Fatal heart failure	46	46	0	–
Angina	1921	1923	2	–
Severe hypoglycaemia	80,745	15,178	–65,567	0[a]
DKA	6353	1391	–4962	4[a]
Number of patient-years	152,436	152,843	407	5.16[a]
Life-years per patient	30.49	30.57	0.08	0.05

continued

TABLE 43 Economic evaluation of DAFNE education vs. no DAFNE education in the original trial population[7] using evidence of effect from the RCT (*continued*)

Diabetes-related complications	Control: no DAFNE education ($n = 5000$)	Intervention: DAFNE education ($n = 5000$)	Increment	Incremental 10-year result from Shearer *et al.*[166]
Cost-effectiveness results (per patient over a lifetime horizon)				
DAFNE intervention cost (£)	0	359	359	545
Discounted insulin cost (£)	9555	10,438	883	456
Discounted cost of long-term complications (£)	57,471	56,642	–829	–2851
Discounted cost of adverse events (£)	2587	518	–2068	–24
Combined total average discounted cost (£)	69,613	67,957	–1656	–2237[b]
Mean discounted QALYs lived if no complications	14.8929	14.9276	0.0347	–
Discounted QALYs lost because of long-term complications	–1.1142	–1.1082	0.0060	–
Discounted QALYs lost because of adverse events	–0.0224	–0.0046	0.0178	–
Combined total average discounted QALYs	13.7563	13.8148	0.0585	0.1220
ICER (unadjusted) (£)	–	–	–28,316	Dominant
ICER (jackknife) (£)	–	–	–28,259	–
Net monetary benefit at threshold of £20,000 per QALY[c] (£)	–	–	2825	4557
Probability that DAFNE education is cost-effective at a threshold of £20,000 per QALY (%)	–	–	92	–

a Per 100 patients.
b Includes –£362 because of a reduction in outpatient reviews.
c Net monetary benefit = ΔQALYs × threshold – Δcosts.

Cost and quality-adjusted life-year results

Discounted over the lifetime horizon, DAFNE education saves £1656 per patient compared with no DAFNE education (£67,957 vs. £69,613). Despite the higher cost of insulin and the cost of the DAFNE intervention, the lower cost of long-term complications and adverse events in the DAFNE education arm resulted in lower overall costs.

Discounted over the lifetime horizon, DAFNE education generated 0.0585 additional QALYs per patient compared with no DAFNE education (13.8148 vs. 13.7563). The QALY gain was a result of increased survival and the reduced incidence of some long-term complications and a reduction in the number of episodes of short-term adverse events experienced.

The mean ICER was –£28,316 per QALY; this would be considered cost-effective (in fact, cost-saving) at the NICE willingness-to-pay threshold of £20,000 per QALY.[168] Jackknifing was used to generate a less biased point estimate of the mean ICER[221] of –£28,259 per QALY.

Uncertainty

Figure 8 presents the results from the PSA. The cost-effectiveness acceptability curve (*Figure 9*) shows that there was a 92% probability that DAFNE education would be cost-effective at a £20,000 per QALY willingness-to-pay threshold.

Table 44 presents the results of the sensitivity analyses. In all scenarios DAFNE education produced more QALYs than no DAFNE education and in some scenarios DAFNE education also resulted in lower costs.

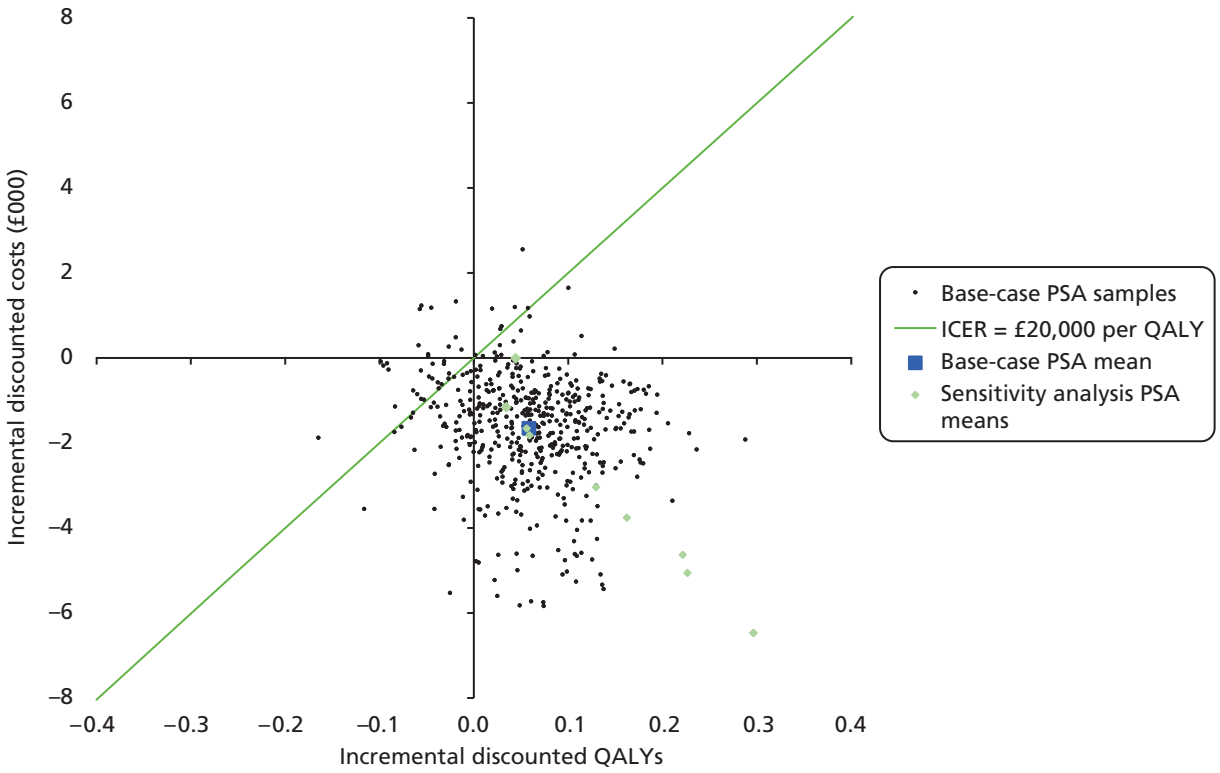

FIGURE 8 The cost-effectiveness of DAFNE education vs. no DAFNE education in the original RCT population[7] on the cost-effectiveness plane.

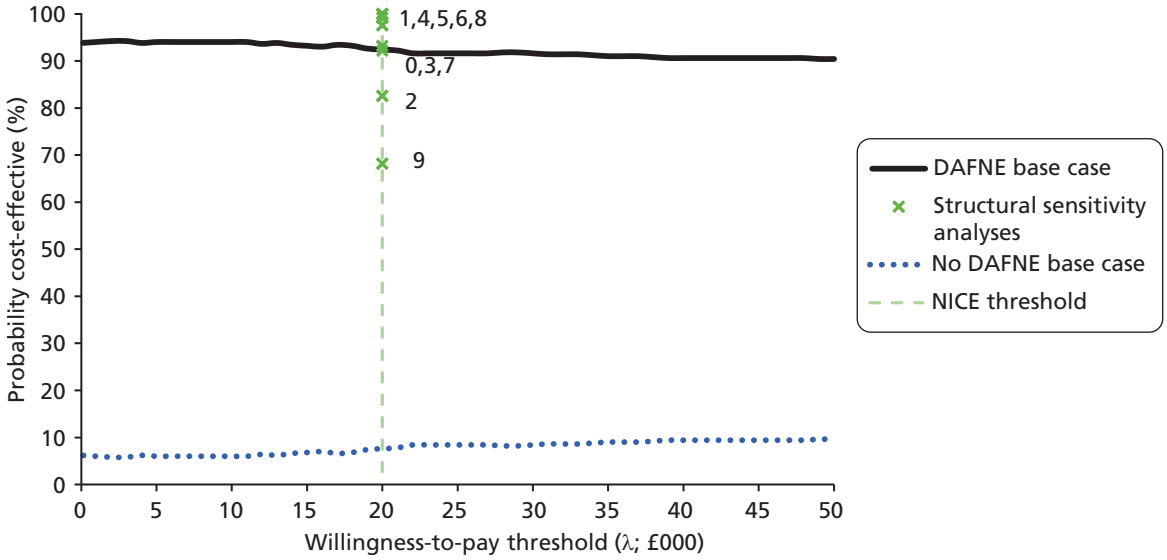

FIGURE 9 Cost-effectiveness acceptability curve: the probability that DAFNE education is cost-effective compared with no DAFNE education in the original RCT population[7] at different willingness-to-pay thresholds. See *Table 44* for a description of the sensitivity analyses.

TABLE 44 Sensitivity analysis results for the economic evaluation of DAFNE education vs. no DAFNE education in the original RCT population[7]

	Sensitivity analysis	Incremental discounted lifetime cost of long-term complications (£)	Incremental discounted lifetime cost of adverse events (£)	Incremental discounted lifetime cost (£) (% different from base case)	Incremental discounted lifetime QALYs (% different from base case)	Net monetary benefit at threshold of £20,000 per QALY (£)	Probability DAFNE education is cost-effective at threshold of £20,000 per QALY (%)	ICER (£)
0	Base case: 12-month HbA_{1c} predicted from long-term data[12] and 4-year HbA_{1c} predicted from long-term data[12] and maintained to year 5	–829	–2068	–1655	0.0585	2825	92	Dominant
1	6-month HbA_{1c} predicted from RCT data[7] and 12-month and 4-year HbA_{1c} predicted from long-term data[12] and maintained to year 5	–2975	–2075	–3757 (–127)	0.1622 (+177)	7031	100	Dominant
2	12-month HbA_{1c} predicted from long-term data[12] and 4-year HbA_{1c} predicted from long-term data[12] and maintained to year 7	–845	–2056	–1659 (–0.2)	0.0561 (–4)	2781	83	Dominant
3	6-month HbA_{1c} predicted from RCT data[7] and 12-month and 4-year HbA_{1c} predicted from long-term data[12] and maintained to year 7	–4315	–2070	–5057 (–205)	0.2215 (+287)	9588	100	Dominant
4	12-month HbA_{1c} predicted from long-term data[12] and maintained to year 7	–2253	–2067	–3041 (–84)	0.1296 (+122)	5634	98	Dominant
5	6-month HbA_{1c} values obtained from original DAFNE RCT data[7] when predicted to remain unchanged at 12 months maintained to year 7	–5757	–2077	–6469 (–291)	0.2965 (+407)	12,398	100	Dominant
6	12-month HbA_{1c} predicted from long-term data[12] and only 1 year of benefit for HbA_{1c}	–311	–2076	–1159 (+30)	0.0344 (–41)	1846	93	Dominant
7	6-month HbA_{1c} values obtained from original DAFNE RCT data[7] when predicted to remain unchanged at 12 months and only 1 year of benefit for HbA_{1c}	–982	–2077	–1820 (–10)	0.0590 (+10)	3001	99	Dominant
8	Impact of DAFNE education on hypoglycaemia and DKA adverse events is assumed to last the same amount of time as HbA_{1c} maintenance (5 years) instead of a lifetime	–829	–421	–8 (+100)	0.0444 (–24)	2825	92	Dominant

The mean results from the sensitivity analyses are also represented in *Figures 8–9*, showing that the majority of the scenarios support the conclusion from the base-case analysis that DAFNE education is cost-effective compared with no DAFNE education.

Results for DAFNE education compared with no DAFNE education in the DAFNE participant population research database

A similar set of results was obtained for the alternative population for analysis, that is, that represented by the DAFNE research database participants.

Table 45 shows that, in the base case, the incremental differences between DAFNE education and no DAFNE education remain favourable in this wider population group and that, overall, DAFNE education appears to be cost-effective, with an incremental cost overall of –£1494 and a QALY gain per person of 0.0460. Uncertainty analysis shows that the probability of DAFNE being cost-effective under this base case is 97%.

TABLE 45 Economic evaluation of DAFNE education vs. no DAFNE education in the DAFNE participants research database using evidence of effect from the research database

Diabetes-related complications	Control: no DAFNE education ($n = 5000$)	Intervention: DAFNE education ($n = 5000$)	Increment	Incremental 10-year result from Shearer *et al.*[166]
Clinical results (total incidence in whole cohort over a lifetime horizon)				
Microalbuminuria	2740	2744	4	–
Macroalbuminuria	2098	2099	1	–
ESRD	1913	1910	–3	–
Death from ESRD	1157	1151	–6	–
Background retinopathy	1277	1300	23	–
Proliferative retinopathy	923	918	–5	–
Macular oedema	1012	1030	18	–
Blindness	112	111	–1	–
Clinical neuropathy	1813	1816	3	–
Amputation	532	532	0	–
Non-fatal MI	1231	1235	4	–
Fatal MI	1244	1252	8	–
Non-fatal stroke	252	252	0	–
Fatal stroke	70	71	1	–
Non-fatal heart failure	534	536	2	–
Fatal heart failure	32	33	1	–
Angina	1350	1353	3	–
Severe hypoglycaemia	98,148	18,938	–79,210	0[a]
DKA	5402	1297	–4104	4[a]
Number of patient-years	162,301	162,589	288	5.16[a]
Life-years per patient	32.46	32.52	0.06	0.05

continued

TABLE 45 Economic evaluation of DAFNE education vs. no DAFNE education in the DAFNE participants research database using evidence of effect from the research database (*continued*)

Diabetes-related complications	Control: no DAFNE education ($n = 5000$)	Intervention: DAFNE education ($n = 5000$)	Increment	Incremental 10-year result from Shearer *et al.*[166]
Cost-effectiveness results (per patient over a lifetime horizon)				
DAFNE intervention cost (£)	0	359	359	545
Discounted insulin costs (£)	9726	10,618	891	456
Discounted cost of long-term complications (£)	48,065	47,448	–617	–2851
Discounted cost of adverse events (£)	2677	549	–2128	–24
Combined total average discounted cost (£)	60,468	58,974	–1494	–2237[b]
Mean discounted QALYs lived if no complications	15.1785	15.2026	0.0241	–
Discounted QALYs lost because of long-term complications	–0.9184	–0.9137	0.0047	–
Discounted QALYs lost because of adverse events	–0.0219	–0.0046	0.0172	–
Combined total average discounted QALYs	14.2382	14.2842	0.0460	0.1220
ICER (unadjusted) (£)	–	–	–32,463	Dominant
ICER (jackknife) (£)	–	–	–32,367	–
Net monetary benefit at threshold of £20,000 per QALY[c] (£)	–	–	2414	4557
Probability that DAFNE education is cost-effective at £20,000 per QALY threshold (%)	–	–	97	–

a Per 100 patients.
b Includes –£362 because of a reduction in outpatient reviews.
c Net monetary benefit = ΔQALYs × threshold – Δcosts.

In the sensitivity analyses, although slightly different results are obtained, DAFNE remains cost-effective under each scenario (*Table 46*).

The uncertainty in the model parameters has been illustrated further using a cost-effectiveness plane (*Figure 10*) and a cost-effectiveness acceptability curve (*Figure 11*).

Discussion

The results of this study confirm and extend those of the previous Shearer *et al.*[166] economic evaluation, which suggested that DAFNE training was cost-effective over a 10-year time horizon, generating 0.122 additional QALYs for a cost saving of £2200 per patient. The current results are slightly different from those of the previous economic evaluation, suggesting that DAFNE education generates 0.0585 additional QALYs for a cost saving of £1656 per patient over a lifetime horizon. This is because the assumptions regarding the HbA_{1c} effect of the DAFNE intervention were more conservative in the current study, there is new evidence suggesting lower rates of hypoglycaemia and DKA as well as lower numbers of events for some of the long-term complications in DAFNE participants and a longer time horizon was used in the current study. Similarly, by using the evidence from the DAFNE research database to evaluate the present-day cost-effectiveness of DAFNE education compared with no DAFNE education, DAFNE education generates 0.0460 additional QALYs for a cost saving of £1494 per patient over a lifetime horizon.

TABLE 46 Sensitivity analysis results for the economic evaluation of DAFNE education vs. no DAFNE education in the DAFNE participants research database

	Sensitivity analysis	Incremental lifetime discounted costs of long-term complications (£)	Incremental lifetime discounted costs of adverse events (£)	Incremental discounted lifetime costs (£) (% different from base case)	Incremental discounted lifetime QALYs (% different from base case)	Net monetary benefit at threshold of £20,000 per QALY (£)	Probability that DAFNE education is cost-effective at threshold of £20,000 per QALY (%)	ICER (£)
0	Base case: 12-month HbA_{1c} predicted from research database data, maintained to year 5	–617	–2128	–1494	0.0460	2414	97	Dominant
1	12-month HbA_{1c} predicted from research database data, maintained to year 7	–947	–2135	–1816 (–22)	0.0697 (+51)	3210	99	Dominant
2	12-month HbA_{1c} predicted from long-term data[12] and 4-year HbA_{1c} predicted from long-term data[12] and maintained to year 5	–54	–2117	–929 (+38)	0.0237 (–49)	1403	84	Dominant
3	Impact of DAFNE education on hypoglycaemia and DKA adverse events is assumed to last the same amount of time as HbA_{1c} maintenance (5 years) instead of a lifetime	–617	–452	181 (+112)	0.0326 (–29)	471	64	5558

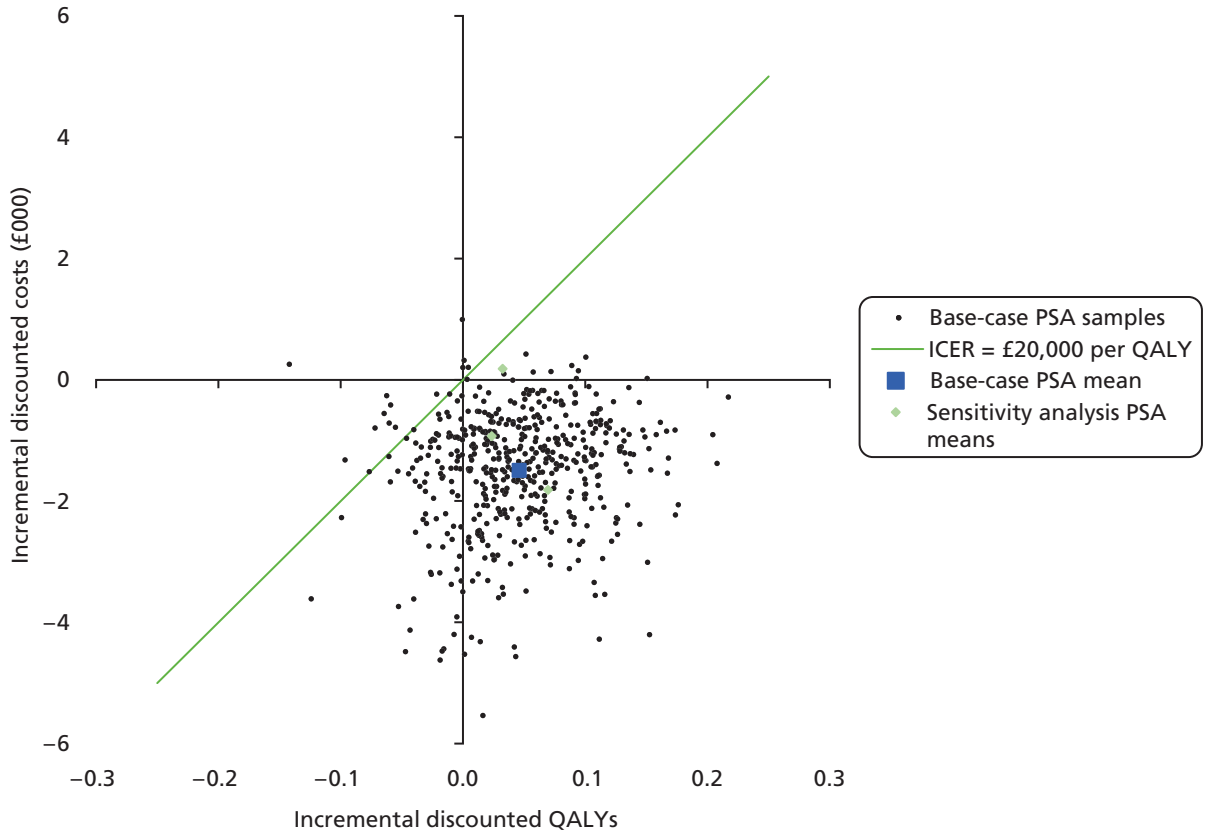

FIGURE 10 The cost-effectiveness of DAFNE education compared with no DAFNE education in the research database population on the cost-effectiveness plane.

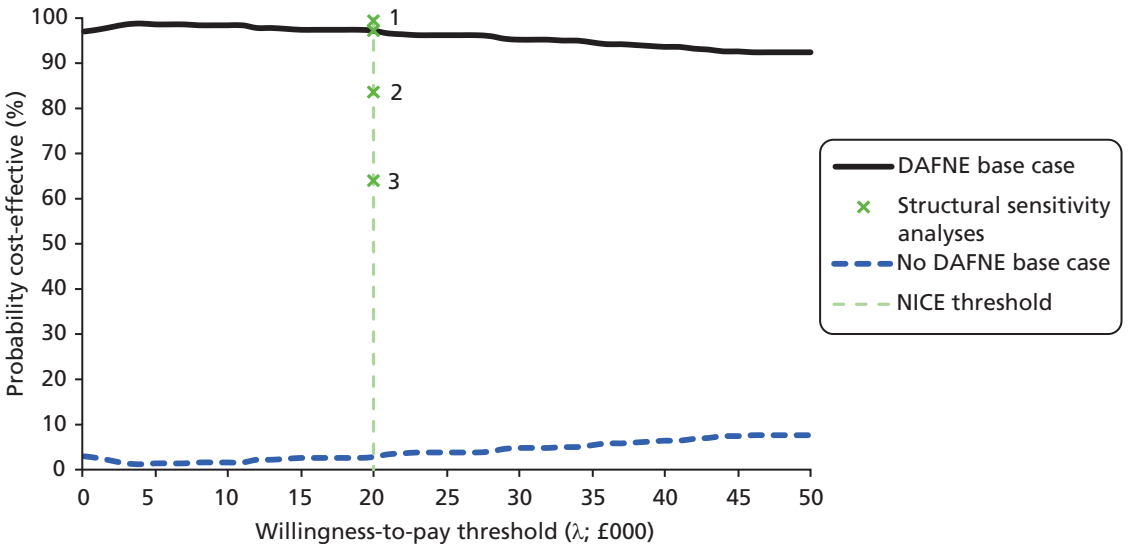

FIGURE 11 Cost-effectiveness acceptability curve: the probability that DAFNE education is cost-effective compared with no DAFNE education in the original RCT population at different willingness-to-pay thresholds.

This study improves on the accuracy of the previous economic evaluation of the DAFNE programme by including macrovascular complications, allowing for a heterogeneous HbA_{1c} response to DAFNE education, extending the time horizon and conducting PSA. Limitations of the current study include the restriction of the modelled population to those adults meeting the DAFNE RCT entry criteria.[7]

Conclusions

The current study builds on a previously reported economic evaluation of the DAFNE programme to estimate the cost-effectiveness of the structured education programme compared with no DAFNE education. The results of the current modelling, using version 1.2 of the Sheffield Type 1 Diabetes Policy Model, confirm that DAFNE education appears to be a cost-effective intervention (indeed, cost-saving in the base case and the majority of the sensitivity analyses) and support its provision by the NHS to people with type 1 diabetes in the UK.

Cost-effectiveness of 5-week compared with 1-week DAFNE education

Introduction

As of 2012 it was estimated that there were 2.5 million people with a confirmed diagnosis of diabetes in the UK, responsible for 10% of the NHS budget.[222] Type 1 diabetes is responsible for 10% of this diabetic population.[222]

A structured education programme is 'a planned and graded programme that is comprehensive in scope, flexible in content, responsive to an individual's clinical and psychological needs, and adaptable to his or her educational and cultural background'.[223] The DAFNE course is a 5-day outpatient course aiming to teach individuals about CP counting and insulin dose adjustments.

However, it is not always convenient for individuals to attend an intensive 5-day programme because of work and other committments. Given that many relevant structured education courses are delivered on a 1 day a week basis for up to 8 weeks,[98] and the possible biases associated with using observational data from the original DAFNE trial,[7] a separate RCT was undertaken.

This study aimed to estimate the cost-effectiveness of two alternative delivery strategies for the DAFNE programme by using data from the 5 × 1-day DAFNE RCT for within-trial analyses (short term) and modelling analyses (long term). Full details of all analyses conducted are intended for publication.

Methods

Within-trial analyses

The within-trial analyses were based on individual-level data collected during the 1-year follow-up after the completion of the trial. The within-trial resource use covered insulin, admissions, NHS contacts, other medication and the intervention. This information was collected from RCT participants using designated questionnaires.

Long-term modelling

Longer-term cost-effectiveness was assessed using version 1.2 of the Sheffield Type 1 Diabetes Policy Model (see *Development of the Sheffield Type 1 Diabetes Policy Model*).[183] The model was used to estimate the long-term cost-effectiveness of the two arms in the DAFNE 5 × 1-day RCT.

Long-term cost-effectiveness was evaluated from the perspective of the NHS. The outcomes of the model were lifetime costs and QALYs. The within-trial costs were based on insulin, admissions, NHS contacts, other medication and the intervention whereas the long-term model costs were based on the cost of developing a particular diabetes-related complication. Both costs and QALYs were discounted at a rate

of 3.5% in line with recommendations from NICE and the UK Treasury.[168,224] For each annual cycle, patient progression to a more severe health state was modelled using the Monte Carlo simulation technique, which allowed the development of multiple complications for a single patient. A total of 5000 patients were simulated based on a lifetime horizon, and 500 PSA runs were undertaken in line with the internal capacity of the Simul8 software program used.

Statistical analysis

The participants were individually randomised using a random block size, stratified by centre, and a web-based remote randomisation system to either a 1-week course or a 5-week course.[101]

The missing observations in the cost and utility data were completed using the multiple imputation approach. The predictive mean matching method was used to estimate the imputed utility values as this method is suitable for predicting variables that are bounded, continuous and distributed non-normally, such as the left-skewed EQ-5D data.[225]

Treatment effectiveness in terms of changes in glycated haemoglobin for the 5 × 1-day randomised controlled trial

The 5 × 1-day DAFNE RCT results were examined to develop a regression model predicting HbA_{1c} level at 12 months conditional on baseline HbA_{1c} and arm of the trial, that is, 1-week DAFNE education compared with 5-week DAFNE education (*Table 47*).

Results

Within-trial results

Table 48 provides a summary of the within-trial analysis undertaken for the DAFNE 5 × 1-day RCT. The costing analysis based on the within-trial data shows that the mean cluster-adjusted cost per individual was £9.94 more expensive for the 5-week arm than for the 1-week arm during the 12-month trial period.

TABLE 47 Regression for 12-month HbA_{1c} treatment effect from the 5 × 1-day RCT: 1-week and 5-week arms

	Coefficient	Standard error	95% CI
Intercept	1.6440	0.4899	0.6634 to 2.6246
5-week arm	0.1278	0.1301	–0.1327 to 0.3883
Baseline HbA_{1c}	0.7884	0.0609	0.6665 to 0.9103

12-month HbA_{1c} = intercept + coeff × baseline HbA_{1c} + coeff × treatment arm (1 = 5-week arm, 0 = 1-week arm) + error.

TABLE 48 Within-trial analysis summary for the DAFNE 5 × 1-day RCT

Arm	Complete-case QALYs (SD)	Baseline QALYs (SD)	Adjusted difference (SD)[a]	Complete-case cost (SD) (£)	Adjusted difference[a] (SD) (£)	Adjusted bootstrapped ICER (£) (cost-effectiveness probability, %[b])
1 week	0.8529 (0.2129)	0.8561 (0.2225)	0.0252 (0.0180)	1102 (468)	9.94 (63.90)	786 (91.2)
5 weeks	0.8532 (0.2130)	0.8238 (0.2364)		1112 (368)		

a Refers to the within-cluster correlation adjustment undertaken by the xtgee command in Stata 12 (StataCorp LP, College Station, TX, USA) and the regression-based adjustment for the baseline.
b Refers to the probability that the 5-week arm is cost-effective at a £20,000 per QALY threshold.

Using the regression-based approach to adjust for baseline values, the utility difference between the two arms was 0.0252 for the complete-case data. Similar to the cost difference, the utility difference between the two arms was not statistically significant at the conventional significance levels.

Although the cost and utility values were very similar for the two arms, there was considerable uncertainty around the within-trial utility values.

Long-term modelling results

Table 49 provides the results of the economic evaluation of 1-week compared with 5-week DAFNE training using evidence from the DAFNE 5 × 1-day RCT. Using the data on complete cases, the modelled lifetime cost for the 1-week arm was £44,911 and for the 5-week arm was £45,687, a difference of £776. The costs calculated for each arm are the sum of the insulin costs, the long-term complication and adverse event costs that were modelled for a lifetime and discounted back to the present and the observed within-trial costs used to replace the first-year costs in the long-term model.

TABLE 49 Economic evaluation of 1-week vs. 5-week DAFNE education using evidence from the DAFNE 5 × 1-day RCT

Diabetes-related complications	Control: 1-week DAFNE education ($n = 5000$)	Intervention: 5-week DAFNE education ($n = 5000$)	Increment
Clinical results (total incidence in whole cohort over a lifetime horizon)			
Microalbuminuria	2589	2602	13
Macroalbuminuria	1847	1864	17
ESRD	1569	1585	16
Death from ESRD	889	901	12
Background retinopathy	1237	1260	23
Proliferative retinopathy	725	741	16
Macular oedema	932	939	7
Blindness	90	91	1
Clinical neuropathy	1606	1626	20
Amputation	513	520	7
Non-fatal MI	1664	1656	–8
Fatal MI	1693	1689	–4
Non-fatal stroke	342	341	–1
Fatal stroke	98	97	–1
Non-fatal heart failure	727	723	–4
Fatal heart failure	45	45	0
Angina	1843	1832	–11
Severe hypoglycaemia	18,606	18,488	–118
DKA	717	740	23
Number of patient-years	156,077	155,752	–325
Life-years per patient	31.22	31.15	–0.07

continued

TABLE 49 Economic evaluation of 1-week vs. 5-week DAFNE education using evidence from the DAFNE 5 × 1-day RCT (*continued*)

Diabetes-related complications	Control: 1-week DAFNE education ($n = 5000$)	Intervention: 5-week DAFNE education ($n = 5000$)	Increment
Cost-effectiveness results (per patient over a lifetime horizon)			
DAFNE intervention cost (£)	359	371	12
Discounted insulin cost (£)	6884	6973	89
Discounted cost of long-term complications (£)	37,222	37,894	671
Discounted cost of adverse events (£)	446	449	3
Combined total average discounted cost (£)	44,911	45,687	776
Mean discounted QALYs lived if no complications	15.0350	15.0102	–0.0248
Discounted QALYs lost because of long-term complications	–0.8906	–0.9010	0.0104
Discounted QALYs lost because of adverse events	–0.0036	–0.0037	–0.0001
Combined total average discounted QALYs	14.1407	14.1055	–0.0352
ICER (unadjusted) (£)	–	–	–21,677
ICER (jackknife) (£)	–	–	–21,541
Net monetary benefit at threshold of £20,000 per QALY[a] (£)	–	–	–1466
Probability that DAFNE education is cost-effective at £20,000 per QALY threshold (%)	–	–	20

a Net monetary benefit = ΔQALYs × threshold – Δcosts.

The model estimated the long-term QALY difference as 0.0352 in favour of the 1-week arm, which corresponds to 12.86 days per person in perfect health.

Using the PSA samples (*Figure 12*), the long-term model reported higher uncertainty than the within-trial analysis because of the long-term complications and adverse events observed within the lifetime (maximum 100 years) of each individual. For the full cohort the probability of the 5-week arm being cost-effective at a £20,000 per QALY threshold was 20% (*Figure 13*).

Discussion and conclusions

In addition to the within-trial analyses, this study used a long-term simulation model to assess the cost-effectiveness of the 1-week and 5-week arms in the DAFNE 5 × 1-day RCT, namely the Sheffield Type 1 Diabetes Policy Model, which improved on the previous economic evaluation of the DAFNE programme by incorporating macrovascular complications, allowing for a heterogeneous HbA_{1c} response to DAFNE, extending the time horizon and conducting PSA analyses.

Based on both the within-trial analyses and the long-term model, it has been shown that the mean utility values in the 1-week and 5-week arms are similar. Given the small differences in mean cost per patient between the two arms, the results suggested that both the 1-week training method and the 5-week training method could be used by the NHS to deliver structured education programmes to individuals with type 1 diabetes. The within-trial analyses showed that the probability that the 5-week arm was cost-effective was 95.2%. By simulating the long-term complications based on the full cohort data from the trial and by acknowledging the effect of these complications on costs and utilities, the health economic analyses undertaken using the Sheffield Type 1 Diabetes Policy Model showed that the probability of the 5-week arm being cost-effective over the 1-week arm was 20%.

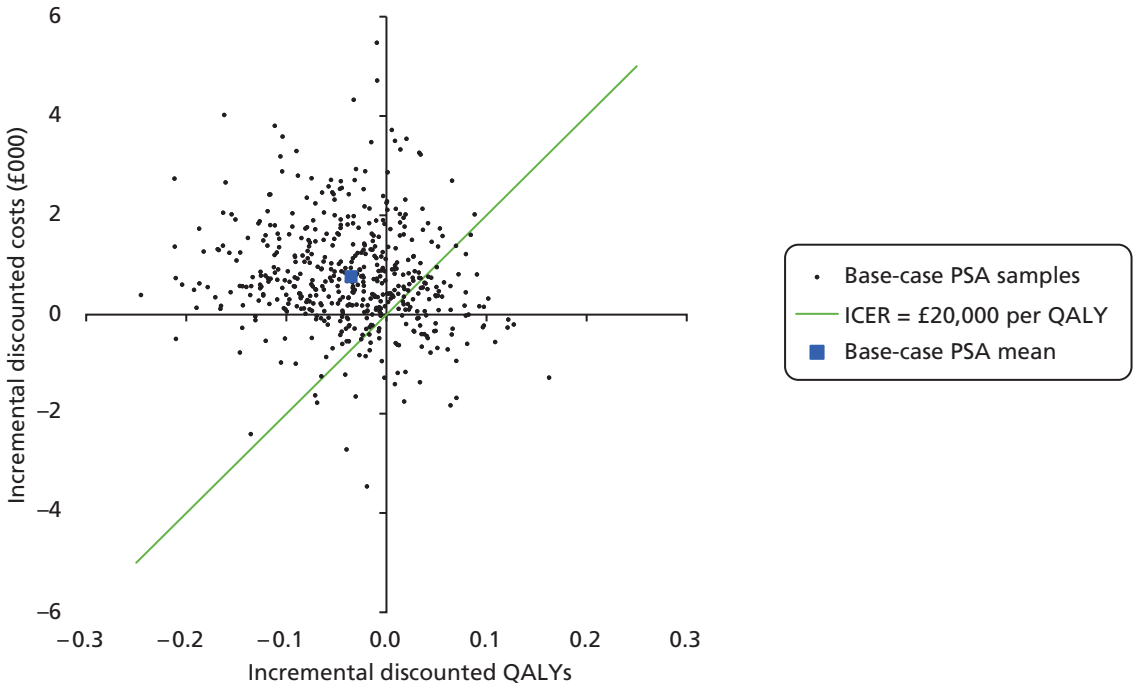

FIGURE 12 The cost-effectiveness of 1-week vs. 5-week DAFNE training using evidence from the DAFNE 5 × 1-day RCT on the cost-effectiveness plane.

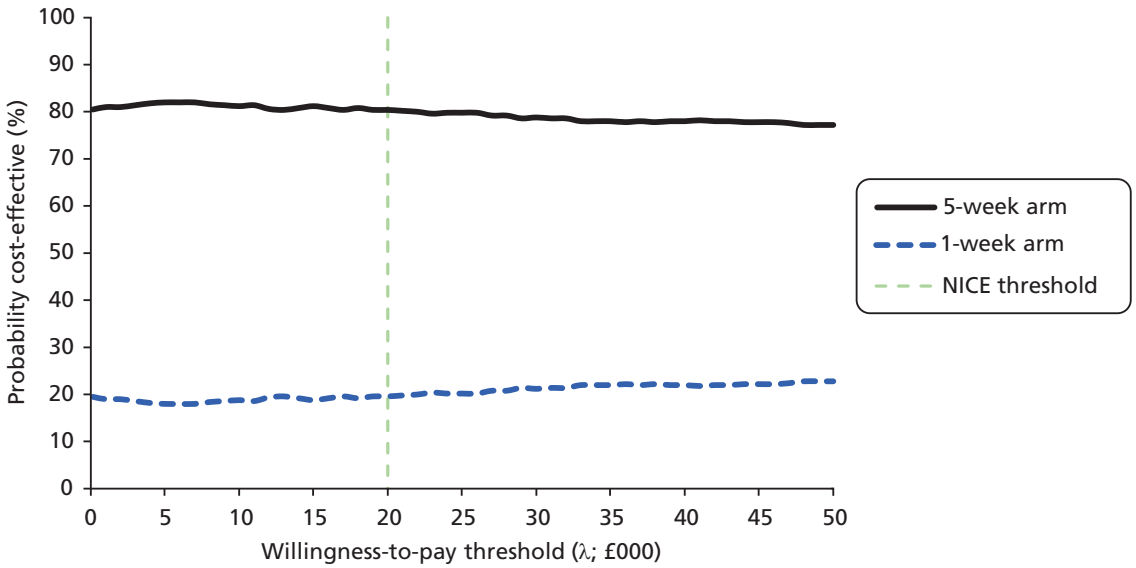

FIGURE 13 Cost-effectiveness acceptability curve: the probability that the DAFNE 1-week arm is cost-effective compared with the DAFNE 5-week arm in the DAFNE 5 × 1-day RCT population at different willingness-to-pay thresholds.

The generalisability of the results of this study is limited to cohorts with similar characteristics, such as cohorts of adults (aged ≥ 18 years) for whom UK-based costs are used to analyse resource use. However, the development of the Sheffield Type 1 Diabetes Policy Model is important not only for the original DAFNE and DAFNE 5 × 1-day RCTs but also for RCTs of other interventions for people with type 1 diabetes, as long-term analyses of ongoing trials in other type 1 diabetes populations will be undertaken by adapting the Sheffield Type 1 Diabetes Policy Model.

In conclusion, the results of this study suggest that the 5-week delivery method for DAFNE structured education programmes is likely to be slightly more cost-effective than the 1-week delivery method in the short-term (1 year) within-trial analysis but that the lifetime analysis marginally favours the 1-week arm over the 5-week arm. The small differences in projected utilities, costs and incidence rates between the two arms suggest that both delivery methods could be used by the NHS. This conclusion appears robust to sensitivity analyses of baseline HbA_{1c} levels and the persistence of the HbA_{1c} effect after completion of the programme.

Modelling patient psychology and behaviour alongside economic outcomes

Aims

This study aimed to explore statistical modelling methodologies to predict individual clinical responses to DAFNE education from psychosocial characteristics and incorporate psychosocial predictors into the Sheffield Type 1 Diabetes Policy Model to investigate the cost-effectiveness of providing DAFNE education to subgroups of predicted responders and of providing a follow-up intervention to subgroups of predicted non-responders. Full details of all analyses conducted have been reported elsewhere.[217,218]

Methods

Multiple linear regression and logistic regression were used to formulate prediction models of HbA_{1c} response to DAFNE education.

Response to DAFNE education can be defined in a number of ways. To explore different models for incorporation in the cost-effectiveness model, regression analyses were conducted with the following factors as the dependent variable:

- 12-month HbA_{1c} value (controlling for baseline HbA_{1c} level) using multiple linear regression
- absolute change in HbA_{1c} level from baseline to 12 months using multiple linear regression
- binary 'response to DAFNE' variable defined in terms of a HbA_{1c} reduction of ≥ 0.5% from baseline to 12 months using logistic regression.

Composite scores from questionnaires collected in the DAFNE psychosocial study (see *Chapter 3*) and demographic variables were included as potential predictor variables.

Two sets of analyses were conducted:

1. baseline psychosocial predictors of response were examined to investigate whether or not the 12-month response to DAFNE training can be predicted before attending the DAFNE course
2. the initial change in psychosocial predictors (3-month scores minus baseline scores) was examined to investigate whether or not the 12-month response to DAFNE training can be predicted from initial psychosocial outcomes at 3 months post-DAFNE training.

Each of these were conducted for all three of the dependent variables described above, giving six models. Analyses of all six models followed the same procedure:

- univariate regression was conducted for each predictor variable to investigate their individual predictive power for HbA_{1c} response
- multivariate regression was then conducted for all variables that were significant univariate predictors of HbA_{1c} response
- interaction terms between covariates were investigated
- hierarchical entry of predictor variables and R^2 change statistics was used to identify the most parsimonious model that did not result in a substantial loss of predictive power for HbA_{1c} response compared with a more complex model.

The Sheffield Type 1 Diabetes Policy Model version 1.1 was adapted to incorporate the resulting prediction models so that HbA_{1c} change after receiving DAFNE education was simulated individually for each patient based on the predictive regression equations.

Note that in this exploratory analysis we made a different assumption about the duration of the maintained effect of DAFNE education on HbA_{1c} level (compared with the analyses of DAFNE education and no DAFNE education in *Cost-effectiveness of DAFNE education compared with no DAFNE education*). In the exploratory analysis we used evidence from an audit database concerning the long-term difference between DAFNE education and no DAFNE education from year 2 onwards (quantified at 0.3%), which is now published.[31]

In the analysis presented here we assumed that this 0.3% HbA_{1c} difference lasted for the rest of the patients' lifetime. This contrasts with the assumption that we preferred in the base case in the original RCT, which assumed a maintained effect on HbA_{1c} levels up to 44 months based on the Speight *et al.*[12] analysis of longer-term follow-up of the original trial participants. Patients not receiving DAFNE education were assumed to experience no change in HbA_{1c} from baseline (this assumption was tested in sensitivity analysis).

The model was run for 5000 patients for a period of 50 years. All of these analyses were undertaken on the same population as in the psychosocial study ($n = 262$) (see *Chapter 3*). Note that version 1.1 of the model used utility decrements from the literature prior to the publication of the study by Alva *et al.*[174] and our completion of the analysis of utilities from the DAFNE programme.[170] The utilities used are reported in *Table 50*. Note also that version 1.1 of the model assumes that the rates for hypoglycaemia and DKA are the same for both DAFNE education and no DAFNE education as this version was developed before the analysis of the research database, which produced the regressions in *Table 32* that are used in the later version of the model (version 1.2).

Analyses

Three scenario analyses were conducted on the evidence derived from the psychosocial study: an update to the cost-effectiveness analysis of DAFNE education compared with no DAFNE education and two scenarios to investigate the cost-effectiveness of two new policies (*Table 51*). For follow-up intervention scenarios, assumed benefits of 0.25%, 0.5% and 1.0% reductions in HbA_{1c} were tested to investigate how much benefit the intervention would need to provide to be deemed cost-effective.

TABLE 50 Utility parameters used in version 1.1 of the Sheffield Type 1 Diabetes Policy Model

Health state or event	Utility	Beta distribution		Source
		Alpha	Beta	
Baseline utility value				
Male with type 1 diabetes and no complications	0.672	3022.176	1475.11	Coffey *et al.*[176]
	Disutility decrement	**Gamma Distribution**		
		Alpha	**Beta**	**Source**
Complications or covariates				
Female with type 1 diabetes and no complications	–0.033	17.01563	0.001939	Coffey *et al.*[176]
Blindness	–0.208	256	0.000813	Assumption
Macroalbuminuria	–0.017	2.89	0.005882	Coffey *et al.*[176]
ESRD	–0.023	0.725652	0.031696	Coffey *et al.*[176]
Clinically confirmed neuropathy	–0.055	30.25	0.001818	Coffey *et al.*[176]
PAD with amputation	–0.116	25.43667	0.004561	Coffey *et al.*[176]
Background retinopathy	–	–	–	Assumption
Proliferative retinopathy	–	–	–	Assumption
Macular oedema	–	–	–	Assumption
MI (assumed equivalent to heart failure)	–0.058	6.950413	0.008345	Coffey *et al.*[176]
Stroke	–0.018	0.669421	0.026889	Coffey *et al.*[176]
Heart failure	–0.058	6.950413	0.008345	Coffey *et al.*[176]
Angina	–0.090	24.00912	0.003749	Clarke *et al.*[172] (UKPDS 62)
Severe hypoglycaemia	–0.071	Samples	Samples	Walters *et al.*[226]
DKA (assumed equivalent to severe hypoglycaemia but without an ongoing utility decrement because of fear of hypoglycaemia)	–0.001	Samples	Samples	Walters *et al.*[226]

PAD, peripheral arterial disease.

TABLE 51 Scenario analyses conducted with the adapted Sheffield Type 1 Diabetes Policy Model

RQ	Scenario	New policy ('intervention')	Comparator	Additional information
–	0	Current practice: provide DAFNE education to everyone	No DAFNE education	For comparison with published cost-effectiveness analysis of the DAFNE programme[166]
1	1	Provide DAFNE education only to patients predicted to respond by 12 months from their baseline characteristics	Current practice: provide DAFNE education to everyone	Tested using baseline prediction models
2	2a	Provide a structured follow-up intervention to patients predicted not to respond to DAFNE education by 12 months from their initial response by 3 months	Current practice: do not provide a structured follow-up intervention	Follow-up intervention cost £150.[a] Tested using 3-month prediction models
	2b			Follow-up intervention cost £359.[b] Tested using 3-month prediction models

a This cost corresponds to approximately 2 days of the 1-week DAFNE group course, 2 hours with a diabetes specialist nurse and 6 hours with a DAFNE educator or approximately three support text messages per day for a year.
b This is the same cost as the cost of the original DAFNE course, i.e. £359 per patient to repeat the DAFNE course.

Prediction model results

Baseline prediction models

The final multiple linear regression model of the 12-month HbA_{1c} value on baseline predictors (model A) included baseline HbA_{1c} level and baseline fear of hypoglycaemia (adjusted $R^2 = 0.535$) (*Table 52*).

The final multiple linear regression model of the change in HbA_{1c} level on baseline predictors (model B) included BMI, baseline fear of hypoglycaemia and gender (adjusted $R^2 = 0.054$) (*Table 53*).

The final logistic regression model of 'response to DAFNE' on baseline predictors (model C) included baseline HbA_{1c} level and baseline thoughts about diabetes seriousness (*Tables 54* and *55*).

Initial change predictors

In univariate multiple linear regression analyses of 12-month HbA_{1c} value on initial change predictors none of the 3-month change variables were significant and therefore no further analyses were conducted.

The final multiple linear regression model of change in HbA_{1c} level on initial change predictors (model E) included initial change in fear of hypoglycaemia, initial change in diabetes knowledge, BMI and gender (adjusted $R^2 = 0.064$) (*Table 56*).

TABLE 52 Final multiple linear regression model of the 12-month HbA_{1c} value on baseline predictors (model A)

Predictor variable	Coefficient	Standard error	*p*-value
Constant	1.365	0.432	0.002
Baseline HbA_{1c} level	0.752	0.047	< 0.001
Baseline fear of hypoglycaemia	0.018	0.006	0.004

TABLE 53 Final multiple linear regression model of absolute change in HbA_{1c} level on baseline predictors (model B)

Predictor variable	Coefficient	Standard error	*p*-value
Constant	0.652	0.492	0.187
Baseline fear of hypoglycaemia	0.014	0.007	0.045
BMI	–0.043	0.017	0.012
Gender	–0.309	0.150	0.041

TABLE 54 Final logistic regression model of 'response to DAFNE' on baseline predictors (model C)

Predictor variable	Coefficient	Standard error	*p*-value
Constant	–3.636	1.014	< 0.001
Baseline HbA_{1c} level	0.520	0.110	< 0.001
Baseline thoughts about diabetes seriousness	–0.147	0.061	0.016

TABLE 55 Results from the final logistic regression model of 'response to DAFNE' on baseline predictors (model D)

	Observed		
Predicted	Non-responder	Responder	% correct
Non-responder	129	20	86.6
Responder	59	32	35.2
Overall % correct			67.1

TABLE 56 Final multiple linear regression model of absolute change in HbA_{1c} level on initial change predictors (model E)

Predictor variable	Coefficient	Standard error	*p*-value
Constant	0.657	0.462	0.157
Initial change in fear of hypoglycaemia	–0.017	0.010	0.086
Initial change in diabetes knowledge	–0.063	0.038	0.097
BMI	–0.028	0.017	0.105

The final logistic regression model of 'response to DAFNE' on initial change predictors (model F) included baseline HbA_{1c} level, initial change in fear of hypoglycaemia, initial change in diabetes knowledge and the interaction of these two initial change predictor variables (*Tables 57* and *58*).

Cost-effectiveness results

The cost-effectiveness results suggest that over a 50-year time horizon DAFNE education dominates no DAFNE education, generating more QALYs for lower costs (*Figure 14*).

Providing DAFNE training only to predicted responders was dominated by current practice, generating fewer QALYs for higher 50-year costs, and this result was insensitive to the prediction model used (*Figure 15*). The foregone potential HbA_{1c} gains that predicted how non-responders could have benefited, had they received DAFNE training, translated into higher rates of diabetes-related complications and therefore higher costs when providing DAFNE training only to predicted responders.

The results using prediction model E to define who receives follow-up treatment suggest that if a follow-up intervention costed £150 it would need to provide a 12-month HbA_{1c} reduction of between 0.5% and 1% for all patients to be considered cost-effective at the NICE threshold of £20,000 per QALY[168] (*Figure 16*). The results using prediction model F to define who receives follow-up treatment suggest that providing follow-up is a dominant strategy even at a 12-month treatment effect of only a 0.25% reduction in HbA_{1c} level. The incremental effects were small, however, suggesting that providing a follow-up

TABLE 57 Final logistic regression model of 'response to DAFNE' on initial change predictors (model F)

Predictor variable	Coefficient	Standard error	*p*-value
Constant	–6.313	1.269	< 0.001
Baseline HbA_{1c} level	0.704	0.150	< 0.001
Initial change in diabetes knowledge	0.223	0.100	0.025
Initial change in fear of hypoglycaemia	0.026	0.022	0.237
Interaction term: initial change in diabetes knowledge × initial change in fear of hypoglycaemia	0.026	0.012	0.022

TABLE 58 Results from the final logistic regression model of 'response to DAFNE' on initial change predictors (model F)

	Observed		
Predicted	Non-responder	Responder	% correct
Non-responder	92	16	85.2
Responder	36	37	50.7
Overall % correct			71.3

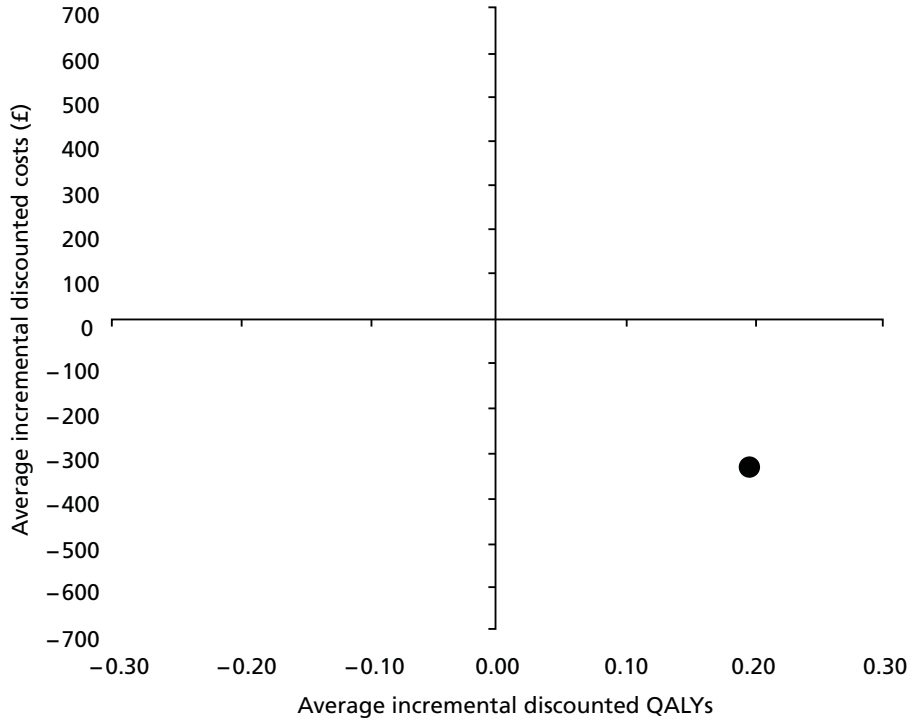

FIGURE 14 The cost-effectiveness of DAFNE education vs. no DAFNE education on the cost-effectiveness plane.

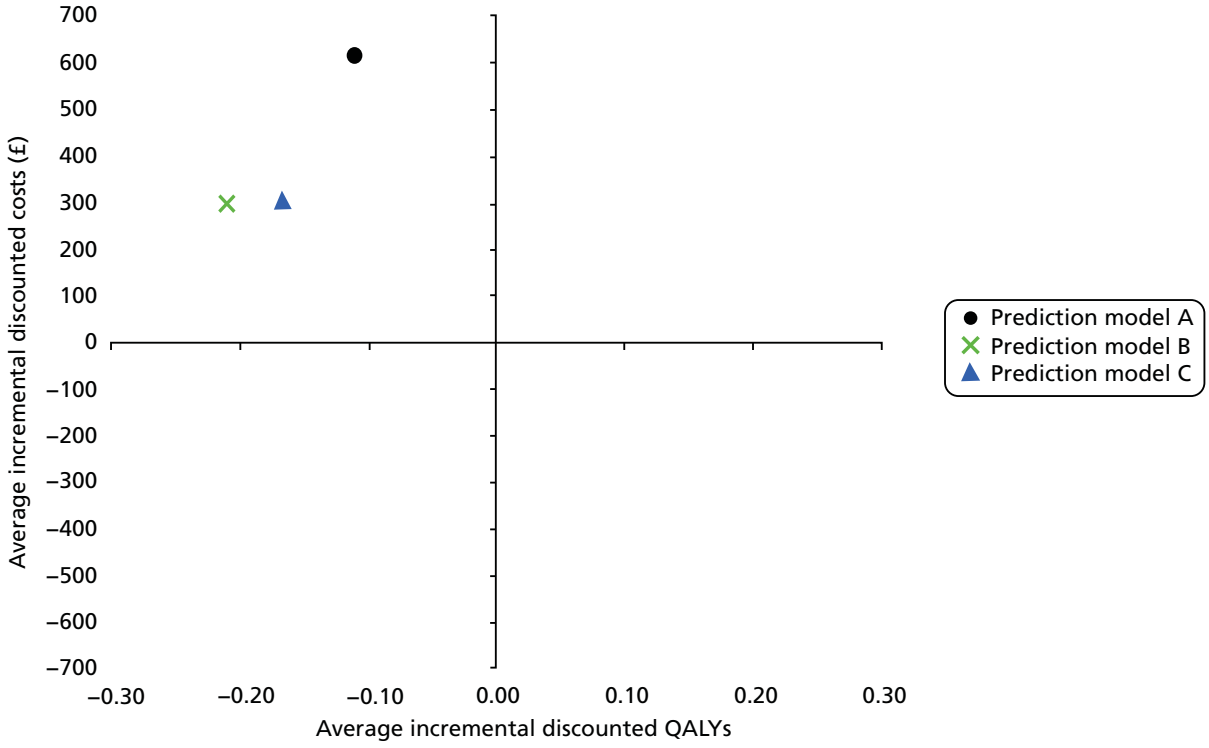

FIGURE 15 The cost-effectiveness of providing DAFNE education only to predicted responders vs. current practice presented on the cost-effectiveness plane.

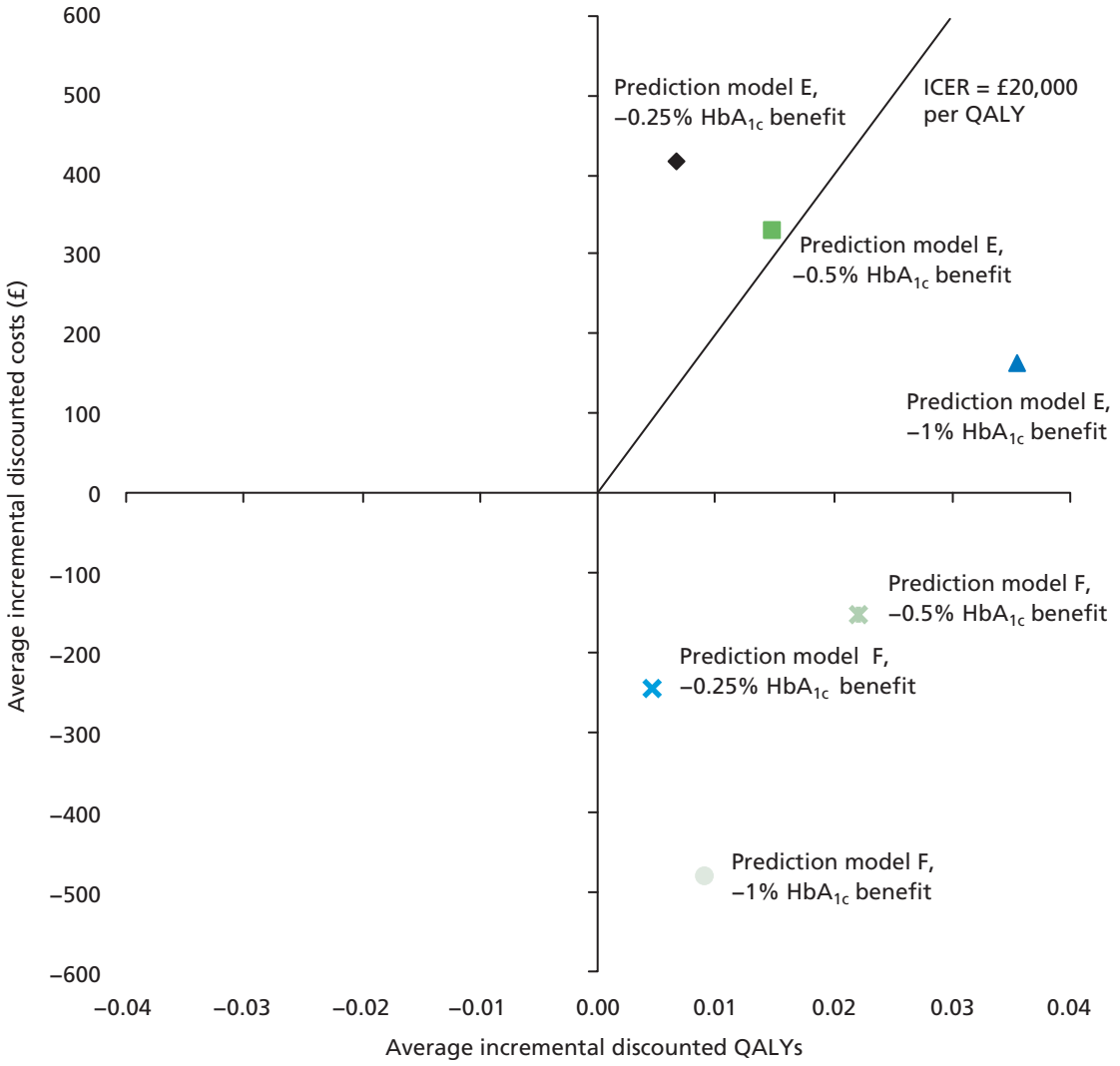

FIGURE 16 The cost-effectiveness of providing a follow-up intervention costing £150 vs. current practice presented on the cost-effectiveness plane.

intervention does not have a large effect on long-term costs and QALYs, irrespective of the prediction model used. The results were insensitive to the price of the follow-up intervention (*Figure 17* shows the same results for a follow-up intervention costing the same as the full cost of the DAFNE course).

Discussion and conclusions

This study explored modelling methodologies to predict individual clinical response to the DAFNE intervention from psychosocial predictor variables and integrated the results of the statistical prediction models with a patient-level simulation cost-effectiveness model. The methodologies employed have several limitations but the adapted patient-level simulation model offers the opportunity to investigate RQs about the cost-effectiveness of the DAFNE education that could not be assessed using previously published cost-effectiveness models of type 1 diabetes.

The results suggest that it would not be cost-effective to target DAFNE education only to a subgroup of predicted responders, but that it could be cost-effective and potentially even dominant (generating more benefits at a lower cost) to offer a follow-up intervention to predicted non-responders. Despite its limitations, the method adds value to the cost-effectiveness evidence on the DAFNE programme as it provides an insight into how patients' individual psychosocial characteristics link to long-term clinical outcomes and therefore to the cost-effectiveness of the intervention.

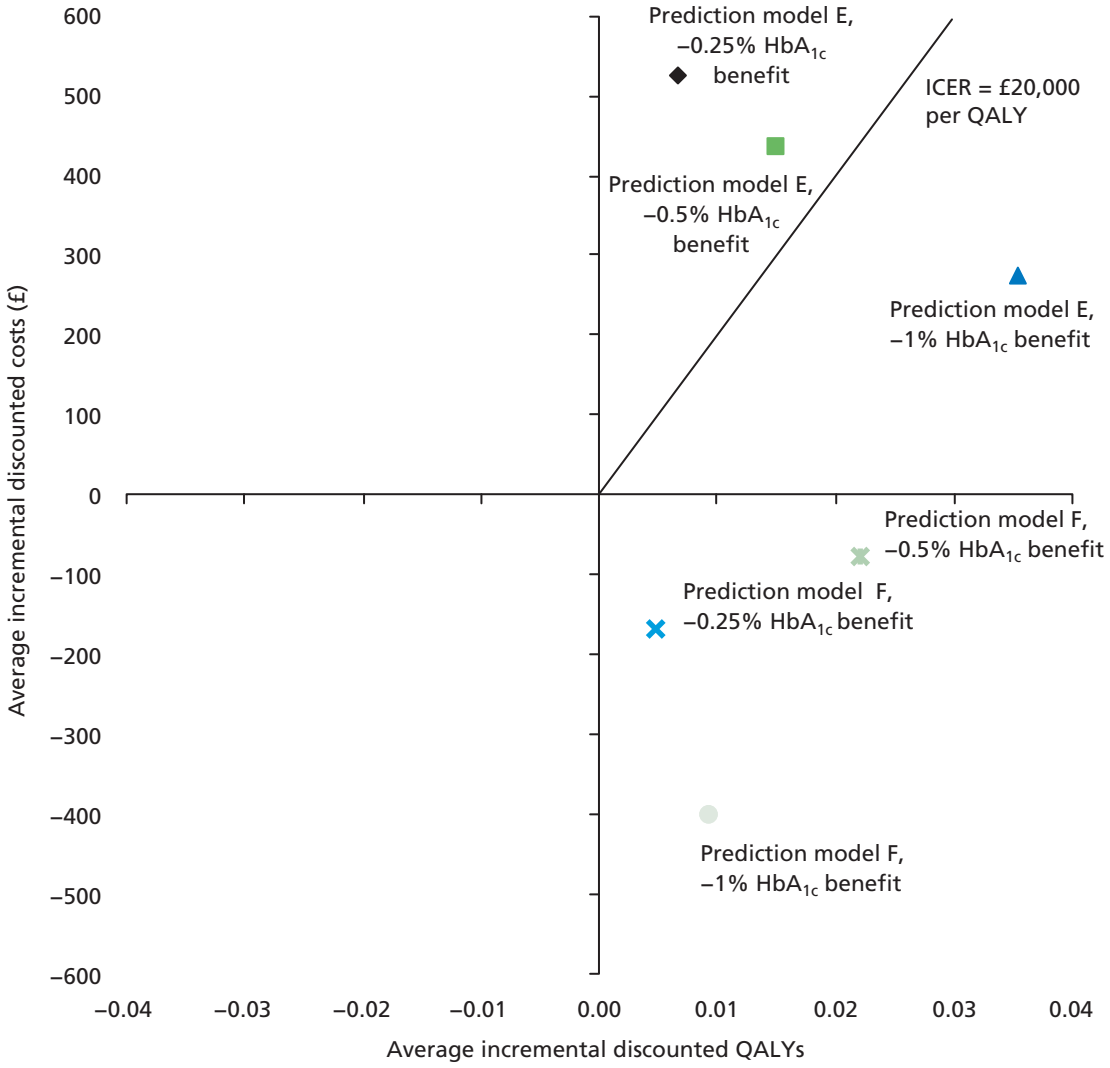

FIGURE 17 The cost-effectiveness of providing a follow-up intervention costing £359.10 vs. current practice presented on the cost-effectiveness plane.

Note that version 1.1 of the model was used to undertake these exploratory analyses. Using version 1.2 of the model there are some differences in the cost-effectiveness of DAFNE education compared with no DAFNE education (see *Cost-effectiveness of DAFNE education compared with no DAFNE education*), with DAFNE education appearing to be slightly more cost-effective using version 1.2 than when using version 1.1. The central finding from this exploratory analysis of psychological and behavioural factors (i.e. that there is not enough predictive power in the models predicting responders before undertaking the course to make them useful decision tools for course participation) will be unaffected by moving to version 1.2 of the model.

The adapted Sheffield Type 1 Diabetes Policy Model and the methodological framework presented offer many opportunities for further research in this area, including evaluation of other DAFNE policies, making alternative adaptations to the patient-level simulation model and application of the framework to other type 1 diabetes interventions. Policy questions such as those addressed by the current study cannot be investigated without consideration of psychosocial and behavioural factors; therefore, when relevant, health economic modellers should consider theoretical and applied models of health behaviour when designing simulation models.

Chapter 9 Conclusions, implications for clinical practice and recommendations for future research

Introduction

The DAFNE education programme has provided a unique test-bed to conduct research not only to improve type 1 diabetes management but also to learn more about the benefits (and limitations) of educational interventions that train people to self-manage diabetes and long-term conditions more generally. The overall approach used in this NIHR research programme brought together a multidisciplinary team with expertise in the development and evaluation of complex educational interventions in diabetes research, involving diabetes health-care professionals (doctors, DAFNE educators, diabetes specialist nurses and dietitians), social scientists (with expertise in both qualitative and quantitative methods), health economists, statisticians and patients. The integrated workstreams of the programme were designed so that the results from one would inform and improve the others. This dictated the timing of the workstreams, with the research database developed first; these data then fed into the psychosocial studies and health economics analyses. Learning from the psychosocial study contributed to the development and interpretation of the two RCTs and the DAFNE-HART pilot.

The development of the research database not only supported established workstreams but also enabled further RQs to be identified and addressed (see *Chapter 2*). The psychosocial study (see *Chapter 3*), in particular the qualitative component, underpinned our interpretation of many of the data generated in other workstreams and our overall conclusions. The psychosocial work also contributed to the design, implementation and analyses of the two RCTs and the intervention addressing hypoglycaemia problems (see *Chapters 4–6*). Furthermore, aspects of the qualitative work, combined with learning obtained from the pump pilot, helped to inform the design of the HTA-funded pump trial, REPOSE (in a separate application), as well as supporting the development of the DAFNE-HART pilot. Members of the health economics workstream utilised the data from the psychosocial study (both qualitative and quantitative) to develop a new type 1 diabetes economic model and confirm the cost-effectiveness of DAFNE educaton compared with no structured education.

A summary of the findings and conclusions from all workstreams is provided in the following sections.

Objective 1: to develop an electronic database to record outcomes and progress, and explore whether or not it was possible to collect research data routinely in busy units (see *Chapter 2*)

We constructed a database to record clinical outcomes and support other workstreams. Data were collected at baseline and annually on demographics, and biomedical, health-related and psychosocial outcomes. From December 2008 we enrolled 2002 patients, 82% of those eligible. In *Chapter 2* we report follow-up ascertainment up to the end of March 2013. However, because of a substantial lag between data collection and data entry, and because some sites continued to collect and enter data after the end of the period of the grant, actual ascertainment up to the end of December 2013 was 79%, 71% and 62% at 12, 24 and 36 months respectively.

We established that creating a high-quality research database was feasible within clinical practice to evaluate educational interventions but to do this effectively requires either additional administrator support and/or routine electronic data capture and input.

Objective 2: psychosocial studies to determine factors and experiences that explain why individuals do well or badly after receiving DAFNE training (see *Chapter 3*)

A combination of qualitative (interview and observation) and quantitative (questionnaire) methods was employed with 262 adults with type 1 diabetes, who were assessed before commencing DAFNE training and at intervals over 1 year. The quantitative model developed in this study, based on social learning theory, explained between 14% and 20% of the variance in HbA_{1c} levels and between 28% and 62% of the variance in diabetes-specific QoL over 1 year. Thus, demographic and psychosocial characteristics showed minimal explanatory power for glycaemic control but good explanatory power for diabetes-specific QoL. Qualitative data suggest that assessing numeracy, critical for insulin dose adjustment and CP counting, would help to determine whether or not additional training and support are required both before and during structured education. Analyses showed that, although DAFNE courses imparted knowledge and skills, they were less effective at helping participants to establish key self-management practices such as regular diary/record keeping. Revising course curricula may facilitate the complex and ongoing behaviour change required to achieve effective self-management. Technological innovations to reduce the complexity of self-management and support while facilitating behaviour change domains are important areas to develop.

Objective 3: to undertake two randomised controlled trials (one pilot) to improve the self-management of type 1 diabetes and develop an intervention for patients with hypoglycaemia problems (see *Chapters 4–6*)

Developing and evaluating a course delivered over 1 day a week for 5 weeks

Methods

This was designed as a non-inferiority RCT. Adults with type 1 diabetes were randomised to receive either a standard 1-week DAFNE course or a 5-week DAFNE course. An embedded qualitative study helped to understand and interpret the outcomes.

Results

In total, 213 patients were randomised in seven centres across England and 160 completed the study procedures. For patients with a baseline HbA_{1c} level of $> 7.5\%$, the mean change in HbA_{1c} level was –0.20% at 6 months ($p = 0.016$) and –0.18% at 12 months ($p = 0.055$). The incidence of severe hypoglycaemic episodes fell by 82% in the 12 months after DAFNE education compared with the 12 months before (estimated relative risk 0.18; $p = 0.04$). Psychosocial outcomes improved significantly by 6 months and were maintained at 12 months. For all outcomes the difference between treatment arms was not significant. Qualitative interviews revealed that patients were overwhelmingly in favour of the format of training that they received.

Conclusions

There were no major differences in outcomes between the 5-week course and the 1-week course. Glycaemic control improved by less after the 5-week course but the incidence of severe hypoglycaemic episodes was reduced. As participants valued both formats highly, and some found it easier to attend one type than the other, we will provide both formats in the future.

Feasibility/pilot study of a 5-day course providing both DAFNE education and insulin pump training

We conducted a pilot feasibility study exploring the potential of a trial in which participants were randomised to DAFNE training involving either MDI or insulin pumps. DAFNE educators developed a 5-day

curriculum incorporating both DAFNE principles and the skills necessary to use an insulin pump. Of 160 eligible individuals, 55 were randomised to either the pump course or the MDI course, of whom 47 both completed the course and attended the 6-month follow-up. Improvement in HbA_{1c} level was observed in those attending the pump course, comparable to that seen in the original trial; the incidence of severe hypoglycaemia was also reduced and psychosocial outcomes improved. Participants generally remained on their allocated therapy over the 6 months.

This pilot study demonstrated the feasibility of the proposed full multicentre RCT, including a robust power calculation for the primary end point, and helped in obtaining HTA funding for the full trial.

Developing an additional intervention for patients who experience hypoglycaemic problems after DAFNE training: DAFNE-HART

Following recognition of the importance of hypoglycaemia to patients on the DAFNE programme from the psychosocial studies (see *Objective 2*), we collaborated with the diabetes research programme at King's College Hospital, London, in the design and piloting of a 6-week intervention that emphasised hypoglycaemia avoidance and addressed unhelpful beliefs concerning hypoglycaemia unawareness, incorporating motivational enhancement and cognitive–behavioural approaches. In total, 24 people with type 1 diabetes, impaired hypoglycaemia awareness and problematic hypoglycaemia attended a pilot course and were reviewed 3 months later – one was lost to follow-up. In the remaining 23, the Gold score (a measure of unawareness) improved (from 5.5 to 4.4; $p < 0.001$). The annualised rate of severe episodes of hypoglycaemia fell from a median (range) of 3.5 (0–70) to 0 (0–40) ($p = 0.14$), with a fall in the rate of moderate episodes from a median (range) of 14 (0–100) to 1 (0–11) per 6 weeks. Depression scores (using the HADS) improved from 5.4 to 4.6 ($p = 0.04$). HbA_{1c} levels remained stable. We conclude that this intervention helps individuals with impaired hypoglycaemia awareness to reduce hypoglycaemia that persists following DAFNE training.

Objective 4: to utilise user involvement to develop more effective interventions (see *Chapter 7*)

Dose Adjustment For Normal Eating programme graduates were represented on different workstreams through the DUAG. A longitudinal evaluation of the impact of DUAG members on the work of the research programme was undertaken, including an evaluation of the training provided at the start. We used a mixed-methods approach including (1) semistructured interviews and (2) non-participant observation at DAFNE meetings at which users were present.

User involvement in the DAFNE research programme was not maximised because users were not involved at the grant-writing stage and some DUAG members found it difficult to represent the spectrum of DAFNE participants.

The findings suggest that, if users are assigned to different workstreams, it is preferable to assemble the groups first and deliver training on research methods later. This allows users to bond while the research team and users establish training needs.

The DUAG members gave useful support to the work of the DAFNE-HART and DAFNE 5 × 1-day trials. This included developing participant information, and discussing inclusion and exclusion criteria while emphasising the contributions that service users can make.

At DUAG's request, users were not paid for their time but received expenses. The resulting difficulty in obtaining time off work might explain why users could not attend all meetings. In future programme grants, investigators should cost users' time to maximise attendance.

Objective 5: to use economic evaluation to assess the cost-effectiveness of interventions over the short and long term (see *Chapter 8*)

The health economics workstream included the development of a health economic model of type 1 diabetes, the re-estimation of the cost-effectiveness of DAFNE education compared with no DAFNE education using the new model, the estimation of the cost-effectiveness of a 5-week DAFNE course compared with a 1-week DAFNE course, and the integration of psychological and behavioural characteristics into the model.

This work builds on a previously reported economic evaluation of the DAFNE programme to estimate the cost-effectiveness of the structured education programme compared with no DAFNE training. The results of the current modelling using version 1.2 of the Sheffield Type 1 Diabetes Policy Model confirm that the DAFNE programme appears to be a cost-effective intervention (indeed, cost-saving in the base case and the majority of the sensitivity analyses) and support its provision by the NHS to people with type 1 diabetes in the UK. Other results include a set of health-related QoL values for people with type 1 diabetes with varying degrees of diabetes-related complications, and that predicting HbA_{1c} response to DAFNE training from individuals' psychosocial characteristics and restricting access to training based on these predictions would not be cost-effective. The Sheffield Type 1 Diabetes Policy Model can be used to answer future policy questions relating to the treatment and self-management of type 1 diabetes.

Key conclusions

1. DAFNE training confers major benefits in improving different aspects of QoL and is highly valued by participants but is less effective in improving and sustaining blood glucose control than other European countries, using different health-care systems.
2. Courses do not always help participants instil and habituate key self-management practices, such as regular diary/record keeping, into their lives.
3. DAFNE graduates need structured professional support following training, which is currently unavailable or is provided ad hoc.
4. Demographic and psychosocial characteristics have minimal explanatory power in terms of predicting glycaemic control but good explanatory power regarding prediction of diabetes-specific QoL over 1 year of follow-up after DAFNE course attendance.
5. There were no major differences in outcomes between the 5-week DAFNE course and the 1-week DAFNE course. Glycaemic control improved by less after the 5-week course than in the original DAFNE trial, although the incidence of severe hypoglycaemia was reduced.
6. The insulin pump pilot study demonstrated the feasibility of the proposed full multicentre RCT, including a robust power calculation for the primary end point. It also contributed to the success in obtaining HTA funding for the full trial.
7. The DAFNE-HART intervention may help individuals with impaired hypoglycaemia awareness to reduce the risk of hypoglycaemia.
8. The DAFNE programme is a cost-effective intervention compared with no structured education and is even cost-saving in most analyses and, despite its limited HbA_{1c} benefit, this supports its provision by the NHS to people with type 1 diabetes in the UK. The 1-week and 5-week versions of the course are similarly cost-effective.
9. User involvement was particularly useful in contributing to the work of the RCTs but could have been maximised by involving users at the grant-writing stage. Training for users should be delayed until their participation is established. In future programme grants, investigators may need to ensure resource for users' time to maximise attendance.
10. It is feasible to run a research database of quality within clinical practice to evaluate self-management interventions such as the DAFNE programme but to do this effectively requires either additional administrator support and/or routine electronic data capture and input.

Implications for clinical practice

This programme of work set out to answer a series of related RQs, which are summarised in the previous sections. These questions have generated ideas for future research, which are outlined in the next section. However, they also have implications for current and future clinical practice, which is the subject of this section. We have been careful not to speculate beyond the results of the research work.

Both the RCT and the observational data confirmed that systematically teaching adults with type 1 diabetes the skills to use and adjust insulin safely was highly valued by DAFNE participants and resulted in marked falls in the risk of severe hypoglycaemic episodes or admissions with uncontrolled high blood glucose values. The overall level of blood glucose control as measured by HbA_{1c} improved by less than in the original DAFNE trial. Nevertheless, the health economic analyses still showed that with these outcomes the intervention was cost-effective and generally cost-saving.

These findings strongly support the importance of providing high-quality structured training to support the skills of diabetes self-management to all individuals in this age group. The DAFNE intervention is characterised by a full 5 days of training delivered by diabetes educators who are formally trained and who undergo regular peer review to ensure that the programme is delivered as designed and to a high standard.

However, DAFNE training is provided in only around one-third of secondary care diabetes units in the country. Other centres often deliver training that is of a shorter duration, without a written curriculum, using educators who have had minimal or no formal training to deliver structured education. Furthermore, many centres are running structured education courses without any form of independent assessment of their ability to deliver courses as designed.

External peer review of teaching is expensive, requiring the provision of resources to pay the reviewer both for their time and for travel. It is a major cause for concern that commissioners often refuse to fund courses (such as the DAFNE programme) that include peer review on the grounds of cost.

It may also be the case that, when centres attempt to save money by reducing the length of the course, failing to undertake peer review or limiting the number of educators providing training, the course that they provide is less effective. Such courses may then fail to provide adults with diabetes with the skills that they require to self-manage their condition effectively. Indeed, there is evidence that shorter courses fail to improve blood glucose levels or the incidence of hypoglycaemia[99] and have only minimal positive effects on some psychosocial outcomes.

During this work we explored whether or not outcome data from participants could be collected as part of routine clinical delivery with minimal additional financial input. We had hypothesised that these results could be used to compare outcomes from different centres and identify those centres whose results were poor in terms of glucose control or failing to reduce the incidence of episodes of hypoglycaemia. However, we found that clinical teams struggled to consistently collect even a relatively modest set of data items. We concluded that if additional outcome data (e.g. rates of hypoglycaemia) are to be collected and used in clinical practice then additional resources, mainly administrative, will need to be found.

The challenges that participants face when they are reviewed by diabetes professionals who are not DAFNE trained also has implications for a diabetes unit. In many centres only two or three of the clinical team undertake DAFNE training on the grounds of cost. This means that patients often see professionals following their course who are unfamiliar with the approach. This is a major barrier for patients in sustaining DAFNE self-management skills. Thus, the clinical implication for DAFNE centres and their teams is that as many professionals as possible should be DAFNE trained (or at the very least be aware of the principles of diabetes self-management as taught in their own centres).

This principle also extends to primary care teams. Most people with type 1 diabetes receive their care in secondary care settings. However, DAFNE participants are frequently asked to attend their GP surgery or will see a GP or practice nurse for reasons other than diabetes. It is likely that problems with diabetes may well be raised at these visits, in between hospital appointments. It is therefore important that primary care teams are aware of DAFNE principles, including the need to allow DAFNE participants to use as many glucose strips as they need to manage their diabetes effectively. In rural areas, where access to hospital is limited, primary care teams have also been trained to deliver DAFNE courses very successfully.

Much of the work undertaken in this research programme applies to other long-term conditions, such as type 2 diabetes, cystic fibrosis and home renal dialysis, in which patients are required to learn and administer quite complex health-related self-management skills. Perhaps the most important finding from our work is that, although many participants find that a brief, time-limited intervention teaching skills alone enables them to manage their condition in the short term, many struggle to maintain this over months and years. Thus, the need for structured ongoing professional support to ensure that those with long-term conditions sustain effective self-management is an important generic message.

Another important learning point from our work is that merely providing skills does not necessarily lead to desired changes in behaviour. We now believe that structured training/education courses should incorporate emerging theories of behaviour change. This may lead to better and more sustained outcomes; a hypothesis that applies to other long-term conditions.

Finally, although we found it challenging to collect outcome data in routine clinical practice, with additional administrative support we were able to compare outcomes between different centres. We showed that centre differences did exist and that some achieved better outcomes in terms of glucose control and hypoglycaemia than others. It was beyond the remit of our work to explore what lay behind these differences but an important component of future work should be to investigate the reasons for these differences. This would include educator behaviour, the fidelity with which the intervention is delivered and a detailed analysis of case mix.

Proposals for future work

1. Perhaps the most important finding of this programme was that teaching the rationale behind and the skills of FIIT in a stand-alone intervention was insufficient to ensure that most individuals initiate and sustain effective self-management. We now strongly believe that long-term conditions need integrated skills training and structured lifelong professional support. Thus, structured education in self-management needs to include a package that instils the principles of self-management and then supports individuals and their families to achieve success. This should be applied to other long-term conditions.
2. We should modify the current DAFNE curriculum to incorporate the emerging understanding of behaviour change to instil and habituate key self-management behaviour in addition to key competencies.
3. An assessment of numeracy, critical for insulin dose adjustment and CP counting, may help to identify the need for additional training/support.
4. Technological innovations to reduce the complexity of insulin dose calculation, record keeping and blood glucose pattern recognition combined with addressing behaviour change domains (knowledge, motivation and goal setting) are important areas to incorporate into improved educational interventions seeking to improve diabetes self-management.
5. Models of structured follow-up involving professionals warrant development and evaluation. Technological interventions may contribute to overcoming the barriers identified above and enable participants to incorporate effective self-management strategies and behaviours into their everyday lives.

6. We should seek funding to conduct a multicentre RCT of the DAFNE-HART intervention for individuals with hypoglycaemia unawareness.
7. In future work we should ensure that users contribute to all elements of the research, including the workstreams that should be included, what aspects of technological support we might develop and how they should be designed.
8. We should ensure that future work includes a detailed assessment of the fidelity of educational interventions, including the extent to which educators maintain the principles on which DAFNE training is based.

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Contribution of authors

All authors were involved in writing/reviewing/approval of appropriate sections of the final report.

Simon Heller (Professor of Clinical Diabetes, lead applicant) was the Chair of the Programme Steering Group and led on the insulin pump pilot study. He was responsible for the overall concept of the research programme, the design and approval of the workstreams, ensuring integration for achievement of the programme objectives, the approval of the study designs, the analyses and interpretation and the submission of the report.

Julia Lawton (Professor of Health and Social Science) was a co-applicant and member of the Programme Steering Group. She was responsible for the development of the concept of the research programme, led on the specific qualitative studies in the psychosocial programme, was responsible for developing and managing the qualitative studies in the psychosocial study, DAFNE-HART trial and DAFNE 5 × 1 day trial and contributed to all of the data analysis.

Stephanie Amiel (RD Lawrence Professor of Diabetic Medicine) was a co-applicant and member of the Programme Steering Group. She was involved in developing the concept of the research programme, was the lead investigator on the DAFNE-HART workstream including data analysis and interpretation and contributed to the design of the pump pilot study.

Debbie Cooke (Lecturer in Health Services Research) was a member of the Programme Steering Group and the Database Group. She co-led on the psychosocial study (quantitative), contributed to the study design, data collection, analysis and interpretation and had an advisory role with regard to the quantitative scales for the DAFNE 5 × 1-day RCT and the pump pilot study.

Peter Mansell (Consultant Diabetes Physician) was a co-applicant and member of the Programme Steering Group and Chair of the Database Group. He was the lead of the database workstream, co-ordinated and managed the study, contributed to the design of the database and reviewed data release applications and approved the release of data to DAFNE investigators.

Alan Brennan (Professor of Health Economics and Decision Modelling) was a co-applicant and member of the Programme Steering Group. He was the lead on the health economics workstream, contributing to the conception, design and data interpretation of all health economics substudies.

Jackie Elliott (Lecturer in Diabetes) was a member of the Programme Steering Group and the Database Group. She was the lead on the DAFNE 5 × 1-day RCT workstream, contributed to the design of the study, data collection and data analysis and interpretation and led on analyses evolving from the research database data collection.

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Appendix 1 Principal investigators (consultant diabetologists) and participating centres

Professor Stephanie Amiel and Dr David Hopkins, King's College Hospital, London, UK.

Dr Daniel Darko, Central Middlesex Hospital, London, UK.

Dr Simon Eaton, North Tyneside General Hospital, North Shields, UK.

Dr Mark Evans, Addenbrooke's Hospital, Cambridge, UK.

Professor Simon Heller, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.

Dr Anne Kilvert, Northampton General Hospital, Northampton, UK.

Dr Ian Lawrence, University Hospitals of Leicester NHS Trust, Leicester, UK.

Dr Peter Mansell, Queen's Medical Centre, Nottingham, UK.

Dr Rustam Rea, Derby Hospitals Foundation Trust, Derby, UK.

Dr Mohammed Kamruddin, Hull Royal Infirmary, Hull, UK.

Appendix 2

DAFNE self-management questionnaire (see *Chapters 2* and *4*)

Sustaining DAFNE principles (see *Chapter 4*)

Self-Management Questionnaire

Some people tell us that what they learn on the DAFNE course can be difficult to follow once they have finished the course. We would like to know how you have managed so that we can further improve the DAFNE course and follow-up arrangements to better suit people's needs. Please answer the following questions as honestly and accurately as you can.

Please think about the **last 2 weeks** when you are answering the questions.

1. (a) On average, over the last 2 weeks, how many blood tests have you done each day? *Please mark one answer.*

0	1	2	3	4	5	6	7 or more
☐	☐	☐	☐	☐	☐	☐	☐

1. (b) On average, over the last 2 weeks, how often did you record those blood tests in your DAFNE diary*? *Please mark one answer.*

Never	Rarely (about 25% of the time)	Sometimes (about 50% of the time)	Often (about 75% of the time)	All of the time
☐	☐	☐	☐	☐

2. (a) Over the last 2 weeks, how often did you use carbohydrate counting to work out your insulin dose? *Please mark one number.*

Never	Rarely (about 25% of the time)	Sometimes (about 50% of the time)	Often (about 75% of the time)	All of the time
☐	☐	☐	☐	☐

* DAFNE Diary: paper or electronic but in DAFNE format with blood glucose levels, carbohydrate portions (CPs), insulin and correction doses.

2. (b) Over the last 2 weeks how often did you record carbohydrate portions (CPs) in your DAFNE diary? *Please mark one answer.*

Never	Rarely (about 25% of the time)	Sometimes (about 50% of the time)	Often (about 75% of the time)	All of the time
☐	☐	☐	☐	☐

3. (a) Over the last 2 weeks, on how many days did you look at your DAFNE diary to reflect on and review your blood glucose levels? *Please mark one answer.*

None	*1-4 days*	*5-9 days*	*10-13 days*	*Every day*
☐	☐	☐	☐	☐

3. (b) Over the last 2 weeks did you ever adjust your insulin ratios or background insulin (BI) based on information you recorded in your DAFNE diary? *Please mark one answer.*

Yes	*No*	*Did not need to*	*Adjusted insulin but not using DAFNE diary*
☐	☐	☐	☐

When answering the following questions, please think about your experience over the last 2 weeks or state what you would normally do if this has not been your experience in the last 2 weeks.

4. (a) Over the last 2 weeks, did you have any high pre-meal blood glucose levels that needed correcting with extra quick acting (QA) insulin?

Yes	*No*
☐	☐

4. (b) On average, how much of the time do you correct high pre-meal blood glucose levels? *Please mark one answer.*

Never	Rarely (about 25% of the time)	Sometimes (about 50% of the time)	Often (about 75% of the time)	All of the time
☐	☐	☐	☐	☐

4. (c) Above what blood glucose level would you correct high pre-meal blood glucose with extra quick acting (QA) insulin?

Please write: ☐☐.☐

5. (a) Over the last 2 weeks, did you have any low pre-meal blood glucose levels that needed correcting with less quick acting (QA) insulin?

Yes	*No*
☐	☐

5. (b) On average, how much of the time do you correct low pre-meal blood glucose levels? *Please mark one answer.*

Never	Rarely (about 25% of the time)	Sometimes (about 50% of the time)	Often (about 75% of the time)	All of the time
☐	☐	☐	☐	☐

5. (c) Below what blood glucose level would you correct low, pre-meal blood glucoses with less quick acting (QA) insulin?

Please write: ☐☐.☐

6. At which of these blood glucose levels have you treated your hypos over the last 2 weeks? *Please tick **all** that apply..*

less than 2.5 mmol/l	2.6-3.5 mmol/l	3.6-4.5 mmol/l	4.6-5.5 mmol/l	Greater than 5.5 mmol/l	It depends on how I feel I would not always test
☐	☐	☐	☐	☐	☐

7. Do you apply DAFNE principles with regards to:

a) physical activity (e.g. swimming, gardening, DIY, walking)

Yes ☐ *No* ☐

b) alcohol

Yes ☐ *No* ☐

c) illness

Yes ☐ *No* ☐

Thank you for taking the time to fill in this questionnaire. Please hand this in to us or return it in the pre-paid envelope.

Sustaining DAFNE Principles

People sometimes tell us that they have difficulty following some of the DAFNE principles over time. To further improve the DAFNE course and follow-up support, we would like to know how you have managed **since attending your course** and over time. Please answer the following questions as honestly and accurately as you can.

1. (a) Since **completing** your DAFNE course, have you made any changes to your quick-acting (QA) insulin ratios? *Please mark one answer.*

Yes ☐ No ☐ Don't know ☐

1. (b) Did you make this decision…? *Please tick all that apply.*

- ☐ Independently
- ☐ After seeking advice from a healthcare professional
- ☐ In response to advice received from a healthcare professional (e.g. at a clinical review)
- ☐ Other *(please specify)*_____

2. (a) Since **completing** your course, have you made any changes to your background insulin (BI) doses? *Please mark one answer.*

Yes ☐ No ☐ Don't know ☐

2. (b) Did you make this decision…?…? *Please tick all that apply.*

- ☐ Independently
- ☐ After seeking advice from a healthcare professional
- ☐ In response to advice received from a healthcare professional (e.g. at a clinical review)
- ☐ Other *(please specify)*_____

3. How, in the future, would you make a change to either quick-acting ratios or background insulin? *Please tick all that apply.*

- ☐ Independently
- ☐ By seeking advice from a healthcare professional
- ☐ Wait until next review appointment to speak with a healthcare professional
- ☐ Don't know
- ☐ Other *(please specify)*_____

4. (a) In a typical week, how many times do you use corrective doses of insulin? *Please mark one answer.*

☐ 0 – 3 ☐ 4 – 6 ☐ 7 – 10 ☐ 11 – 14 ☐ >15

4. (b) In a typical week, do you think the number of corrective doses of insulin you use is...? *Please mark one answer.*

☐ About right ☐ Less than I should ☐ More than I should

5. When reviewing your blood glucose readings, what timeframe best reflects your experiences? *Please mark one answer.*

I focus on readings from the previous day	I focus on readings over 2 to 3 days	I focus on readings over 4 to 7 days	I focus on readings over longer periods of time	I do not regularly review readings
☐	☐	☐	☐	☐

6. (a) What blood glucose targets are you **currently** aiming to achieve?

Pre-breakfast	____to_____	or less than _____	Don't know ☐
Pre-lunch	____to_____	or less than _____	Don't know ☐
Pre-dinner	____to_____	or less than _____	Don't know ☐
Pre-bed	____to_____	or less than _____	Don't know ☐

6. (b) On **completing** your course, what blood glucose targets were you aiming to achieve?

Pre-breakfast	____to_____	or less than _____	Don't know ☐
Pre-lunch	____to_____	or less than _____	Don't know ☐
Pre-dinner	____to_____	or less than _____	Don't know ☐
Pre-bed	____to_____	or less than _____	Don't know ☐

7. Looking back, do you think you received the best format of DAFNE delivery?
Please mark one answer.

☐ I attended a 1 week course, I think this format would be better than a 5 week course
☐ I attended a 1 week course, but think a 5 week course would have been better
☐ I attended a 5 week course, I think this format would be better than a 1 week course
☐ I attended a 5 week course, but think a 1 week course would have been better
☐ I do not think that one format would be better than the other

8. If you were to be offered further follow-up support, would you prefer this to be?
Please mark one answer.

☐ In a group setting
☐ In a group setting, followed by some individual input
☐ On an individual basis, face-to-face with a health care professional
☐ On an individual basis, via telephone with a health care professional
☐ On an individual basis, via e-mail / online with a health care professional
☐ Other (please specify)_____

Appendix 3 Research plan

Original research plan

Overall theme and interaction between the different areas of the programme

The different elements of the programme will interact so that the results from one will inform and improve the others. Thus, the database will not only highlight patients doing well or badly but will also identify where the psychosocial research should be targeted. The psychosocial work will both identify the essential components of educational interventions in diabetes and contribute to the RCT analyses and development of the 'repeater's' course. Finally, the health economic study will assess cost-effectiveness both in the DAFNE programme overall and in the RCTs. This integration dictates the timing of the workstreams, with database development feeding into the psychosocial work and RCTs and the repeater's course being developed after the psychosocial research.

Setting up a research database

A basic database can monitor the overall effectiveness of the DAFNE intervention but more comprehensive data can answer RQs and support prospective studies. We have already developed a simple web-based database that has audited collaborative data. However, the current data set is too complex for routine usage and needs developing to be a research resource.

We will construct a two-tier web-based database consisting of:

i. Basic biomedical data (HbA_{1c}, weight, severe hypoglycaemia, DKA, pregnancy, use of insulin pumps and death). All centres will enter these data annually for all patients to allow us to compare outcomes between centres.
ii. A more advanced database in 10 of the most active centres. These include the original three centres and an additional seven centres, which together account for > 75% of current DAFNE graduates.

The extended database will:

- Include psychosocial measures (e.g. SF-36 and DSQOL), insulin type, other therapy and adverse events. This will inform the psychosocial research and generate other data such as the effect of different insulins and highlight centres and educators producing better results.
- Record adverse end points, including cardiovascular events, severe hypoglycaemia, DKA, laser therapy, etc., to allow economic modelling and identify individuals for further study.
- Record data from the RCTs described below.

This work will evaluate the DAFNE intervention as it rolls out, part of developing a complex educational intervention. We are collaborating with others delivering structured education in type 1 diabetes and such a database could record outcomes for all individuals in the UK participating in such programmes.

A mixed-methods approach to understanding the psychosocial issues around structured educational interventions in diabetes

We will:

i. Inform the development of future programmes, including follow-up. The findings will inform the evaluation of the RCTs described below and could be applied to structured education in self-management in type 2 diabetes and other long-term conditions.
ii. Identify and/or develop appropriate measures for the evaluation of future programmes.
iii. Devise ways of matching patients to appropriate education programmes on the basis of initial psychological assessments.

Procedure

We will employ an integrated, mixed-methods approach encompassing (a) a prospective qualitative design and (b) a quantitative repeated-measures longitudinal design. Using these two methodologies will both enable access to patients' cognitive representations of their illness and treatment, and enable insight to be gained into complex beliefs and attitudes predicting outcome. The sample for the qualitative component will be part of a larger sample for the quantitative component, and the junctures at which data are collected will coincide. This will enable findings from both components to be mutually illuminating.

The qualitative component

This will comprise (i) non-participant observation of DAFNE programmes and (ii) repeat, in-depth interviews with DAFNE participants. It will be undertaken by a full-time researcher over 2 years.

Non-participant observation The researcher will observe complete DAFNE programmes (six to eight programmes in at least three DAFNE centres). Naturalistic enquiry, in which people and events are observed in situ, is vital to enter the DAFNE 'black box' and gain an in-depth understanding of what actually happens and why. Observational research undertaken in other medical settings has demonstrated that, through spontaneous interactions between patients and/or staff, and as a result of patients' own priorities and needs (which may differ from those identified by staff), informal patterns of care may arise that diverge from a service's formal aims and objectives.

Data will be recorded as detailed descriptive field notes, the standard procedure in observational research. Any DAFNE participants not giving informed consent will be excluded but our experience shows that respondents quickly forge relationships with the researcher and value their efforts to understand matters from their perspectives. We anticipate, therefore, that most respondents will join the observational research.

In-depth interviews Following completion of each course, the researcher will (1) interview all consenting participants (staff and patients) and (2) undertake follow-up interviews with patients 6 and 12 months later. The interviews with staff and patients on programme completion will enable them to reflect on their understandings and experiences of what took place during the course and why. In both cases, observations generated will be used to inform the areas explored and to focus discussions. For patients, interviews will also explore if, to what extent and in what ways their needs and expectations were (or were not) met; likes/dislikes of the course; changes in attitudes towards, and knowledge of, their diabetes and its management; perceived needs for future care; and other issues arising as a result of the observational research (which cannot yet be predicted). A comparative analysis of the staff and patient interviews will be undertaken enabling (possible) discrepancies in their understandings of the aims, objectives and outcomes of the DAFNE programme to be examined.

The follow-up interviews with patients at 6 and 12 months will help to understand why many graduates struggle to retain the benefits of DAFNE training (especially sustaining intensive self-management) and why some fare better than others post course and to explore patients' perceptions of how they could be better supported long term. Specifically, interviews will record changes in commitment to self-care (since last interview), barriers to/facilitators of diabetes management (and how and why these have changed), understanding of whether or not the DAFNE approach is being adhered to, types of service contact and support received and unmet needs for support. They will also explore issues arising from an analysis of (1) earlier interviews and (2) initial quantitative data (see *The quantitative component*). Whenever possible, interview data will be linked to psychological and clinical outcomes [both the psychological scales described in *The quantitative component* and biomedical outcomes (HbA_{1c}, weight, hypoglycaemia) will be collected 6 monthly] and comparative analyses undertaken. For instance, the accounts of respondents who sustain good glycaemic control will be compared with the accounts of those who do not to understand barriers to/facilitators of self-care post course. Interviews will also be analysed longitudinally (i.e. individual patients' accounts will be compared at baseline and 6 and 12 months) to understand factors that may foster/undermine self-care and other issues over time.

Interviews (around 1 hour) will take place in a setting of the respondents' choosing (probably at home) and (subject to consent) will be tape-recorded and transcribed in full.

We aim to observe six to eight programmes, each attended by around six to eight patients and two educators. Assuming that most participants consent to be interviewed, interview data will comprise:

i. approximately 15 interviews with educators
ii. approximately 90 interviews with patients (30 patients interviewed on completion of the DAFNE programme and then 6 and 12 months later; in a similar study, attrition was negligible).

Previous research shows that this will provide a comprehensive data set to enable a diversity of perspectives to be examined, a full range of issues to be explored and theme saturation to occur in key areas (i.e. no new findings or questions emerge from an analysis of the data).

Analysis will be ongoing and iterative, starting once the observations and interviews begin. The study will be informed by the principles of grounded theory and the method of constant comparison, which involves concurrent data collection and analysis, together with systematic efforts to check and refine developing categories of data. Themes and hypotheses identified in the early phases of data collection as well as early findings from the quantitative component will inform the areas of investigation in later phases (e.g. follow-up interviews). Regular meetings (between JL and the research fellow, DR) will explore respondents' underlying reasoning, discuss deviant cases and reach agreement on recurrent themes and findings. Once consensus on themes has been achieved, a qualitative data-indexing package will be used to facilitate coding and retrieval.

The quantitative component

Design A repeated-measures longitudinal questionnaire study will explore both the short- and long-term predictors and mediators of outcome in patients undergoing the DAFNE programme, to inform the development of future intervention studies. Outcomes will be assessed at baseline, immediately post intervention and at 6 and 12 months after baseline.

Methods

- *Sample size*. The recruitment of a further 200 participants will allow structural equation modelling to be conducted (minimum recommended sample size for structural equation modelling is 200) (see *Chapter 3*, *Methods*)
- *Participants*. Participants will be recruited from centres already participating in the DAFNE programme. Inclusion and exclusion criteria will be those pertaining to eligibility for inclusion in the programme.
- *Measures*.
    - Profile and demographic characteristics: All participants will complete a profile and demographic questionnaire assessing marital status, housing, employment, occupation, ethnicity, education, home ownership and age.
    - Outcome measures:
        - Quality of life – quality of life will be assessed using the DSQOLS, a reliable and valid measure[17]. Specifically designed for the German study on which the UK DAFNE programme is based, it is included to allow important comparisons to be made between the UK and the German studies. In addition, a generic measure of QoL, SF-36, will allow comparison with healthy control subjects and other long-term conditions. The two components of the SF-36 (physical and mental) are derived from responses to 12 items that assess subjective well-being, the extent to which pain or physical disability interferes with daily life and the extent to which the respondents have restricted their activities as a result of emotional distress.[171]

- PMD – PMD will be assessed using a brief questionnaire version of the PMD Interview, validated in both adults and adolescents. It assesses two constructs, beliefs about the seriousness of diabetes and treatment effectiveness.
- Emotional well-being – this will be assessed using the WHO-5 Well-Being Index, a short, self-administered questionnaire related to positive mood. It is a reliable measure of emotional functioning and a good screener for depression.
- Self-efficacy – diabetes-specific self-efficacy will be assessed using the CIDS scale, a reliable and valid measure of diabetes-specific self-efficacy in patients with type 1 diabetes.
- Adherence – this will be assessed using the SCI-R, a psychometrically sound self-report measure of perceived adherence to diabetes self-care recommendations among adults.
- Social support – this will be measured with the SSQ6.

Statistical analysis A repeated-measures random-effects model will be used, building a model that tracks individuals over time and models predictors of outcome, allowing for within-person correlations.

Our mixed-methods approach will involve a number of RQs, for example (1) Which components of the DAFNE intervention are critical to success? and (2) Are there specific patient/disease/treatment characteristics that determine outcome in terms of HbA_{1c} and/or QoL? Regular discussion with clinicians will ensure that the most useful areas are explored in the two components of the psychosocial study. We anticipate that the qualitative work will generate new hypotheses as well as result in the development of new measures, which will be tested in the quantitative work. Aspects of the qualitative research will also be driven by findings from the quantitative research (for instance, if the quantitative study identifies changes in diabetes distress after course attendance, the qualitative work can explore and uncover the reasons why). The quantitative work will also drive the qualitative work with regard to specific hypotheses. One such hypothesis is that patients with long-standing type 1 diabetes with established approaches to self-management (which may be ineffective) find adapting to the DAFNE approach more difficult than newly diagnosed patients. This can be tested using a quantitative approach with follow-up using qualitative methodology to identify and explore the barriers to change, patient expectations and whether participants' goals and targets were achieved. In time, this work will enable educators to modify the course or perhaps develop pre-course work to improve the effectiveness of the programme.

This will be one of the first studies to bring together quantitative and qualitative approaches in an integrated and systematic manner. Hence, we will document and share our experiences to help develop and inform the methodological approaches used in health service research.

Interventions

A trial of continuous subcutaneous insulin infusion plus DAFNE education compared with DAFNE education and multiple injection therapy

Specific background

There is increasing pressure to provide CSII to more people with type 1 diabetes based on the recognition that intermittent injections of insulin have major limitations. Pump therapy may produce more stable glucose levels and reduce nocturnal hypoglycaemia. Early studies showed little benefit but recent largely uncontrolled trials indicate that those on CSII have better control than those on multiple injections. A recent meta-analysis reported that the HbA_{1c} level was 0.5% lower in those using insulin pumps than in those using insulin injections.

Pump therapy is expensive: treating 1% of all patients with type 1 diabetes in the UK would cost £1.5M pounds a year, although if this improved glycaemic control then the savings from reduced complications might outweigh the costs. NICE has suggested that those with type 1 diabetes who experience

problematic hypoglycaemia after using insulin analogues to achieve tight control should be offered pump therapy.[227] However, if these recommendations were strictly followed then far more people with type 1 diabetes than the 1–2% of the adult population with type 1 diabetes that it estimates would meet the recommendations would be offered CSII.

What is unclear is to what extent improved glycaemic control is the result of the technology rather than the skill in adjusting insulin. Those using pumps need training in CP counting and insulin dose adjustment. Thus, we hypothesise that improved glycaemic control and QoL with insulin pumps is the result of better self-management skills learnt during pump training and not the technology.

If our hypothesis is correct, many patients may not need pump treatment, allowing resources to be targeted at those most likely to benefit. However, such a trial can be undertaken only in centres delivering high-quality and consistent structured education, that is, within the DAFNE collaborative.

We therefore propose a RCT in which patients needing structured education are randomised to attend a DAFNE course where they are trained in either insulin self-management using multiple injections or CSII.

Participating centres will be experienced in delivering DAFNE training and pump therapy. Patients awaiting DAFNE training will be invited to participate and those consenting will be randomised to attend either a standard 5-day DAFNE course using multiple injections or a modified 5-day course with additional CSII training. Participants will complete questionnaires before the start of the course with a baseline evaluation of biomedical and psychosocial measures. We will also record outcome measures at 6 and 12 months. The trial will be evaluated using the RE-AIM approach (Reach, Efficacy, Adoption, Implementation, Maintenance) (see *Measuring outcomes*) with HbA_{1c} as a primary outcome.

We currently train educators to deliver the DAFNE intervention using a 3-day DAFNE educators programme; this will be modified to include the use of CSII. Within the collaborative there are at least five centres that are experienced users of CSII and others are interested in participating.

Based on an ICC of 0.1 within training groups and groups of eight participants per randomisation group, for 80% power at a two-sided 5% significance level we will need 166 participants, which will involve 20 training groups, to detect a difference of 0.5% in HbA_{1c} level, the smallest clinically relevant difference. We will include an additional 10% to allow for dropouts, which will mean 22 training groups and 176 participants in all. This will involve five centres each running four courses (two standard DAFNE courses and two pump + DAFNE courses) with an additional course of each type to be run in one of the five centres. Analysis will be by ITT.

Addendum: it was finally agreed that this would be reduced to a pilot RCT only, the results of which could inform a future larger RCT.

Comparing a standard 5-day DAFNE course with an intermittent intervention, delivered over 5 consecutive weeks on 1 day a week

Specific background

Despite its success, across the collaborative we estimate that around 25% of potential attendees refuse DAFNE training, often stating that their employer will not allow a full week off to attend the course. Furthermore, there are other reasons to explore delivering the course in a different format. Proponents of a 5-consecutive-day model believe that intense peer support developing during the week helps to maintain skills afterwards. Others maintain that a course over 5 consecutive weeks is better as it allows patients to gain more practice during the weeks between. Many DAFNE educators work part-time and wish to run a weekly course, a request currently resisted by the collaborative in the absence of evidence that this

approach works. Other non-DAFNE UK courses largely use a 1 day a week model and report comparable outcomes, albeit in observational studies. Proving that DAFNE training is as effective when taught at weekly intervals would introduce flexibility into its delivery across the collaborative. It would also allow more individuals with type 1 diabetes to receive structured education and increase patient choice.

We will therefore compare the DAFNE intervention delivered according to the original 5-day curriculum with the DAFNE intervention delivered over 5 weeks with participants attending for 1 day each week. Our hypothesis is that the benefit of a structured education programme with similar contact time will be the same whether delivered over 1 week or 5 weeks.

Study design

We will invite centres with the capacity to deliver both courses to participate. Patients currently on the waiting lists would be invited to join the trial and consent to be randomised to attend either the traditional 5-day course or a course held on 1 day a week over 5 weeks. Participants would then receive similar follow-up (a 6-week group visit) and be reviewed as usual in each centre. We will evaluate the course over 1 year using the RE-AIM format described in *Measuring outcomes* (primary outcome HbA_{1c}).

Power calculations and numbers Using a non-inferiority design, a clinically relevant difference in HbA_{1c} level of 0.5%, a SD of 1.25 and groups of eight participants per randomisation group, for 80% power at a two-sided 5% significance level we will need 128 participants, which will involve 16 training groups. An additional 10% to allow for dropouts will mean 18 training groups and 144 participants in all. This will involve four centres each running four courses (two 5-day and two 5-week courses) with an additional course of each type to be run in one of the four centres. Analysis will be per protocol.

Measuring outcomes

In both trials we will use the RE-AIM framework to evaluate the interventions:

1. *Reach*. What proportion of the target population participate in the intervention? Demographics will be collected at baseline. Attendance –the proportion of patients who decline to participate in the trial and reasons for non-participation.
2. *Efficacy*. Biomedical markers – HbA_{1c}, weight/height (BMI), severe hypoglycaemia, insulin dose. Psychosocial measures – these will include scales as described earlier including DSQOLS and SF-36 for economic analyses.
3. *Adoption*. In both trials the precise costs will be calculated and additional training provided to facilitators will be recorded. The costs and the potential cost benefit of the alternative strategies will be calculated at 12 months in both groups. In the pump trial this includes how many patients remain on pump treatment.
4. *Implementation*. The consistency and skill of the educators will be measured by peer review in both trials.
5. *Maintenance*. Individuals in both groups will be compared at baseline and 6 and 12 months.

Qualitative research will be undertaken alongside the two RCTs to enhance understanding of their outcomes. In-depth interviews will conducted with patients randomised to the adapted DAFNE courses within the two RCTs (i.e. 5-week DAFNE or DAFNE plus CSII). We will not interview patients randomised to 'standard' DAFNE courses as the psychosocial work described earlier is addressing their experiences. The methodology in the RCT studies will, whenever possible, map to that used in the psychosocial study, maximising the compatibility of the data.

Comparative analyses of RCT and 'standard' DAFNE interview data will be undertaken to develop an understanding of any differences and similarities in the biomedical and psychosocial outcomes of the RCTs. JL will oversee the analysis of data from both the psychosocial study and the RCTs, thereby maximising the potential synergy between them.

We will also use the RCT interviews as a timely opportunity to explore more general issues around peoples' motivations for taking part in RCTs and their understandings of, and views about, randomisation, etc. This is an area in which qualitative work is needed, as, to date, most research has been reliant on questionnaires, which typically restrict responses within a predetermined framework and give a poor indication of what respondents actually consider the most salient issues to be.

Addendum: the agreed insulin pump pilot study would not include a qualitative component.

Post-award addendum: to inform a later major RCT, a decliner survey was undertaken to investigate any barriers to participation.

Developing a 'repeaters course'

In both the UK and Germany (where the DAFNE intervention was developed) it is clear that skills training alone is insufficient for patients with psychological difficulties or who perceive too many barriers to change their approach to self-management. We need to develop and evaluate a course incorporating the psychosocial research described earlier for those who do not benefit from a standard course. The Düsseldorf group have evaluated the results of such a course and, although HbA_{1c} levels did not change (remaining at around 8%), severe hypoglycaemia was reduced.[228] However, we would target DAFNE graduates who struggle to implement the approach who have poor glycaemic control (> 9%) and major psychological difficulties with coming to terms with diabetes. We will use the psychosocial work to develop an additional intervention that will probably include exploring barriers to change and approaches such as motivational interviewing. We envisage that this will also be a group intervention although clearly the precise design will depend on the outcomes of the psychosocial research. By the end of the programme we will have designed and piloted the course in at least two centres in preparation for a formal trial.

Although we will prioritise these three trials, with additional capacity we could also develop a course for patients with type 2 diabetes who require intensive insulin therapy, perhaps jointly with the DESMOND (Diabetes Education in Self Management, On-going and Newly Diagnosed) group as we are also part of this initiative. The DAFNE 'test-bed' would also permit more effective evaluation of new therapies, including new types of insulin and expensive technologies such as CGM, perhaps in partnership with pharmaceutical companies. Our research environment 'controls' for the level of structured education and offers the opportunity to measure the 'real' benefit of often expensive 'technologies' among individuals skilled in diabetes self-management.

Post-award addendum: with input from knowledge gained in the psychosocial study and after consultation with DAFNE stakeholders, a post DAFNE training follow-up course was developed to help those experiencing severe hypoglycaemia associated with hypoglycaemia unawareness, The DAFNE-HART course was developed and piloted in two major DAFNE centres (see *Post award: development of the research plan during the programme*).

User involvement

Encouraging patients' and carers' participation in NHS research and development can improve both the quality and the relevance of research. Two DAFNE graduates sit on the executive group that manages the DAFNE collaborative and we have a functioning user group whose potential is not fully exploited because of a lack of resource. The user group will be invited to comment and advise on the development of research instruments during the programme. DAFNE graduates will join the management group and the steering committees of the two RCTs. To ensure that they participate effectively, we have arranged that users will attend four 1-day specially designed training sessions at the Trent Research Development Support Unit for users involved in research activity.

Little formal work has been carried out in the UK to evaluate the effectiveness and support provided to patients and public involved in research, representing a significant gap in knowledge. We will adapt a monitoring and evaluation form [developed by the North Trent Cancer Research Network (NTCRN) Consumer Research Panel] to be completed by professionals and users following every research involvement activity. This will explore the views of professionals compared with those of users, with both groups considering aspects of involvement that worked well or not so well and lessons learned. The monitoring and evaluation form will be thematically analysed and reported to allow comparisons between groups.

Post-award addendum: to gain greater insight into the impact of PPI, an independent mixed-method external evaluation of the impact of user involvement on the work of the DAFNE research programme was undertaken. A research team at the University of Sheffield, with expertise in the evaluation of user involvement, carried out a longitudinal evaluation of the impact of DUAG members throughout the life of the DAFNE research programme. This replaced the original planned evaluation form (see *Post award: development of the research plan during the programme*).

Economics

The three components of the economic evaluation will combine the database, psychological and clinical trial-based studies to calculate the cost-effectiveness of the developing DAFNE programme and provide evidence, techniques and infrastructure to evaluate related interventions in future.

Quality of life, utility and quality-adjusted life-years

Information on health-related QoL is being collected in each component of the programme. It is proposed to use the SF-36 throughout, allowing analysis across the database, psychosocial study and clinical trial evaluations in terms of QoL. The SF-36 can be converted into a single-index utility measure to examine QALYs. The planned analyses include examining the short-term effects of DAFNE interventions on utility. We will study the effects of success in undertaking DAFNE training on individual items or domains of the SF-36 as well as utility and QALYs. This will extend the known QoL effects from the original clinical trial into a more generalisable quality of life impact, understood in the context of other diseases. The long-term follow-up of the database will enable analysis of the level of maintained QoL improvements. In the clinical trials we will examine the differences not only between treatment arms but also between those who are successful and those who are unsuccessful within each arm.

We will also investigate the relationship between the disease-specific QoL instrument DSQOLS and the SF-36 and hence utilities and QALYs. This will explore whether or not an algorithm can be derived to convert DSQOLS results into utilities, enabling previously analysed and reported results using this scale to be converted into data for economic evaluation.

Resource use and cost data for economic evaluation alongside the randomised controlled trials

An economic evaluation will be undertaken alongside each of the proposed trials, taking a NHS perspective as recommended by NICE.[227] The intervention(s) in the trials will be costed on the basis of staff time, materials and other expenses and in terms of numbers of staff by grade and hours put in to preparation and delivery, as well as accounting for any dropouts. Hospitalisations or adverse events will be costed using standard unit and NHS reference costs.

Long-term cost-effectiveness modelling

Cost-effectiveness analysis of the DAFNE trial used the reduction in HbA_{1c} level to predict reduced complications and improved mortality and QALYs. We will extend this modelling with an updated search for evidence including recent studies showing HbA_{1c} as an independent risk factor in heart disease. The cost-effectiveness model will also incorporate evidence from the database on longer-term outcomes.

Post-award addendum: during the course of the interviews with 5-week participants, issues that had not been explored with the 1-week standard course were uncovered. Thus, a further interview study of the RCT control arm standard 1-week course participants was undertaken (see *Post award: development of the research plan during the programme*).

Post award: development of the research plan during the programme

Developing a 'repeaters course': the DAFNE-HART study

Aims and objectives of the study

The main aim was to develop a pilot intervention for people with type 1 diabetes and hypoglycaemia unawareness to reduce the number of severe hypoglycaemic episodes that they have.

The subsidiary aims were to:

- determine whether or not a pilot intervention can teach people with type 1 diabetes and hypoglycaemia unawareness to recognise that certain beliefs that they hold about hypoglycaemia unawareness are unhelpful
- determine whether or not this pilot intervention can help them change their behaviour
- determine whether or not this pilot intervention can improve their awareness of low blood glucose symptoms
- determine whether or not this pilot intervention can improve their quality of life.

In a collaboration between King's College Hospital, London, and Sheffield Teaching Hospitals NHS Foundation Trust, two centres with experience in the management of hypoglycaemia, we designed and piloted a 6-week intervention that revised principles of hypoglycaemia avoidance and addressed unhelpful beliefs concerning hypoglycaemia unawareness, incorporating motivational enhancement and cognitive–behavioural approaches.

A qualitative substudy was built into the DAFNE-HART pilot study to:

1. understand and explore patients' experiences of living with problematic hypoglycaemia through impaired hypoglycaemia awareness and its impact on their everyday lives (to better understand patients' motivations for attending/not attending the intervention)
2. establish patients' reasons for declining to take part in the pilot intervention
3. explore course attendees' reasons for attending, their likes and dislikes of the pilot intervention and their views about how the course might be improved.

Twenty-four people with type 1 diabetes and persistent problematic hypoglycaemia post DAFNE training, defined as having a Gold score of ≥ 4 and three or more episodes of blood glucose < 3 mmol/l in 2 weeks without symptoms and/or two or more episodes of severe hypoglycaemia (defined as requiring third-party assistance) since DAFNE training, and at least one in the last 2 years, attended the pilot course and were reviewed 3 months later. Data collection included biomedical outcomes, hypoglycaemia unawareness utilising the Gold score, severe hypoglycaemia frequency and depression and anxiety scores. Additionally, a 7-day CGM collection was performed.

The qualitative study included non-participatory course observation and interviews with course attendees within 2 weeks of completing their course. All patients who declined to take part in the pilot intervention were invited to take part in an interview to explore their experiences of living with hypoglycaemia unawareness and their reasons for declining.

Initial analysis of patient interviews (decliners and course attendees) highlighted that family members also appeared to play a central role in the detection and management of hypoglycaemia and, as the experiences, and information and support needs of this group have not been explored in previous research, the qualitative substudy was expanded to include an additional aim:

4. to understand and explore the experiences of family members living with, and caring for, people with hypoglycaemia unawareness; the impact of hypoglycaemia unawareness on their own lives; and their information and support needs. Recruitment packs were sent out to patients who had taken part in the interviews with a request to pass these packs on to a partner/adult family member who helped them to manage hypoglycaemia. These packs contained an information sheet and an invitation for family members to opt in to the interview study.

5 × 1-day qualitative booster study

The protocol for the qualitative study was revised to include a subsample of patients ($n = 20$) who had attended a 1-week (5-day) DAFNE course as part of the 5 × 1-day trial. These patients were interviewed once within 2 weeks of completing their course. The decision to include this subsample was made after an analysis of the baseline interviews conducted with trial participants who had attended a DAFNE course spread over 5 weeks revealed that they were overwhelmingly positive about the randomisation outcome and recommended that future DAFNE courses be delivered using the 5-week format. To establish whether this recommendation should be followed or if it was an artefact of trial participation, we interviewed a booster sample of 1-week (5-day) course participants and compared their experiences of, and views about, attending a 1-week (5-day) course with those of participants who had attended a DAFNE course spread over 5 weeks within the context of the trial.

User involvement

External evaluation of user involvement

Originally, as stated in the grant application, user involvement in the DAFNE research programme was to be evaluated using a structured evaluation form (modelled on that developed by the NTCRN Consumer Research Panel), completed at regular intervals by both DUAG members and DAFNE researchers. However, a view was taken early on in the programme that these evaluation forms would not allow for the collection of detailed descriptive accounts of the experiences of involvement from the perspectives of DUAG members and DAFNE researchers. Consequently, a decision was reached to commission an independent, mixed-method external evaluation of the impact of user involvement on the work of the DAFNE research programme. A research team at the University of Sheffield, with expertise in the evaluation of user involvement, carried out a longitudinal evaluation of the impact of DUAG members throughout the life of the programme. Research methods used in the evaluation included non-participant observation at DAFNE research meetings at which DUAG members were present and yearly stakeholder interviews with DUAG members and DAFNE researchers. This external, mixed-method evaluation yielded rich, context-specific qualitative data on the impact of user involvement on research processes and outcomes, which would not have been possible using the evaluation method originally articulated in the grant application.

EME
HS&DR
HTA
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