DAFNE*plus*

A cluster randomised controlled trial of the DAFNE*plus* (Dose Adjustment for Normal Eating) intervention: A lifelong approach to promote effective self-management in adults with type 1 diabetes

RESEARCH PROTOCOL
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Sheffield Clinical Trials Research Unit (CTRU)

A cluster randomised controlled trial of the DAFNE*plus* (Dose Adjustment for Normal Eating) intervention: A lifelong approach to promote effective self-management in adults with type 1 diabetes

This document describes the protocol for a clinical trial, and provides information about procedures for the recruitment and treatment of participants during the trial, as well as details about the intervention and its evaluation. The protocol is not intended for use as a guide to the treatment of other patients.

Contents

Abbreviations

AE	Adverse Event
BCT	Behaviour Change Technique
BCW	Behaviour Change Wheel
CI	Chief Investigator
COM-B	Capability Opportunity Motivation and Behaviour Model
CRF	Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
CTRU	Clinical Trials Research Unit
DAFNE	Dose Adjustment for Normal Eating
DMMP	Data Monitoring and Management Plan
GCP	Good Clinical Practice
GP	General Practitioner
MDI	Multiple Daily Injection
NIHR	National Institute for Health Research
NHS	National Health Service
PI	Principal Investigator
PPI	Public and Patient Involvement
QALY	Quality Adjusted Life Year
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
ScHARR	School of Health and Related Research
SOP	Standard Operating Procedure
T1D	Type 1 Diabetes
TMG	Trial Management Group
TSC	Trial Steering Committee

General information

This project is funded by the National Institute for Health Research through their Programme Grants for Applied Research Programme.

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Role of study sponsor and funder
Neither the funder nor the sponsor has had any role in study design, data collection or analysis, decision to publish, or preparation of manuscripts.

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Protocol amendments since Version 1.0

Protocol version 1.0 dated 22.03.18 amended to Protocol version 2.0 dated 04.07.2018. Summary of main changes:

1. The collection of HbA1C at the 6-month time point was omitted from the original protocol; after consideration the Trial Management Group have agreed that collection of this data is an important indicator of effectiveness which is consistent with outcomes in related trials and so an approach is planned to the funding body to support collection of this data. The protocol and related study documents have been amended on the basis that this data will be collected.

2. In the original protocol we stated:
'It is important to note that the selection of this primary psychological outcome measure of diabetes-specific quality of life is contingent on the results of another study being conducted as part of the DAFNEplus programme grant. The YourSAY survey (IRAS 228898) will report in Spring 2018 at which point, the study team may recommend an amendment to the trial protocol.'

Based on the results of this survey, and input from the PPI group, we have changed the patient reported outcomes included as measures and the time points at which they are administered, pages 21-22, and 24-25.

3. In the original protocol we stated that we would audio record and transcribe all sessions, this is impractical and we now plan to sample sites and sessions for recording. This is detailed in the protocol, pages 36-37, and information sheets and consents have been revised to reflect this.

4. Digitally recorded informed consent for health care professionals has been agreed, page 15.

5. Clarification of the adverse event and serious adverse event process, pages 23-24.

6. Clarification of wording for data handling, in light of the 2018 General Data Protection Regulations, page 41.

Protocol amendments since Version 2.0

Protocol version 2.0 dated 04.07.2018 amended to Protocol version 3.0 dated 05.12.2018.

Summary of main changes:

1. The main purpose of this amendment is to clarify the inclusion/ exclusion criteria. In the previous protocol (version 2.0) there was some ambiguity about whether or not investigators could use their judgement, about inclusion of participants with HbA1c above 12% and participants with serious diabetic complications or co-morbidities. We have revised the wording in figure 1 (RCT flow diagram) and the study inclusion/ exclusion criteria to explicitly allow inclusion of such participants at the investigators discretion. (figure 1 (page 14) and pages 16/17)
2. We have clarified the level of attendance for study participants, at DAFNE and DAFNEplus courses and at the follow up appointments for DAFNEplus, required for classification as adherent to intervention or control. (pages 19-20)
3. We will use the Diabetes Strength and Resilience Questionnaire at 9 months, this was not specified in the previous version of the protocol. (see table 1, page 26)
4. We have clarified that the primary method of monitoring will be remotely with site visits at the discretion of CTRU and the study sponsor. (page 43)
5. We have added Dr Johana Nayoan to the Trial Management Group (page 7).

Protocol amendments since Version 3.0

Protocol version 3.0 dated 05.12.2018 amended to Protocol version 4.0 dated 30.01.2019.

Summary of main changes:

1. To amend the footnote on page 21 of the protocol to clarify the classification of the study as a trial of a complex intervention.

2. Five functions of the trial software were identified by the MHRA as requiring classification as a medical device (class 1). Four of the five functions have now been CE marked. One function has not been included for use in the software for the trial as it fell into a higher risk class. This was an additional function that was not essential for the trial. This does not change the classification of the study to a device study. It remains a trial of a complex intervention.

   The four CE marked functions are:

   - Insulin Total Daily Dose (TDD) Calculation on secure website (raw data presented + algorithm to allow for % missing data)
   - Bolus Advice Adherence Tool (trend analysis to track if advice followed)
   - Hba1c Prediction Model
   - Diabetic Exercise management tool (Simple and Advanced)

     The function not included is the Advanced Bolus Advisor App for calculation of quick acting (QA) insulin dose from carb counting.

3. The Study Manager Pat Phillips has been replaced by Elaine Scott (page 4)

4. Northumbria Healthcare NHS Foundation Trust have pulled out from the trial due to staffing shortages. A replacement site is currently being set up.

Protocol amendments since Version 4.0

Protocol version 4.0 dated 30.01.19 amended to Protocol version 5.0 dated 28.03.19.

Summary of main changes:

1. Section 6.2 DAFNEplus intervention arm d) Training:
    a) Added clarification about supervision support. Unable to record and analyse courses due to lack of resources for this, hence the increased support for the first course.

    b) Re-worded information about audio recording at site for first DAFNEplus course – this is now only a sample of sites due to resourcing issues.
2. Section 7.1 Protocolised where participants defer course attendance and require a repeat Baseline assessment.
3. Section 7.4.3
    a) Agreed with TMG and TSC to remove reporting pregnancies as SAEs as unnecessary and pregnancies are documented within data collection forms.
    b) The wording related to the reporting of admission to hospital with severe hypoglycaemia or diabetic ketoacidosis (DKA) has been amended to reflect the need for reporting of these incidents to the CTRU within 24 hours of the event being discovered.
4. Section 10.3.1 Removed questionnaires received at 18 months post-course as this is incorrect.
5. Section 10.4.3.2. Fidelity assessment
    a) Removed wording about recording pre-course assessments for fidelity work due to resourcing /ethical issues and clarification of fidelity work process.
    b) fidelity assessment is now based solely on delivery of BCTs rather than additionally assessing fidelity of delivery of aspects of the intervention that reflect principles for delivering behaviour change interventions. A pragmatic decision was made at some point after the protocol was written and submitted to focus on BCTs in order to reduce the burden for facilitators completing the checklists and because these are the primary active ingredients anticipated to facilitate behaviour change.
    c) Once inter-rater reliability had been established, we had planned to check maintenance of this by double coding at pre-specified intervals. Due to lack of funding for transcription we will be double coding until inter-relater reliability is established and we anticipate that approximately 20% of transcripts will be double coded (which is an established and methodologically sound approach).
6. Principal Investigator table updated:
    a) Essex Partnership University NHS Foundation Trust has withdrawn due to staffing and funding issues. A replacement is in progress.
    b) Sarah Long at UCLH covering for Caroline Maine whilst on maternity leave.
    c) Birmingham Community NHS Foundation Trust have been recruited to the RCT.

7. Updated Trial Management Group membership due to staff changes.

Protocol Amendments since Version 5

Protocol version 5.0 dated 28.03.19 amended to Protocol version 6.0 dated 09.09.19

1. Hull and east Yorkshire Hospital Trust has changed its name to Hull University Teaching Hospitals NHS Trust
2. Trial Management Group – Ellen Bradley has left the University of Sheffield to move to a new post at Nottingham University. Jose Schutter has replaced her as research assistant at the CTRU. Mohammad Eissa, research associate from the department of Electrical and Electronic Engineering at the University of Sheffield has joined the TMG. Dr Stephanie Stanton-Fay has returned from maternity leave to continue with her work on the fidelity evaluation. Dr Kathryn Hamilton has moved on to work on other studies.
3. Trial Steering Committee - Ms Roz Davies, PPI representative, has resigned her post. Mr Ramnath Elaswarapu is now our NIHR Programme manager.
4. Section 4.2 Exclusion criteria - HbA1c value has been included in mmol/mol units as well as a percentage as some sites report in mmol/mol, rather than as a percentage.
5. Section 6.2. d) DAFNEplus Training – the section on supervision given to sites by the DAFNEplus trainers has been clarified. Sessions will not be audio recorded as it was recognised that there are not adequate resources to do so.
6. Fidelity section 10.4.3.2 Follow-up sessions are not being audio recorded for practical and logistical reasons
7. Foot note 3 on p22 has been removed as it is no longer applicable
8. 10.4.3.3 Self-reported fidelity of delivery – the footnote has been removed as this is no longer relevant

Protocol Amendments since Version 6

Protocol version 6.0 dated 09.09.19 amended to Protocol version 7.0 dated 08.06.20

1. Section 4.1 Recruitment has been expanded to include how participants for the 12-month interviews will be recruited.
2. Sections 10.1-10.2 of the Process evaluation have been amended to include changes to the participant qualitative interviews to address the changes effected by COVID-19.
3. Section 6.2.b – DAFNEplus intervention technology has been expanded to include information regarding the availability of the DAFNEplus technology beyond the end-point of their trial participation
4. Section 7.4.2 re Serious Adverse Events has been modified as it is no longer Clinical Trial Unit Policy that site staff have to read SOPs
5. Appendix 4 Project Gantt has been updated to include the VTC paid extension for the trial
6. TMG table amended to include Liz Cross, senior trial manager, who had previously been omitted in error
7. TSC table amended to include Lynne Dawson, new patient representative replacing Roz Davies, who retired from the TSC

Trial Summary

Title	A cluster randomised controlled trial (RCT) of the DAFNE*plus* (Dose Adjustment for Normal Eating) intervention: A lifelong approach to promote effective self-management in adults with type 1 diabetes
Short title	DAFNE*plus* Cluster RCT
Chief Investigator	Professor Simon Heller, Professor of Clinical Diabetes, University of Sheffield
Trial Objectives	The primary objective is to assess the effects of the intervention on glycaemic control, as measured by HbA1c at 12 months.
Trial Configuration	Multi-centre cluster randomised controlled trial with process evaluation and economic evaluation, comparing DAFNE*plus* to standard DAFNE for adults with type 1 diabetes.
Setting	Fourteen secondary care diabetes centres in the National Health Service in England and Scotland
Sample size estimate	The expected sample size of 662 patients in the study allows for 15% attrition at 12 months and 25% not meeting the primary analysis population criteria of baseline HbA1c greater than 7.5%, to result in a primary analysis population of 422 participants. Taking into account the design effect associated with the cluster design of the study with an ICC=1.5%, the sample size achieved along with an alpha of 5% has 92% power to detect a difference of 0.5% between the two treatments, which is considered a clinically relevant change.
Number of participants	662 participants – 47 per centre. In addition, we aim to recruit 20 DAFNE*plus* facilitators to take part in qualitative interviews for the process evaluation.
Randomisation	Upon recruitment of centres and following ethical approval, the participating centres will be randomised on a 1:1 basis to control or the intervention arm of the trial, using a covariate constrained methodology.
Outcome measures	The primary outcome measure is glycaemic control, defined as the HbA1c at 12 months, in those entering the trial with an HbA1c >7.5% (58 mmol/mol). HbA1c will also be collected at 6 months. Participants will complete psychological outcomes at baseline, post-course, 3 months, 6 months, 9 months and 12 months after course completion. Biomedical outcomes will be recorded at 6 and12-months post course, and qualitative interviews with participants in the intervention arm will also take place at baseline, post-course and at 3 and 12 months after course completion. At the 24-month point, a separate analysis of glycaemic control (and episodes of severe hypoglycaemia, if available), will take place.
Statistical Methods	The primary analysis will assess the difference between the two treatment groups in the participant's HbA1c at the 12-month follow-up appointment which will be completed on an intention to treat basis using a multiple linear regression model with coefficients estimated using generalised estimating equations (GEE) to account for the clustering design.

1. Introduction

1.1 Background and Rationale

The successful management of type 1 diabetes (T1D) requires those affected (>300,000 adults in the UK) (1) to keep their blood glucose levels sufficiently close to normal to avoid long-term complications including blindness, renal failure, amputations and premature death (2). In this condition, unlike in type 2-diabetes, there is an absolute insulin deficiency, and so insulin must be injected subcutaneously, and tablet therapy is not yet possible. Insulin can prevent high blood glucose and acute, life threatening emergencies such as diabetic ketoacidosis, as well as the long-term complications (above). However, current methods of insulin delivery are unable to reproduce the normal physiology of the pancreatic insulin-secreting beta cells which, in those without diabetes, control blood glucose precisely and automatically at all times (3).

Preventing complications depends upon an individual's ability to self-manage their condition, calculating precise insulin doses based on accurate estimations of food intake before every meal using frequent blood glucose measurements, and accounting for fluctuations in physical activity, illness, stress and hormones. If people with T1D are unable or unwilling to calculate and administer their insulin doses correctly, their blood glucose either runs high, increasing the risks of complications, or else falls too low leading to hypoglycaemia. Hypoglycaemia, if severe, can result in acute cognitive impairment, confusion, collapse and injury, coma or even death (4). Fear of hypoglycaemia leads some people to compromise their diabetes management (deliberately running their blood glucose high) to avoid such episodes, placing themselves at risk of long-term complications. Thus, people with T1D must acquire complex self-management knowledge and skills, and have the motivation and ability to apply them effectively every day of their lives. The responsibility of diabetes healthcare professionals (HCPs) is to ensure that all people with T1D have the opportunity to acquire these skills and are supported in applying them successfully in real life.

Dose Adjustment for Normal Eating (DAFNE) is a clinical education programme run within the National Health Service (NHS), designed to teach and improve self-management skills in *flexible* intensive insulin therapy to improve both glucose control and quality of life in adults with T1D. It is a 5-day training course for adults with T1D, delivered in small groups. DAFNE has been delivered to over 43,000 adults in the UK. The publication of the DAFNE RCT in 2002 (5) established the importance of structured education courses to teach diabetes self-management skills training to enable people with diabetes to live successfully with this lifelong condition. The subsequent rollout of DAFNE training across the UK has enabled many individuals to meet these demands and achieve their goals, but over half still struggle to control glucose levels consistently. Recent research confirmed that after attending a DAFNE course, people have better quality of life, better control of blood glucose levels and are admitted to hospital less often for diabetes emergencies (6). However, it showed that whilst DAFNE graduates find the course helpful, after it has finished, some find it difficult to implement and sustain the skills needed to maintain optimal blood glucose levels and find it hard to get suitable support

from HCPs (6). In follow up, average HbA1c (glycated haemoglobin), the intermediate measure of glucose control that best predicts risk of diabetes complications, remains above recommended targets in the UK (7,8).

The DAFNE*plus* programme grant aims to modify the existing DAFNE curriculum and incorporate techniques for initiating and sustaining behaviour change, develop structured follow-up support and develop, test and assess how digital information communication technology can be incorporated to benefit both patients and healthcare professionals. The aim of the research programme is to investigate whether the DAFNE*plus* programme will produce improved and sustainable diabetes self-management behaviour and better glucose control than currently achieved, without compromising quality of life in the longer term. This protocol describes the final stage of this programme grant, funded by the National Institute for Health Research Programme Grants for Applied Research (RP-PG-0514-20013), which is to run a cluster randomised controlled trial to evaluate the clinical and cost-effectiveness of the new DAFNE*plus* programme compared with standard DAFNE.

2. Aims and objectives

The primary aim of this study is to conduct a cluster randomised controlled trial (RCT) comparing the new DAFNE*plus* intervention to the existing DAFNE programme to answer the following question:

In adults with T1D, will modifying the existing DAFNE curriculum and developing structured professional input, using learning from our recent research, behaviour change theory and new forms of technological support, produce improved and sustained diabetes self-management behaviours, leading to better glucose control than currently achieved, using the existing DAFNE intervention, without compromising quality of life?

The primary objective is:

To assess the effects of the intervention on glycaemic control, as measured by HbA1c at 12 months.

The secondary objectives of this trial are:

- To assess the effects of the intervention on the diabetes-specific quality of life.
- To assess the medium term effect of the intervention on glycaemic control as measured by HbA1c using data at 6 months.
- To assess the effects of the intervention on diabetes distress and other biomedical outcomes: (severe hypoglycaemic episodes, diabetic ketoacidosis, weight, body mass index, blood pressure and lipids).
- To undertake a mixed methods process evaluation to aid understanding of the RCT findings, and to inform decision making about the implementation of DAFNE*plus* in clinical care post-trial.
- To assess fidelity of delivery of the DAFNEplus intervention.
- To undertake a health economic analysis to determine the cost-effectiveness of DAFNE*plus* versus standard DAFNE.

3. Trial Design

The study will use a pragmatic cluster randomised controlled trial design. A cluster RCT design is required since 'contamination' of the control arm may occur if DAFNE healthcare professionals, trained in the new programme delivered standard DAFNE, hence randomisation of DAFNE centres rather than individuals (9). Figure 1 shows the flow of participants through the trial. Key elements of the trial design are summarised below, with more detailed descriptions later in the protocol.

Participants
This study aims to recruit adults with T1D referred to DAFNE courses at participating centres. Potential participants will be identified by local diabetes clinicians, who will use the standard criteria for referral to DAFNE.

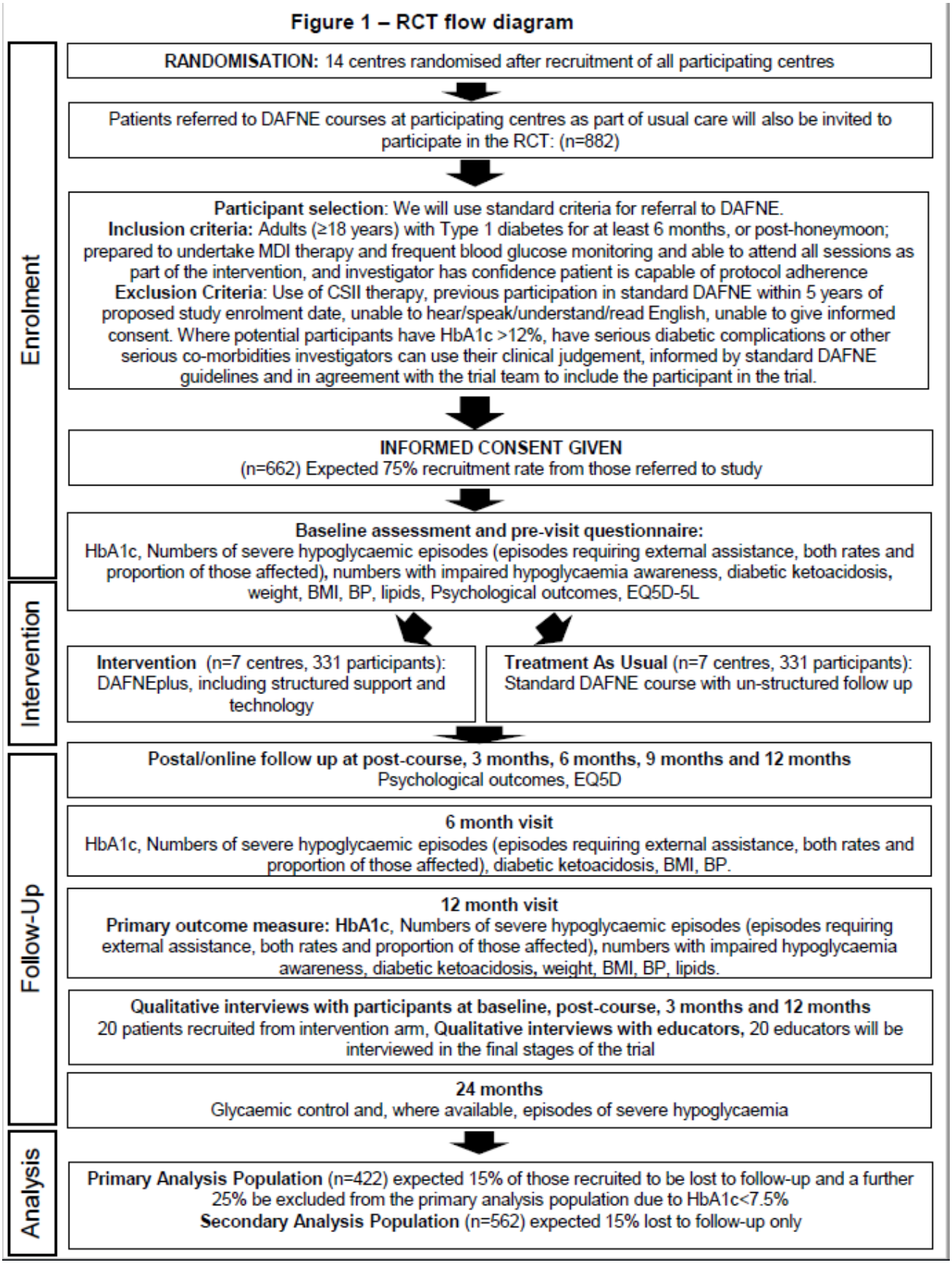
Intervention
Following informed consent, participants who are in sites allocated to the intervention arm will attend the DAFNE*plus* course one day per week, over five consecutive weeks, which includes the use of technology to transmit and display blood glucose data to support pattern recognition and interpretation (and provision of a bolus calculator to support insulin dose calculations) and up to five structured follow-up appointments in the 12 months after the course.

Control
Participants who are recruited at the control sites will receive treatment as usual and will attend the DAFNE course one day per week, over five consecutive weeks. A bolus calculator will be provided to participants in the control arm to support calculation of insulin dose. There will be no structured follow-up appointments beyond those provided in usual care.

Outcomes
The primary outcome measure is glycaemic control, defined as the HbA1c at 12 months' post-course, in those entering the trial with an HbA1c >7.5% (58 mmol/mol).

Participants will complete psychological outcomes in the form of a postal or online questionnaire at baseline, post-course, 3 months, 6 months, 9 months and 12 months post course. Biomedical outcomes will be recorded at 6 and 12-months post course. Qualitative interviews with participants in the intervention arm will also take place at baseline, post-course and 3 and 12 months post course. The full list of outcome measures is provided in section 7 of this protocol.
At the 24-month point, a separate analysis of glycaemic control (and episodes of severe hypoglycaemia, if available), will take place.

Figure 1 – RCT flow diagram



4. Selection and withdrawal of participants

4.1 Recruitment

All patient participants will be identified from current caseloads of adults with type 1-diabetes from each participating centre. Patients on the DAFNE waiting lists for both the 5 week and 1 week DAFNE course in participating centres, and where relevant, patients from the current caseload, will be sent an invitation letter and patient information sheet prior to the course. A member of the clinical team in participating centres will telephone potential participants after sending the letter to discuss whether or not they are interested in principle in taking part in the research. If they are interested, they will be asked to consent to participation in the research at their baseline visit. In both arms of the trial, if they do not want to take part in the research they will be offered attendance at a standard DAFNE course that is not part of this trial, if that is their wish. Reasons for non-participation will be recorded.

In order to maximise recruitment to the courses, a reserve list of eligible patients will be held at participating centres for each course. Where other potential participants not be able to join the research, patients from the reserve list will be invited to participate, where necessary and/or feasible. In addition, eligible patients may be invited to take part by their healthcare professional during routine face-to-face appointments, or via telephone. They will be given a verbal explanation of the research and a participant information sheet to review. As above, if they are interested in taking part, they will be invited to attend a baseline visit at which point they will be asked to consent to participate. Trial information meetings will also be held during the recruitment period at a number of locations in the study sites. The purpose of the meetings will be to provide further information about the trial, to answer questions and to consent those interested into the study.

Written informed consent will be obtained from all participants. Members of the local study team at participating centres will be responsible for taking informed consent from potentially eligible study participants at the DAFNE centres. They will explain the details of the study and provide a participant information sheet, ensuring that the participant has sufficient time to consider participating. They will also answer any questions that the participant has concerning study participation.

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The member of the local study team and the participant shall both sign and date the consent form before the person can participate in the study. The participant will receive a copy of the signed and dated forms and the original will be retained in site files. A second copy will be filed in the patient's notes and a signed and dated note made in the notes that informed consent was obtained for the study. General Practitioners (GPs) will be notified by letter that their patient is taking part in the research, and they will be sent a copy of the participant information sheet.
Due to the development to collect information regarding the effects of the COVID-19 pandemic upon some aspects of the trial, a number of qualitative

interviews will also be undertaken with participants at the 12-month stage of the trial only. These participants will be purposively selected by the Process evaluation team. Participants will have consented to be contacted for interview as outlined in the process above. The original consent outlined above is still considered valid when participants are contacted regarding the 12-month interview. Qualitative researchers from the University of Edinburgh will contact the participant in the first instance to discuss the 12-month interview. If the participant would like to take part in an interview the central study team (CTRU) will post out a Participant Information Sheet (PIS). The qualitative researcher will arrange a potential interview time with the participant, discuss any questions arising from the PIS, and affirm consent verbally from the participant.

Written informed consent will also be taken from healthcare professionals in participating sites by members of the central study evaluation team:

- To have DAFNE or DAFNE*plus* sessions audio recorded
- To complete self-report delivery checklists
- To participate in interviews in the intervention arm.

In some circumstances these healthcare professionals will not be seen face-to-face and in these instances a researcher will seek informed consent over the telephone. The researcher will read each statements from the consent form and ask the healthcare professionals to state whether or not they consent to the statement, the researcher will initial each box where consent is agreed. Once all statements have been agreed to, the participant will state her name and the date will be stated by the researcher obtaining consent. The conversation regarding consent will be digitally recorded. Once the researcher has signed the consent form, a copy will be sent to the healthcare professional for their records and the encrypted audio file will be stored in the electronic Trial Master File.

4.2 Inclusion and exclusion criteria

The eligibility criteria for study centres is as follows:

1. Adult diabetes centre delivering DAFNE;
2. At least three DAFNE educators trained in delivering the 5-week model of DAFNE;
3. Delivery of sufficient DAFNE courses per year to recruit study sample.

Patients eligible for or referred to DAFNE courses at participating centres as part of usual care will be eligible to be invited to participate in the RCT, and we will use standard criteria for referral to DAFNE. Those consenting will attend a baseline visit up to approximately 4 weeks prior to the course start date.

Inclusion criteria:

1. Adults (≥18 years);

2. Diagnosis of type 1 diabetes for at least 6 months, or post-honeymoon;[1]
3. Prepared to undertake multiple daily injection (MDI) therapy;
4. Prepared to undertake frequent self-monitoring of blood glucose;
5. Confirms availability to attend all sessions as part of the intervention;
6. Investigator has confidence that the patient is capable of adhering to all the trial protocol requirements.

Exclusion criteria:

1. Current use of continuous subcutaneous insulin infusion (CSII) pump therapy
2. HbA1c > 12%/108 mmol/mol (Investigators can use their judgement, informed by standard DAFNE guidelines and in agreement with the trial team, to include participants with HbA1c >12%/108 mmol/mol).
3. Serious diabetic complications (e.g. blindness, renal dialysis). (Investigators can use their clinical judgement, informed by standard DAFNE guidelines and in agreement with the trial team).
4. Other serious co-morbidities e.g. psychosis, diagnosed eating disorder (Investigators can use their clinical judgement, informed by standard DAFNE guidelines and in agreement with the trial team).
5. Previous participation in standard DAFNE course less than 5 years before proposed study enrolment date
6. Unable to speak/hear/understand/read write in English
7. Unable to give written informed consent

4.3 Criteria for withdrawal from trial treatment

The decision regarding participation in the study is entirely voluntary, and consent regarding study participation may be withdrawn at any time without affecting the quality or quantity of future medical care. No study-specific interventions will be undertaken before informed consent has been obtained. The investigator will inform the participant of any relevant information that becomes available during the course of the study that might affect their desire to continue in the study, and will discuss their continued participation with them. If applicable they will be asked to sign revised consent forms. If the consent form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended consent form by the REC and use of the amended form (including for on-going participants).

Participants have the right to withdraw from the study at any time without providing any explanation if that is their wish. The reasons for leaving the study will be recorded on a case report form (CRF), where given. Participants who withdraw from the intervention will still be invited to complete the outcome assessments and asked if they provide permission for their HbA1c data to be collected from their medical notes, unless they have specified that they wish to have no further involvement in the study.

[1] The honeymoon period refers to the time when, post-diagnosis, people start taking insulin injections, and their insulin producing cells sometimes recover for a while. The dose of insulin needed might reduce during this period, and some people might even need to stop using insulin for a while, but eventually it will be needed again. The criteria for referral to DAFNE at least 6 months after diagnosis is to allow for the honeymoon period to have passed before attendance at the course.

Participants may be withdrawn from the study either at their own request or at the discretion of the local Principal Investigator (PI). The PI may withdraw a participant in the interest of the participant (e.g. if continuation in the intervention or the study was considered to be causing undue stress) or due to a deviation from the protocol. Participants who are withdrawn on the grounds of incorrect eligibility would be excluded from the per protocol analysis, as opposed to the full study. Participants may discontinue the intervention or be withdrawn from the study for the following reasons:

- Withdrawal of consent,
- Major changes to their health status preventing their continued participation,
- Unable or unwilling to undertake protocol requirements.

Participants will be informed (via the information sheet and consent form) that should they withdraw, the data collected up to that point cannot be erased and may still be used in the final analysis (in an anonymised form). Data from the trial should not be erased as it should be possible to recreate a participant's participation up to their point of withdrawal. A participant would be classed as complete if they have continued in the study until the last protocol defined intervention (final outcome assessment at 12 months), although there may be missing data for individual participants.

5. Randomisation and blinding

5.1 Randomisation

Upon recruitment of centres and following ethical approval, the participating centres will be randomised on a 1:1 basis to control (standard DAFNE courses) or the intervention arm (DAFNE*plus* course) of the trial. As there are numerous stratification variables that have been identified as clinically important and the small number of randomising centres, a covariate constrained methodology (10) will be employed. The centres will be matched on the number of patients within the centre, number of educators within the centre and number of previous DAFNE courses delivered (as a marker of centre experience) to balance centres between the two arms of the trial.

5.2 Blinding

Due to the nature of the intervention, it is not possible for members of the study team working directly with participants or the intervention to be blinded. Additionally, the blinding of the statistician is problematic due to the cluster level randomisation. Statisticians are usually involved within TMG discussions and have access to status reports where the potential for unintentional unbinding is a high possibility. It is considered important for the statistician to be included in these aspects of the trial management and so after discussion with senior statisticians at the CTRU and the independent statistician on the TSC, it has been deemed acceptable that the statisticians are not blind within this study.

This is under the agreement that the statistical analysis plan will be signed off early in the data collection phase and no outcome data split by treatment group will be seen by the statisticians until this has been finalised.

6. Trial treatment

6.1 DAFNE (control arm)

DAFNE (Dose Adjustment for Normal Eating) is a skill-based structured education programme for adults with type 1 diabetes (T1D) delivered in the NHS. Two evidence-based models of delivering standard DAFNE are in operation, whereby the course is delivered during five sessions over one week, or over five separate weeks. The five-week model of DAFNE is based upon an adaptation of the original one-week course, as described elsewhere (11). Each course is delivered to 7 participants on average (minimum of 4 and maximum of 8 participants). The aim of the course is to train people with T1D in the skills to manage their condition effectively. It covers numerous topics in a progressive modular based structure. In addition to the five days of the course, participants are asked to attend a baseline appointment before the DAFNE course, and they are also typically invited to attend an optional group follow-up session 6-8 weeks after the course. They may also attend routine appointments every 6-12 months and seek ad-hoc support from local diabetes clinicians after the course. For the purposes of this study, the control arm will be the 5-week model of standard DAFNE in order to minimize the differences with the DAFNE*plus* delivery model (see 6.2 below) and focus the distinction on the new aspects of content and delivery. All participants in the control arm will be given access to a bolus calculator to support with calculating insulin dose. There will be no structured follow-up appointments beyond those provided in usual care. To qualify as adherent for statistical purposes, participants will need to have attended the equivalent of 4 days of the course including days one and two which are mandatory; it is acceptable to include half days in the total.

6.2 DAFNE*plus* (intervention arm)

DAFNE*plus* will be delivered by practising DAFNE educators in the NHS[2]. These will be healthcare professionals including diabetes specialist nurses, dietitians and physicians, all of whom will be using DAFNE training as an integral part of the management of T1D in adults. DAFNE*plus* is a complex intervention, defined by the Medical Research Council (12) as having 'several interacting components', described in summary below.

The development of the content and structure of the DAFNE*plus* programme was informed by the Behaviour Change Wheel (BCW) framework (13). The intervention's proposed functions are served by behaviour change techniques (BCTs), specified in the hierarchical Behaviour Change Technique Taxonomy v1 (BCTTv1) (14), which are its 'active ingredients' (15). The DAFNE*plus* intervention contains manual-specified BCTs as its active ingredients proposed

[2] As part of DAFNE*plus*, those delivering the intervention are referred to as 'facilitators', as opposed to 'educators' as per standard DAFNE.

to effect behaviour change (e.g. action planning, goal setting, and information on health consequences of the behaviour), together with principles for delivery specific to the DAFNE*plus* intervention that were identified during an expert consensus process (e.g. focus on the positives, emphasise individual autonomy). The development of the DAFNE*plus* programme was informed by the findings of a systematic review to identify what types of follow-up support following self-management training for adults with type 1 diabetes lead to sustained improvements in glycaemic control; and the synthesis of qualitative evidence about the challenges faced by participants post-DAFNE from the previous programme grant, which in turn informed the behavioural analysis and identification of relevant BCTs.

The DAFNE*plus* programme was developed, piloted and refined during earlier stages of the programme grant (IRAS 208842; IRAS 214683).

The DAFNE*plus* programme comprises three components:

DAFNE*plus* course

The course component of the DAFNE*plus* programme is delivered one day per week, over five consecutive weeks, and is based on a revision of the standard DAFNE five-week curriculum. The existing DAFNE curriculum has been reviewed, updated and modified with a view to strengthening and sustaining blood glucose control in the longer term. Participants attend a pre-course assessment appointment approximately two weeks before the course which serves as their introduction to the programme, and during which they are given access to and trained in the use of the DAFNE*plus* technology and website, as well as a bolus calculator to support calculation of insulin requirements. New sessions included in the DAFNE*plus* course include technology assisted individual review, emotional aspects of diabetes, social support, preparing for behaviour change, and updated action planning support to help participants achieve their goals in relation to self-management of their type 1 diabetes. To qualify as adherent for statistical purposes, participants will need to have attended the equivalent of 4 days of the course including days one and two which are mandatory; it is acceptable to include half days in the total.

a) **Structured follow-up support**

The model of structured follow-up support builds upon the clinical and behavioural skills introduced during the DAFNE*plus* course to enable participants to maximise the efficacy of key DAFNE*plus* principles to improve self-management and maintain glycaemic control. As part of the trial, up to five one-to-one consultations (face-to-face, telephone or in some centres, web-based video calling) with a DAFNE facilitator will be offered, delivered at progressively spaced intervals during the 12 months after the course The purpose of these personalised sessions is to review participants' progress with managing their diabetes, including progress with their action plans, review blood glucose data on the DAFNE*plus* website, address any additional clinical needs and signpost participants to any relevant sources of support. In addition, ad-hoc support by telephone or email (or in some centres, web-based video calling) will be available to participants between sessions, as necessary. Where

possible and practical participants will see DAFNEplus facilitators and designated doctors associated with DAFNEplus for all their diabetes related consultations during the trial to ensure that information and advice given is consistent with the DAFNEplus ethos. To qualify as adherent for statistical purposes, participants will need to have attended a minimum of three follow up sessions.

b) **Digital technology**

The DAFNE*plus* programme incorporates two forms of digital technology via the DAFNE*plus* website and box. Participants will be given access to this at the pre-course appointment, and instruction in its use, so that they can make use of the technology prior to and during the course, and during the period of structured follow-up. The DAFNE*plus* system includes a box (*Withcare+*) which transmits, stores and displays blood glucose (and other) data on a secure-server via the DAFNE*plus* website in formats to help people with T1D and their healthcare professionals recognise and interpret patterns[3]. In addition, the website also includes a section dedicated to online modules to help maintain knowledge of the DAFNE*plus* approach and facilitate behaviour change and to help people with T1D self-manage their diabetes-related behaviours more effectively.
At the study end-point for intervention participants, DAFNEplus facilitators will inform participants of the ongoing support which their site can provide, and of the ongoing availability of the DAFNEplus website and Withcare+ technology, which participants can continue to use if wanted. This aspect of the intervention will continue to be supported until at least March 2022.

c) Training

[3] The DAFNE*plus* system has been developed by members of the research team in Electronic and Electrical Engineering (EEE) at the University of Sheffield over several years and is protected by patent GB2467079.

Five functions of the trial software were identified by the MHRA as requiring classification as a medical device (class 1). Four of the five functions have now been CE marked. One function has not been included for use in the software for the trial as it fell into a higher risk class. This was an additional function that was not essential for the trial. This does not change the classification of the study to a device study. It remains a trial of a complex intervention.

The four CE marked functions are:

i. Insulin Total Daily Dose (TDD) Calculation on secure website (raw data presented + algorithm to allow for % missing data)
ii. Bolus Advice Adherence Tool (trend analysis to track if advice followed)
iii. Hba1c Prediction Model
iv. Diabetic Exercise management tool (Simple and Advanced)

The function not included is the Advanced Bolus Advisor App for calculation of quick acting (QA) insulin dose from carb counting.

A clinical psychologist who specialises in diabetes and is experienced in training diabetes professionals in behaviour change and communication skills will lead the development and delivery of DAFNE*plus* facilitator training.

The training and supervision process has been developed and piloted with facilitators during the DAFNE*plus* pilot study. This was based on a Delphi study exploring 'gaps' in current training and a discussion with psychology team members regarding the additional skills needed to deliver the new course content. The pilot training course was also evaluated during the pilot study and this feedback will continue to feed into further refinement of the RCT training prior to commencement of the trial.

The training programme for this cluster RCT will build on the existing skillset of DAFNE facilitators but also draw on additional behavioural science to deliver the revised curriculum. The content will cover:

a) Familiarisation with the new curriculum and language
b) Training in specific behaviour change techniques and their underlying theory
c) Practical skills acquisition sessions to cover action planning; sustaining behaviour change and managing resistance
d) Familiarisation with the DAFNE*plus* technology and online interface
e) Psychological strategies applied to blood glucose monitoring and pattern review
f) Psychological strategies to support layered learning and sustaining behaviour change during follow up; and
g) Managing the needs of complex participants and holistic care planning (e.g. referral to other agencies).

The training programme, combining didactic and interactive learning, will include elements of self-directed learning and delivery in a group format to the DAFNE*plus* facilitators, over a maximum of five days.

Throughout the trial, each centre will be offered supervision by the clinical psychologist, with support from a DAFNEplus Facilitator, to support delivery of DAFNEplus and troubleshoot relevant issues. Supervision will comprise of:

For the first DAFNEplus course at each centre:
a) A pre-course teleconference
b) Weekly support calls during the first course
c) Weekly e-mail supervision
d) Ad hoc e-mail/phone support

All subsequent courses will receive c) and d). This will allow issues that arise to be addressed in a timely manner during the trial.

7. Assessments and procedures

Table 1 shows a breakdown of the outcome measures.

7.1 Biomedical outcomes

The primary biomedical outcome is glycaemic control, defined by HbA1c at 12 months (using a centralised assay to ensure standardisation), in those entering the trial with HbA1c >7.5% (estimated at 75% of those currently undertaking DAFNE courses based on our research database).

A secondary outcome will be glycaemic control, as measured by HbA1c, at 6 months post course for those entering the trial with HbA1c>7.5%. Additionally, the number of participants achieving either an HbA1c <7.5% (58 mmol/mol) or a decrease in HbA1c of ≥0.5% (≥5.5 mmol/mol) (using a centralised assay to ensure standardisation) will be calculated at both 6 and 12 months post course. These cut-off points are recognised throughout the diabetes research community as being clinically relevant (16). We will also collect and analyse 24-month outcome data (HbA1c and severe hypoglycaemic episodes) and analyse after the main study has closed and been reported.

Other secondary biomedical outcomes will include:

a) Severe hypoglycaemia, as defined by the American Diabetes Association (17), denotes severe cognitive impairment requiring external assistance for recovery, both rates and proportion of those affected;
b) Diabetic ketoacidosis, both rates and proportion of those affected;
c) Weight;
d) Body Mass Index;
e) Blood Pressure;
f) Lipids;
g) Albumin/ creatinine ratio

Demographic information will also be collected from all participants at baseline.

Deferred course attendance and Baseline assessments

Where participants defer attending a course due to illness, for example, but have already had a baseline assessment it may be at least two months between having a baseline and being able to attend the next course.
If the participant attends a course more than six weeks from the date the original baseline central HbA1c was taken, a new baseline assessment needs to be carried out.
We will collect three fields of data again at the new baseline, and keep the old data for these three fields in case of the need for evaluation later. The remaining data will be retained so only a select amount of data would be requested again from the participant.
It was agreed we would collect the following three data fields again:

1. HbA1c if taken >6 weeks
2. Ask the average number of blood glucose checks that the participant has performed each day over the past two weeks
3. Ask about any further serious hypos or DKA events since last assessment

It was also agreed we would capture on the web-based database whether the participant had deferred a course, the date of new baseline and the three new data items and values alongside the original data.

7.2 Psychological outcomes and process measures

Psychological outcomes will be collected via self-completed postal or online questionnaires at baseline, course completion, 3 months, 6 months, 9 months and 12 months (please see Table 1). A more detailed rationale for inclusion of these measures is provided in Section 10. These data are collected in addition to routine demographic and clinical data obtained via the CRFs.

The primary psychological outcome is the measurement at 12 months of the Audit-Dependent Diabetes Quality of Life Questionnaire (ADDQoL-15) (18), a thirty-item measure of diabetes-specific quality of life.

The following secondary psychological outcomes will be assessed:

1. Dawn Impact of Diabetes Profile (DIDP)(58): This is a brief, 7-item scale used to assess diabetes-specific quality of life.
2. Problem Areas in Diabetes Scale (PAID-11) (59): This 11-item scale assesses sub-clinical levels of diabetes distress and has demonstrated sensitivity to change in previous evaluations of DAFNE. It will be used here to compare our results to those earlier studies.
3. Diabetes-specific positive well-being (W-BQ-28)(60): This 4-item, validated and reliable, subscale will be used. In the original DAFNE trial, this scale predicted change in HbA1c.
4. Hypoglycaemia Fear Survey (HFS-11) (61): This newly developed and validated, 11-item, short form version of the original scale will be used.

   Process Measures

5. Diabetes Management Experiences Questionnaire (DMEQ): This 29-item scale assesses satisfaction with diabetes treatment.
6. Self-Regulation/Behavioural Regulation Questionnaire (SRQ-T1D): please see Appendix 3 for detail.
7. Diabetes Strengths & Resilience Questionnaire (DSRQ): This 12-item scale provides a measure of adaptive behaviours and attitudes associated with overcoming challenges with diabetes management and achieving “resilient” outcomes.
8. Confidence in Diabetes Scale (CIDS) assesses beliefs about capabilities (self-efficacy). This 20-item scale will be used to assess participants’ confidence in their ability to engage in different aspects of diabetes self-care behaviours.
9. Diabetes Self-Care Behaviours – SCB-T1D (20): 50 items from the original scale will be used to assess the extent to which participants in both groups are engaging with diabetes self-care behaviours.
10. Hypoglycaemia Confidence Scale (HCS) (25). Confidence in managing hypoglycaemia is a unique aspect of the experience of living with type 1 diabetes. This is assessed through 9 items.

11. Beliefs about consequences of engaging in DAFNE behaviours and weaving diabetes management into everyday routines. Please see Appendix 3 for more detail and rationale.
12. The System Usability Score (27): will be used to gather feedback on the DAFNE*plus* website at follow-up. As recommended by the scale authors the term 'system' will be replaced with 'Glucocollector' for the DAFNE*plus* group and 'bolus calculator' for the DAFNE (control) group.
13. Use and dose received of the DAFNE*plus* programme (28) will be assessed via logs of attendance at group and individual sessions, and use of the DAFNE*plus* website.

    Hypoglycaemia Awareness

14. Hypoglycaemia awareness will also be assessed using self-report methods via the Gold score (26): both percentage with Gold score <3 (i.e. awareness in tact), and percentage of those with baseline score ≥4 (impaired awareness) achieving a clinically relevant improvement of ≥1 point on the 7-point score. The DAFNE measure of hypo awareness will also be used.

7.3 Health economic outcomes

A number of health economic outcomes will be collected via postal or online questionnaires at baseline, post-course, 6 and 12 months (refer to table 1 for specific time-points for each measure):

a) Health status – EQ-5D-5L (29)
b) Health and Self-Management in Diabetes – HASMID (30)
c) Healthcare utilisation using a bespoke questionnaire
d) Contact between professionals and course participants will also be recorded at each site using questionnaires and data from the DAFNE*plus* website (in the intervention arm).

7.4 Safety outcomes

7.4.1 Adverse Events

We require that study centres only report as adverse events episodes of diabetic ketoacidosis and severe hypoglycaemia (severe cognitive impairment requiring external assistance for recovery (17)) which while not requiring admission to hospital have been noted by either the participant or their relative/partner etc. These have been identified as of relevant clinical concern during our previous research (REPOSE study) (16) in this area. These will be recorded on the data collection form and database.

7.4.2 Serious Adverse Events

Study centres are to report Serious Adverse Events (SAEs) promptly as detailed below in section 7.4.3. The definition of an SAE is as follows:

- Results in death;
- Is life threatening* (subject at immediate risk of death);
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect; or
- Any other important medical event that may jeopardise the participant***

* Life threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

*** Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.4.3 Reporting

It is not anticipated that there will be many SAEs related to the DAFNE*plus* or standard DAFNE programmes. We will report any SAEs which are deemed related to the study intervention and unexpected to the Sponsor and the REC within the specified timeframes below.

The local Principal Investigator will assess the event for seriousness, expectedness and relationship to the study.

All events (serious or other based on the definitions above) will be recorded on the data collection form and database.

For any SAEs e.g. admission for infections, admission with severe hypoglycaemia or DKA, the site will complete the Serious Adverse Event form and email the form to the CTRU within 24 hours of the event being discovered.

Pregnancies, or hospitalisations for pregnancy related events, will not be reported as SAEs. Hospitalisations deemed to be related to pregnancy and diabetes complications **will** be reported as SAEs.

A copy of the SAE form must be kept with the Site File.

The CTRU will inform the CI, who is responsible for assessing the seriousness and reporting to relevant regulatory bodies, where appropriate.

SAEs will be reported by CTRU in the periodic safety reports to the Sponsor and the TSC.

Only SAEs that are deemed related and unexpected will be reported by the CTRU to the main REC within the required expedited timeframes (15 days). These will be reported separately to the Sponsor and TSC as they occur.

Table 1 – List of outcome and process measures

Concepts	Questionnaire	Baseline: Pre-course appt	Course Completion	Post-course assessments			
				3m*	6m*	9m*	12m*
Demographic / Clinical							
Glycaemic Control (HbA1c)	N/A	✓			✓		✓
Lipids	N/A	✓					✓
Body mass index (height/weight)	N/A	✓			✓		✓
Blood Pressure	N/A	✓			✓		✓
Episodes of severe Hypoglycaemia	N/A	✓			✓		✓
Episodes of Ketoacidosis	N/A	✓			✓		✓
Demographics	Individual items	✓			✓		✓
Hypoglycaemia awareness	Gold score	✓			✓		✓
Primary Psychological Outcomes							
Diabetes-specific quality of life	ADDQoL-15	✓			✓		✓
Secondary Psychological Outcomes							
Diabetes distress	PAID-11 (short-form)	✓			✓		✓
Diabetes-specific quality of life	DIDP	✓			✓		✓
Diabetes-specific positive well-being	W-BQ28	✓			✓		✓
Fear of hypoglycaemia	HFS-11 (short-form)	✓			✓		✓
Health status	HASMID	✓			✓		✓
Health status	EQ-5DL	✓			✓		✓
Healthcare utilisation	Individual items	✓			✓		✓
Resource allocation	Individual items		✓				
Process Measures							
Diabetes Management Experiences (satisfaction)	DME-Q	✓	✓	✓		✓	
Self-regulatory skills/behavioural regulation	SRQ-T1D*	✓	✓	✓		✓	
Diabetes strengths and resilience	DSRQ	✓	✓	✓		✓	
Beliefs about capabilities: diabetes self-care	CIDS*	✓	✓	✓		✓	
Beliefs about capabilities: hypoglycaemia confidence	HCS	✓	✓	✓		✓	
Diabetes-specific self-care behaviours	SCB-T1D	✓	✓	✓		✓	
Beliefs about consequences of engaging in DAFNE behaviours and weaving diabetes management into everyday routines	Individual items*	✓	✓	✓		✓	
Evaluation of technology (DAFNE*plus* website in intervention group and bolus calculator in control group)	System Usability Scale		✓	✓		✓	

*Description about the development and modifications of these questionnaires and individual items are detailed in appendix three

8. Statistics

8.1 Quantitative analysis

The primary analysis population will be participants that had an HbA1c greater than 7.5% at baseline and the analysis will be completed on an intention to treat (ITT) basis. This primary analysis is to assess the difference between the two treatment groups on the participant's HbA1c at the 12-month follow-up appointment which will be completed using a multiple linear regression model with coefficients estimated using generalised estimating equations (GEE) to account for the clustering design. A 95% confidence interval for the difference between the two treatment groups will be presented. In the event of differences between the two treatment groups with respect to patient demographic, clinical, health-related quality of life measurements and psychological characteristics at baseline, these covariates will be included in the model, along with the participant's baseline HbA1c, to adjust the treatment effect accordingly.

The secondary analysis population is all consenting participants in the trial and analysis will again be completed on an ITT basis. This population will be used to assess the difference in psychological outcomes between the two treatment groups using the same multiple linear regression model as previously described.

A full statistical analysis plan (SAP) will be written and circulated to the Trial Management Group and Trial Steering Committee before being signed-off. All analysis results will be reported according to the revised CONSORT 2010 statement for cluster RCTs (31).

8.2 Sample size

It is expected that there will be 882 patients referred for DAFNE courses within the 15-month recruitment window and of these it is expected 75% (662 patients) will be recruited, equivalent to 47 participants at each of the 14 centres. From current DAFNE data a further 25% are expected not to meet the primary analysis population criteria of baseline HbA1c greater than 7.5%, leaving 497 participants. Finally, we anticipate 15% of participants to be lost to follow-up by the 12-month stage, therefore giving a primary analysis population of 422 participants. The sample size takes into account the design effect associated with the cluster design of the study. With an ICC of 1.5% (from previous DAFNE data) and 30 participants per cluster (422 participants over 14 centres) the design effect is 1.435 leaving the effective total sample size of n=294 participants (n=147 per arm).

Using a two sample comparison of mean HbA1c at the 12-month follow-up with 2-sided alpha of 5%, a correlation of 0.5 between baseline and final values and a standard deviation of 1.45 (from previous DAFNE data), the trial sample gives 92% power to detect a 0.5% difference in HbA1c between the two treatment groups in the study.

9. Health Economics

9.1 Aims and perspective

We will complete an economic evaluation as part of the study so that we are able to understand the cost-effectiveness of DAFNE*plus* compared to the standard DAFNE programme. The economic evaluation will follow guidance set by the National Institute for Health and Clinical Excellence for its Technology Appraisal process (32). The analysis will take an NHS and personal social services perspective, measure health effects in quality adjusted life years (QALYs), discount future outcomes at 3.5% per annum and consider effects and costs over a lifetime time horizon. An economic evaluation alongside the clinical trial (EEACT) and a long-term cost-effectiveness modelling analysis will be conducted. A full Health Economic and Decision Modelling Analysis Plan (HEDMAP) will be written and circulated to the Trial Management Group and Programme Steering Committee before being signed-off.

9.2 Economic evaluation alongside the clinical trial

For the EEACT, we conduct the analysis in line with Ramsey ***et al's*** (33) recommendations for cost-effectiveness analysis alongside clinical trials. Specifically, we will collect data alongside the trial on intervention costs, associated healthcare resource use and a preference based utility measure: the EQ-5D-5L measure (29). The intervention costing process will include training of educators, resource use, and adherence to structured follow up appointments, professional staff time and the technology component. A standard self-reported resource use questionnaire, used previously in the DAFNE*plus* pilot (as well as the 5x1 DAFNE (11) and the REPOSE trials (16)), will ascertain NHS usage in terms of GP, community, outpatient, A&E and inpatients, as well as occurrence of DKA and hypoglycaemic events by level of severity. Unit costs will be taken from standard sources (NHS Reference Costs, British National Formulary, PSSRU). The standard self-reported resource use questionnaire and the EQ-5D-5L will be collected at baseline, 6 months and 12 months. Course costs (administrative and clinical) will be estimated using a bespoke questionnaire for completion by site staff. Our primary analysis will use the EQ-5D-5L valuation study to generate utility scores at baseline, course completion, 6 months and 12 months for each study participant (34). There are on-going discussions about this valuation, and NICE recently produced a position statement recommending that EQ-5D-5L data should also be valued using mapping to the EQ-5D-3L (35,36), and we will therefore undertake a sensitivity analysis using this mapping. There are on-going research studies by the NICE Decision Support Unit and by the DH Economic Evaluation Policy Research Unit that will inform these methods further, and we will take account of the emerging findings and latest guidance coming from these at the time of our analysis. QALYs for each participant will be estimated by calculating the area under the curve defined by EQ-5D utility score, mortality and length of follow-up. The base case analysis will use the complete case data. In a scenario analysis, the missing data will be imputed. The time horizon of this analysis will be limited to the one-year time horizon of the trial. As the effects

and costs of DAFNE*plus* may be incurred beyond the one-year trial time horizon (due to expected differences in the time to onset of diabetes related complications), this evaluation will be considered as the secondary health economic analysis.

9.3 Long-term cost-effectiveness modelling

In the long-term modelling exercise, the resulting evidence base will be incorporated into an updated Sheffield T1D Diabetes Policy Model (37). Demographic variables and resource use (e.g. insulin use, contacts with NHS professionals) will be obtained from the trial data. The Sheffield T1D Diabetes Policy Model will be updated to use statistical models that estimate the clinical effects of DAFNE*plus* compared to DAFNE on HbA1c, the incidence of severe hypoglycaemia and the incidence of DKA. Two long-term modelling analyses will be conducted, the first will use the data collected by the one-year time point and will be submitted as part of the report to the NIHR on the DAFNE*plus* programme grant. This analysis will be updated after the two-year data collection is complete to incorporate the statistical analysis of the two-year follow up data. These statistical analyses of the clinical effects of DAFNE*plus* compared to DAFNE will be pre-specified in the statistical analysis plan. The time horizon of this analysis will be over each simulated individual's lifetime. As such, the long-term modelling will be considered as the primary health economic analysis.

9.4 Outcome measures and uncertainty analyses

In both the EEACT and the long term modelling the main outcome of interest will be the comparison of the incremental cost-effectiveness ratio (ICER) of DAFNE*plus* compared to DAFNE. The ICER will be compared to a maximum acceptable ICER of £20,000 per QALY gained, as this is the lower limit of the ICER range used by NICE to determine if an intervention is cost-effective (32). Uncertainty in the ICER will be determined using: scenario analyses, subgroup analyses (pre-specified with the wider DAFNE*plus* team), probabilistic sensitivity analysis and expected value of information calculations. In particular, uncertainty in the cost-effectiveness of DAFNE*plus* as used in a wider rollout (compared to as utilised in the trial) will be explored in our scenario analyses.

10. Process evaluation

10.1 Aims and research questions

Understanding processes is as important as evaluating outcomes; process evaluations are complementary to outcomes evaluations and provide knowledge and information of equal value. Process evaluations aim to understand the functioning of an intervention by examining its implementation, mechanisms of impact and how contextual factors (i.e. factors external to the intervention/individual receiving the intervention) might affect its delivery and

receipt (28,38). Without this knowledge we may be able to establish from an outcome evaluation that an intervention 'works', but we will be presuming that the intended intervention was delivered and is effective, and we will not necessarily know how, or why, the intervention works and, hence, if it would have the same clinical and psychological effect if rolled out from a trial situation into routine clinical practice. With a complex intervention such as DAFNE*plus* it may well also be that some elements are more vital to its success than others; hence it is very important that we understand and explore the mechanisms of change on outcome from the perspectives of those receiving the intervention, as well as unintended consequences arising from the delivery and receipt of the intervention.

Our overarching research questions are:

1. **Does the DAFNE*plus* intervention 'work' in the ways intended? If not, why not?**

2. **What are the implications of the findings of the process evaluation for the rollout of DAFNE*plus* in routine clinical practice?**

To answer these over-arching questions, a series of over-lapping sub-questions will be explored:

a) What mechanisms change impact on glycaemic control? That is, how do the different elements of DAFNE*plus* (knowledge/skills, technological, structured follow-up), individuals' interaction with these elements, and individual psychological differences trigger changes in and maintenance of key diabetes self-management behaviours? The theoretical model underpinning the DAFNEplus programme assumes that diabetes self-management behaviours are among the principal determinants of glycaemic control[4].

b) What mechanisms of change impact on diabetes-specific quality of life?

c) What are participants' experiences of, and views about, key elements of the DAFNE*plus* intervention** and how do these influence and inform changes in, and maintenance of, key diabetes self-management behaviours over time?

**As a result of work undertaken in the pilot phase and MRC guidance to focus on key areas of uncertainty of greatest interest to academic and clinical audiences, a decision has been made to focus upon the technological and resilience/self-compassion elements of the programme.

Conceptual models detailing these putative relationships are included as appendix one and two

d) To what extent is the intervention delivered as intended and are there variations between sites and individuals as to how the DAFNE*plus* intervention is delivered? What are the reasons for any variations?

e) What impact (practical and emotional) does intervention delivery have on facilitators and their workloads; what resourcing and support would facilitators and their colleagues need to deliver DAFNE*plus* in routine clinical practice?

f) Do any unintended consequences arise from the delivery and receipt of the DAFNE*plus* intervention, for participants and/or facilitators?

Due to onset of the COVID-19 pandemic during the trial and the challenges this presents, two further questions will be addressed:

g) What are participants' experiences of, and views about, transitioning from receiving face-to-face consultations and support to remote/telephone support? What are the implications of this transition on how they think about and self-manage their diabetes and their perceived need for input and support from health professionals? What are their preferences for care delivery (virtual versus face-to-face) moving forwards?
h) What impact has the COVID-19 pandemic had on how participants think and feel about their diabetes (e.g. diabetes-related distress) and their perceived need for input and support from health professionals? How, and in what ways, might the COVID-19 pandemic affect participants' questionnaire responses and the interpretation of trial outcome data?

The data sources for each of the sub-questions are shown in table 2.

Table 2 – Data sources for the process evaluation

Research Question	**Data source(s)**
a) What mechanisms of change impact on glycaemic control?	• Questionnaire study • Process outcomes • Fidelity assessment • Qualitative (from DAFNE*plus* pilot study)
b) What mechanisms of change impact on diabetes-specific quality of life	• Questionnaire study • Process outcomes
c) What are participants' experiences of DAFNE*plus*?	Qualitative
d) To what extent is the intervention delivered as intended?	• Fidelity assessment • Qualitative

e) What impact does intervention delivery have on facilitators and their workloads?	Qualitative
f) Do any unintended consequences arise from the delivery and receipt of the DAFNE*plus* intervention?	• Qualitative • Questionnaire study • Process outcomes • Fidelity assessment
g) What are participants' experiences of, and views about, transitioning from receiving face-to-face consultations and support to remote/telephone support?	• Qualitative
h) What impact has the COVID-19 pandemic had on how participants think and feel about their diabetes (e.g. diabetes-related distress) and their perceived need for input and support from health professionals?	• Qualitative and questionnaire study

The process evaluation is composed of three interlinking components: (1) qualitative, (2) quantitative and (3) assessment of fidelity of delivery.

10.2 Qualitative component

10.2.1 Overview

The qualitative component of the process evaluation will be informed by realist and Normalization Process theory (NPT) (39,40). These choices arise from our recognition that context (i.e. factors external to the DAFNE*plus* intervention and/or the individual receiving the intervention) may influence how the intervention is delivered in different centres and how it is received by different individuals. It is also recognised that, when a complex intervention, such as DAFNE*plus*, is implemented it can have unintended consequences, which may need to be investigated and, hence, that a flexible and adaptive study design will be required.

An iterative, inductive approach will be used wherein data analysis will commence as soon as data collection begins (41). This will allow issues arising during early phases of qualitative data collection to inform questions asked in later phases and possibly also sampling. The qualitative research will also be responsive to other aspects of the process evaluation, including the fidelity work. Hence, while case studies will comprise the main element of the qualitative research (see below), costings have been included to allow, if necessary, one-off interviews to be undertaken with a 'booster' sample of patients, facilitators and/or other individuals in the event that the quantitative/fidelity components of the process evaluation highlight issues which require qualitative explanation. One example might be that, if the fidelity work highlights significant variations between trial sites as to how the DAFNE*plus* intervention is delivered, we may decide to interview additional facilitators to better understand why this might be the case.

10.2.2 Qualitative study design: case study approach

A case study approach will be used because it permits detailed exploration of if, how and why the intervention works in different contexts (42). Each case will comprise: (a) participants who will be interviewed before, during and following completion of DAFNE*plus*, (b) their facilitators who will be interviewed after the participant's closeout from the trial, (c) information about the input and care the participant receives as part of DAFNE*plus* and their engagement with DAFNE*plus* technologies/resources. It will be possible to access this information via clinical records, the Glucollector website and information documented in case report forms and stored on PROSPECT (the CTRU database). Where identifiable clinical information needs transferring between NHS and University sites files will be encrypted and nhs.net accounts or Google Drive will be used. As part of the process evaluation, we will also have access to recordings of participants' face-to-face follow-up sessions with facilitators – these data are being collected for the fidelity assessment work, and data on utilisation of DAFNE*plus* technological components and adherence. Researchers from the University of Edinburgh will also sit in some DAFNEplus sessions as observers, to familiarise themselves with the processes and material to inform the case studies.

Participant Sampling

Two or three participants from each of the seven DAFNE*plus* sites will be selected for the qualitative work, and these individuals will be purposively sampled so there is representation of people of different ages, HbA1c levels, diabetes duration, gender, occupation, educational background, personal circumstance (e.g. single, partnered, parent) and place of residence (e.g. urban and rural locations). For participants who take part in the single interviews at 12-months purposive sampling may also include: whether and to what extent individuals have engaged with Glucollector data, changes in HbA1c from baseline to 6 months; and, measures of diabetes-related distress.

Data collection: participant interviews

Selected participants (n=8) will be interviewed at four time-points: prior to attending their course, following their course, and 3 and 12 months post course. Interviews will be informed by topic guides. Prior to undertaking a follow-up interview, a participant's previous interviews will be reviewed. As well as including more generic questions, follow-up interviews will be tailored to allow for follow-up of specific issues raised by particular individuals. Questions explored in the post course, 3 and 12 month interviews will also take account of a review of information collected in medical records, via DAFNEplus technology and audio recorded follow-up sessions.

Single interviews at 12 months with ≈22 further participants who have received the intervention will also be undertaken. Participants will be purposively sampled by the Process evaluation team as they approach the end of their participation in the trial (12-months). Participants will be sampled from all intervention sites and we will tailor particular questions to particular individuals on the basis of their Glucollector data and questionnaire responses.

Interviews will take place by telephone (unless an individual requests a face-to-face interview) at a time most convenient to the participant. All interviews will

be digitally recorded with consent. It is anticipated that each interview will take 60 minutes to complete.

Facilitator interviews
Each participant's facilitators (n=1-2 per participant) will be interviewed following their close-out from the trial. If the participant received care from more than two facilitators as part of DAFNE*plus* we will ask them to nominate the two individuals from whom they felt they had the most input.

Facilitators will be interviewed once following the participant's close-out from the trial. This decision has been made partly for pragmatic reasons (i.e. we do not want to make excessive demands on the health professionals' time) and also because it will be possible to access information about the participant's care and the decisions made from the contact logs, clinical records and recordings of follow-up sessions. It is also recognised that, if facilitators are made aware that the participant is included in the process evaluation, this might influence or bias the care which is given, although participants will not be prohibited from telling their facilitators they are taking part in the qualitative research should they choose to do so.

Facilitator interviews will explore two key areas: (1) their views about, and experiences of, providing care and support to the case study participant; and (2) the facilitator's more general experiences of recruiting into the trial and delivering the DAFNE*plus* intervention.

Data collection: facilitator interviews
The facilitators' interviews will be informed by topic guides, although each individual's interview will also be tailored to explore issues specific to the participant who forms the focus of the case study (being careful to ensure that patient confidentiality is not breached). Interviews will take place by telephone at a time most convenient to the facilitator and will be digitally recorded.

10.2.3 Data analysis
Each participant's four interviews will be read through repeatedly and cross-compared with particular attention being paid to continuities and changes in their diabetes self-management practices over time, and the reasons for these. To aid comparison and identify where behaviour change has happened and why, 'critical incidents' will be extracted and compared (a 'critical incident' comprises data where a behaviour/decision/experience is described in detail, including the contextual and antecedent factors leading up to it and the consequences arising from it (43,44)). To help identify reasons for behaviour change, maintenance and lapses, data from the facilitator interviews, and recordings of follow-up sessions and case reports will also be used to help interpret and provide context to analysis of participant interviews.

Facilitator interviews will be cross-compared to identify issues and experiences which cut across different accounts (41). Depending on the findings of the fidelity work, facilitator interviews may also be analysed in clusters (e.g. facilitators belonging to 'adherent' vs 'non-adherent' sites), to better understand

reasons for individual/site differences in how the DAFNE*plus* intervention was delivered.

Key objectives of the analysis of the participant interviews are to: (a) inform analysis of the quantitative data collected for the process evaluation; and (b) aid interpretation of quantitative data collected for both the process and outcomes evaluations; (c) provide recommendations for rollout of DAFNE*plus* following the trial and (d) provide recommendations for the delivery of future diabetes consultations (e.g. virtual versus face-to-face). Key objectives of the analysis of the facilitator interviews are to offer insights which might: (a) aid interpretation of the participant case study data; (b) help explain findings from the fidelity work; (c) aid interpretation of trial outcome data; and, (d) offer insights relevant to decision-making about the possible rollout of DAFNE*plus* following the trial.

A key area for reflection
It needs to be recognised that, by interviewing participants at four time-points, and because of the kinds of questions which will be asked, the qualitative study could, potentially, have an impact on how this small group of participants understand, engage with, and experience the DAFNE*plus* intervention. Care will be made to emphasise to participants that the qualitative study is separate to DAFNE*plus* and it is our intention to understand their experiences rather than to influence their behaviours. Whilst we may not be able to diminish the impact that this has on these participants, we hope that the overall impact will be minimal due to the small sample size potentially affected.

10.3 Quantitative component

10.3.1 Overview
A longitudinal, questionnaire study design has been adopted to determine the impact of the RCT on: a) our primary psychological outcome (diabetes-specific quality of life), b) secondary psychological outcomes and c) for the quantitative aspect of the process evaluation. That is, to identify the mechanisms of change that predict glycaemic control and diabetes-specific quality of life.

All participants in the intervention (DAFNE*plus*) and control (DAFNE) arms of the RCT will be given questionnaires to complete at baseline (up to 4 weeks prior to commencing the course) and at course completion, 3, 6, 9, 12 months post-course (see section 7 and Table 1). At baseline, the point at which participants will be more motivated to participate (pre-trial), they will be asked to complete all outcome and process questionnaire measures. To reduce participant burden, at course completion, 3- and 9-months they will only be asked to complete process measures. At 6 and 12-months they will be asked to complete the primary and secondary outcome measures only. Participants will be given the option of completing the questionnaire packs online or as a hard copy. Our choice of questionnaires (see section 7), assessing different constructs, have been selected according to existing knowledge about their association with the trial's primary outcome (HbA1c) and diabetes-specific quality of life (primary psychological outcome), the results of the YOURSAY survey (unpublished), our former work with the DAFNE intervention, and based

on the theoretical framework that underpins the new intervention development work and possible treatment mechanisms (13,45,46). Brevity of the questionnaires and participant burden have also been a key consideration in our rationale for selection.

10.3.2 Analysis

The use of a repeated measures, longitudinal design will permit analysis of our primary and secondary psychological outcomes, as well as both the short- and long-term predictors and mediators of outcome (HbA1c and ADDQoL-15) using Structural Equation Modelling. SEM combines confirmatory and exploratory purposes. We will test our proposed model of the long-term predictors and mediators of outcome and then, if necessary, re-test this based on changes suggested by SEM modification indices (47). The model will partially be informed by the qualitative work (described in 10.2 above).

10.4 Assessment of fidelity of delivery

10.4.1 Introduction

Behaviour change interventions are susceptible to variation in implementation, and are not always delivered as planned (48). Intervention fidelity refers to the methodological strategies used to assess, monitor and enhance the integrity, that is, reliability and validity of behaviour change interventions (48). The extent to which interventions are delivered as planned indicates internal and external validity, and needs to be known if the trial results are to be accurately interpreted and replicated. If fidelity is low, it is uncertain whether a change in outcome variables is due to the intended intervention, or to unknown factors that may have been added or omitted; alternatively, if no positive change is observed, it cannot be determined whether this is due to an inefficient intervention or a lack of intervention fidelity. This means that ineffective treatments risk being implemented and disseminated, and potentially effective treatments prematurely discarded (48).

The development of the content and structure of the DAFNE*plus* programme was informed by the Behaviour Change Wheel (BCW) framework (13). The intervention's proposed functions are served by behaviour change techniques (BCTs), specified in the hierarchical Behaviour Change Technique Taxonomy v1 (BCTTv1; (14)), which are its 'active ingredients' (15). The DAFNE*plus* intervention contains manual-specified BCTs as its active ingredients proposed to effect behaviour change (e.g. action planning, goal setting, and information on health consequences of the behaviour), together with principles for delivery specific to the DAFNE*plus* intervention that were identified during an expert consensus process (e.g. focus on the positives, emphasise individual autonomy). The fidelity analysis will involve assessment of the delivery of BCTs.

Fidelity of delivery of BCTs will also be assessed in the control arm of the trial (standard DAFNE) in order to identify any loss of treatment differentiation between the intervention and control arms as originally designed. Potentially loss of differentiation may result from low fidelity of delivery of additional content

in the DAFNEplus programme, or additional content being delivered in the standard DAFNE programme, either unintentionally or as a result of contamination.

10.4.2 Aims and research questions

The aim is to explore the integrity of delivery of the DAFNE*plus* programme trialled in the RCT.

The research questions are:

- To what extent was the DAFNE*plus* programme delivered as specified in the protocols (course curriculum and follow-up scripts)? Specifically:
    - What proportion of manual-specified content (i.e. BCTs) was delivered by facilitators as intended during the programme sessions?
    - What additional, non-specified BCTs were delivered by facilitators?
    - How did the proportion of manual-specified content delivered differ across sessions and sites?
- What is the extent of treatment differentiation between the content of DAFNEplus and control (standard DAFNE) programmes delivered?

10.4.3 Methods

10.4.3.1 Design

A quantitative fidelity assessment, involving content analysis of intervention materials and transcripts of audio-recorded intervention sessions and provider self-rated fidelity checklists.

10.4.3.2 Observed fidelity of delivery assessment

The direct observation of fidelity via coding of session transcripts will provide an in-depth assessment of fidelity of delivery in a sub-sample of DAFNE*plus* and DAFNE courses.

Participants

Facilitators delivering either the DAFNE*plus* (intervention arm) or standard DAFNE (control arm) curriculum in 6 of the 14 participating sites will have their sessions recorded. It is assumed that each of these sites will have at least three facilitators delivering the DAFNE or DAFNE*plus* programmes (i.e. a minimum of 18 participants). Informed consent will be obtained from all participants at the selected sites (facilitators and patients). As part of the wider RCT, their participation in the programme during the course will be audio-recorded for training and research purposes.

Materials: Coding framework to assess observed fidelity of delivery

A coding framework will be developed to specify the BCTs to be delivered during the five face-to-face DAFNE*plus* days and the f~~our~~? follow-up sessions, and the standard DAFNE course sessions, as specified in the facilitator manual. For each BCT the coding framework will include a definition, examples and criteria for potential operationalisation in the context of the programme.

Sampling and procedure
Six sites (2 control and 4 intervention) will be purposively sampled for audio recording of all sessions. Selection will be informed by variables such as facilitator experience, previous research activity and site activity levels.

Course sessions, delivered face-to-face, will be audio-recorded in both the intervention (i.e. DAFNE*plus*) arm and control arm (i.e. standard DAFNE) (42) at selected sites. Written informed consent for audio-recording sessions will be sought from all participants and facilitators. Participants will be reassured that transcripts of audio-recorded sessions will be fully anonymised to remove any personal or identifiable information. Facilitators will be supplied with a digital audio-recorder and instructions for operating it. Facilitators will audio-record sessions and upload recordings to the University of Sheffield secure server via Google Drive which will be accessed by the study manager and authorised members of the research team. Transcription will be performed by an external transcription service and a confidentiality agreement will be put in place with the transcribers to protect participant's data.

Each DAFNE*plus* programme comprises circa 40 sessions (one 1:1 pre-course session, 35 group 'course' sessions and up to five 1:1 follow-up sessions per participant). Each standard DAFNE course comprises circa 35 group course sessions per participant. Sessions will therefore be purposively sampled for transcription and analysis across both arms, selected sites and courses. Courses will be sampled according to key variables, e.g. geographical location, and the timeline for the trial with earlier courses preferentially sampled due to staff resource. Sessions may be sampled for transcription according to theoretical underpinning of the intervention, and evidenced relation to the outcome.

Analysis
Sampled content of sessions in both the intervention and control arms will be first specified by applying the developed coding framework to the sample of selected course transcripts. Two researchers will independently read through the session transcript line-by-line, using the coding framework to identify and categorise BCTs present in the facilitator's speech. Each identified BCT and delivery principle will be rated as fully, partially or not delivered according to the coding framework definition and criteria. Illustrative examples will be extracted into the framework.

To assess and establish inter-coder reliability, the researchers will meet frequently in coding workshops at the outset of coding (e.g. initially after coding every transcript (49)). Approximately twenty percent of transcripts will be double coded. Inter-rater reliability will be assessed by percentage agreement (50). Reasons for discrepancies will be discussed, and the coding framework developed accordingly. Following Hardeman et al. (49), a minimum level of 75% inter-coder agreement (51), described as 'high' (52,53) will be considered acceptable. After inter-coder reliability has been established, researchers will code the remainder of transcripts independently.

Fidelity of delivery will be assessed following the methods of Hardeman et al. (49) and Lorencatto et al. (50). Each of the BCTs specified in the DAFNE*plus* programme (intervention arm) or standard DAFNE programme (control arm) curriculum/scripts will be listed in a checklist, together with details such as session number and facilitator participant number. The BCTs specified in the coding framework will be rated as: 1) fully present, 2) partially present, or 3) absent but should be present. The proportion of BCTs delivered as intended will be assessed by dividing the number of fully/partially present BCTs by the total number of intended BCTs. Established criteria will be applied to classify extent of observed fidelity of delivery (42): if < 50% of intended content is delivered this will be classified as 'low' fidelity; 51-79% as 'moderate' fidelity, and 80-100%' as 'high fidelity'.

Sessions will be grouped into types based on topics where applicable (for example, the four sessions covering action planning would be grouped into one type). An 'intended content' checklist will be produced for each session, and the session transcript will only be compared to the checklist for the corresponding session or session type, rather than comparison against the full curriculum. Variation in fidelity will be examined according to site and session type. Delivery of any additional content will also be examined by assessing the frequency of delivery of any non-specified BCTs. This will serve to identify adaptations made whilst delivering DAFNE*plus*.

Treatment differentiation will be assessed by comparing the content analyses of transcripts from the intervention (DAFNE*plus*) and control (standard DAFNE) sessions. BCTs that are fully/partially delivered in transcripts from both arms will be compared, and the proportion of BCTs delivered in both arms assessed, with a higher proportion of common BCTs delivered representing less treatment differentiation.

10.4.3.3 Self-reported fidelity of delivery

Participants
All facilitators delivering either the DAFNE*plus* (intervention arm) or standard DAFNE (control arm) curriculum/scripts in each of the 14 participating sites will provide data for the fidelity of assessment delivery. It is assumed that each site will have at least three facilitators delivering the DAFNE or DAFNE*plus* programmes (i.e. a minimum of at least 42 participants). Informed consent will be obtained from all participants (facilitators and patients) as part of the wider RCT.

Materials: Facilitator self-rated checklists
To obtain a global snapshot of fidelity across all DAFNE*plus* courses, including those that are not transcribed and included in the observed fidelity assessment, self-reported facilitator checklists will also be developed and administered to all sites (intervention and control). The checklist will include provision of key information and BCTs that are intended to be delivered (i.e. as specified in the pre-course session script, course curriculum and follow-up support scripts), and how confident and competent the facilitators felt delivering the session components. Facilitators will also be asked to record reasons for any

components not being fully delivered. Different checklists will be developed for each session. Due to the dynamic nature of the intervention and curriculum development it is not possible to provide definitive and finalised versions of these checklists at this time: the checklists will be finalised following the coding of the final version of DAFNEplus.

Procedure
Facilitators will be asked to complete the checklist at the end of each session where possible, or by the end of each day. They will forward completed checklists to Sheffield University CTRU by the end of each day. Facilitators will rate the extent to which they feel they delivered the intervention components listed in the checklists, from 0 (not at all), 1 (partially) to 2 (fully delivered).

Analysis
The proportion of intended components rated as partially/fully delivered by the facilitators will be calculated. The same criteria will be applied to classify extent of fidelity as in the observed measurements: if < 50% of intended content is delivered this will be classified as 'low' fidelity; 51-79% as 'moderate' fidelity, and 80-100%' as 'high fidelity'. Variation in proportion of fidelity of delivery will be examined across: session types, facilitators, and courses.

There are well documented discrepancies between what healthcare providers report delivering and actually deliver (54). Therefore, for the DAFNE*plus* courses where session transcripts have also been coded (as described above), self-reported and objectively verified practice will be directly compared in terms of the proportion of BCTs facilitators report delivering, and that which was identified during the content analysis.

11. Trial supervision

11.1 Trial Steering Committee

The Trial Steering Committee (TSC) consists of an independent chair with clinical and research expertise in the topic area, and four other independent members, including a statistician and two PPI representatives, as the sponsor sees fit and as agreed by the grant awarding body. The TSC will meet at least every 6 months with more frequent meetings as necessary to supervise the overall conduct of the study, and the wider programme grant.

The TSC provides independent supervision for the trial, providing advice to the chief investigator and the Sponsor on all aspects of the trial by ensuring the trial is conducted according to the MRC Guidelines for Management of Global Health Trials (55). If the Chief Investigator and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all other associated with the study, may write through the Trial office to the Chairperson of the TSC, drawing attention to any concerns they may have about the possibility of particular side effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

11.2 Trial Management Group

The trial will be supervised on a day-day basis at the Sheffield CTRU by the Trial Manager with supervision by the Chief Investigator and a Senior Trial Manager. The Trial Management Group (TMG) will consist of Chief Investigator, Study Manager, Clinical Trial Co-ordinator, Data Manager and Trial Statistician and all of the co-applicants. This group reports to the TSC is accountable to the TSC for the implementation of the trial and therefore will monitor recruitment, data management, patient safety, delivery of the intervention, adherence to protocol, timescales and budget management. At each participating centre a local Principal Investigator will report to the TMG via the staff at the Sheffield CTRU.

The core TMG will meet regularly at least once every two months, but rising to at least once per month before key milestones (ethical approval, recruitment initiation etc.). In addition, investigator meetings will be set up during the recruitment phase of the study, at least once every two months, where the site PIs (or another delegated individual) will discuss pertinent issues with the research team, including recruitment, data completion and intervention delivery.

11.3 Data Monitoring and Ethics Committee

We have not convened a Data Monitoring and Ethics Committee for this study, on the grounds that the study is low risk, in line with CTRU Standard Operating Procedure GOV003. This has been approved by the Sponsor and TSC.

12. Data handling and record keeping

Sheffield Teaching Hospitals NHS Foundation Trust (STH) is the sponsor for this study, is based in the United Kingdom, and will act as the data controller for this study. The day to day running of the study is delegated to the Clinical Trials Research Unit (CTRU) in the School of Health and Related Research at The University of Sheffield. Together STH and CTRU will be using information from you and your medical records in order to undertake this study. This means that we are responsible for looking after your information and using it properly. The University of Sheffield will keep paper copies of identifiable information about you for 5 years after the study has finished and securely store electronic data for a minimum of 10 years.

Participant confidentiality will be respected at all times during the study. Data will be collected and handled in line with CTRU Standard Operating Procedures and in accordance with NHS Trust policies at Sheffield Teaching Hospitals NHS Foundation Trust and at each participating site. This will ensure systems are in place to protect confidentiality of participants and the systems are secure.

Participants will be allocated a unique identification number that will be used to identify them throughout the trial. All data collection forms, except those collecting demographic or contact details, will be anonymised and will contain the unique participant identifier.

All consent forms and questionnaires will be kept in a locked filing cabinet in a secured area and will be retained for a minimum of 5 years after study completion, in accordance with the sponsor's archiving requirements. Sheffield CTRU may request consent forms to be sent from the research site to the CTRU via post or email as part of remote monitoring procedures.

Data will be entered into an electronic eCRF, on a secure online database, hosted on University of Sheffield servers. Identifiable data, including audio recordings of interviews and DAFNE/ DAFNEplus sessions, names, addresses and dates of birth, will be shared with Sheffield CTRU and the supporting study team (via the secure online database) and DAFNE*plus* website teams (who provide technical support to participants). Consent will be obtained from the participant for this to occur.

13. Data access and quality assurance

Direct access to source data/documents (including hospital records/notes, clinical charts, laboratory reports, pharmacy records and test reports) will be granted to authorised representatives from CTRU (study manager, research assistant and data managers), the sponsor and host organisations to permit study related monitoring, audits and inspections. Select CTRU staff and members of the wider research and technical teams will have access to personal data including clinical information, audio recordings, names, addresses, phone numbers and email addresses in order to undertake the questionnaire follow-up, organise qualitative interviews, conduct analysis, inform training, and provide technical/IT support, as required. In addition to this, access to the eCRF and questionnaire data will be required for study monitoring and audit purposes.

The study database resides on Sheffield CTRU's in-house data management system. The system uses industry standard techniques to provide security, including password authentication and encryption using SSL/TLS. Access to the system is controlled by usernames and encrypted passwords, and a comprehensive privilege management feature can be used to ensure that users have access to only the minimum amount of data required to complete their tasks. This will be used to restrict access to personal identifiable data. The secure data management system will incorporate quality control procedures to validate the study data. Error reports will be generated where data clarification is required.

Overall responsibility for ensuring that each participant's information is kept confidential will lie with the study sponsor. All paper documents will be stored securely and kept in compliance with the Data Protection Act (1998). Data will be entered directly onto the electronic database hosted by CTRU on behalf of the sponsors. Access to the participant's name and any other identifying details will be restricted to those who need them. After the trial has been completed and the reports published, the data will be stored in a secure physical or electronic location with controlled access.

Data collected via the DAFNE*plus* website has its own secure arrangements in terms of access control, audit, intrusion, detection and prevention.

The nature, frequency and intensity of trial monitoring will be outlined in the site monitoring plan, which will be devised in accordance with the Sheffield CTRU SOPs on Trial Monitoring (QA001) and Data Management Plan (DM009). The primary method of monitoring will be remote monitoring, with site visits undertaken at the discretion of CTRU and the study sponsor. The monitoring plan will explain what will be monitored, which/what proportion of data fields and who will be responsible for conducting the monitoring visits, and who will be responsible for ensuring that monitoring findings are addressed. Investigators and their host Trusts will be required to permit trial-related monitoring and audits, providing direct access to source data and documents as requested either at site or via secure email. Trial participants will be made aware of the possibility of external audit of the data they provide in the participant information. A random selection of consent forms and source data from each centre may be sent via email or post to Sheffield CTRU for monitoring purposes. Both will be sent in a secure manner.

14. Publication

The trial protocol will be published on an open access source. A number of academic outputs will be produced as the data are analysed throughout the trial. Journals will be selected based on the highest possible impact. Other stakeholder specific outputs in relevant formats will also be produced for commissioners, third sector, and user advocacy organisations. A website has been established to promote the work of the trial. All knowledge transfer activity including translation will be informed by input from trial collaborators, the TSC and TMG to ensure the study is meeting the needs of the commissioners and audience.

Outputs from the RCT will include:

a) Presentation of publication of primary (blood glucose control measured by HbA1c), and secondary outcomes including diabetes-specific quality of life, diabetes distress, rates of severe hypoglycaemia, episodes of diabetic ketoacidosis, weight.
b) Additional psychological outcomes including proximal outcomes and process measures predicting glycaemic control
c) Process evaluation
d) Health economic analysis

The outputs from the work will be provided to the 70+ DAFNE centres across the UK, in a form which will enable them to be readily communicated to clinical commissioning groups (in England) and the respective funders in the devolved nations. This will facilitate decisions on establishing and sustaining funding of this enhanced support for adults with T1D in the UK. Through Diabetes UK and the DAFNE collaborative we will communicate our findings to the All Parliamentary Group on Diabetes, the National Clinical Director of Diabetes and NICE.

15. Finance

This study is financed by the NIHR via a Programme Grant for Applied Research, and details have been provided in a separate agreement.

16. Ethics approval

16.1 Governance and ethics approval

The RCT study will not be initiated until the protocol, informed consent forms and participant information sheets have received approval from the Research Ethics Committee (REC), the Health Research Authority (HRA) and local Capacity and Capability is confirmed by the respective National Health Service (NHS) Research & Development (R&D) departments. MHRA approval is not required for this study.

The RCT will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (56); the principles of Good Clinical Practice, and the UK Framework for Health and Social Care Research (57).

16.2 Participation Record Retention & Archiving

During the course of the research all records are the responsibility of the Chief Investigator and must be kept in secure conditions. The sponsor or sponsors representative will hold responsibility for record retention and archiving to relevant procedures. Archiving of the site files and participants' records at each participating centre will be the responsibility of the local R&D department. Funding will be provided for this.

16.3 Protocol compliance and non-compliance

Protocol non-compliances are defined as '[a] noted systematic lack of both the CI and the study staff adhering to Declaration of Helsinki (56) applicable regulatory requirements but not limited to the UK Framework for Health and Social Care Research (57), GCP, Sponsor's and Sponsors' delegated representatives' policies and procedures and any subsequent amendments, which leads to prolonged collection of deviations, breaches or suspected fraud.'

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communication and updates. The Sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated. The study manager (plus, optionally, the CI and sponsor) will assess the non-compliances, decide on a remedial action to be taken, and a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the R&D office will agree an appropriate action, including an on-site audit.

16.4 Trial Organisation and Responsibilities

To ensure the smooth running of the trial and to minimise the overall procedural workload it is proposed that each participating centre should delegate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for the relevant healthcare professional to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research and for reporting any failure in these respects, adverse events or suspected misconduct through the appropriate systems.

Local Coordinator at each centre
Each centre will have a local Principal Investigator who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all medical, nursing and educator staff involved in diabetes services are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

Sheffield Clinical Trials Research Unit (CTRU)
The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Framework for Health and Social Care Research 2017 (57). CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU trial manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D capacity and capability approval has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

17. Regulatory approval

The study will be registered with, and approval gained, from all relevant regulators, including the Research Ethics Committee (REC) and the Health Research Authority (HRA). Confirmation of local capacity and capability will also be sought from each participating NHS trust.

18. Indemnity / Compensation / Insurance

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored trial and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96 (48) will operate in this case. However, it should be stressed that in term of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

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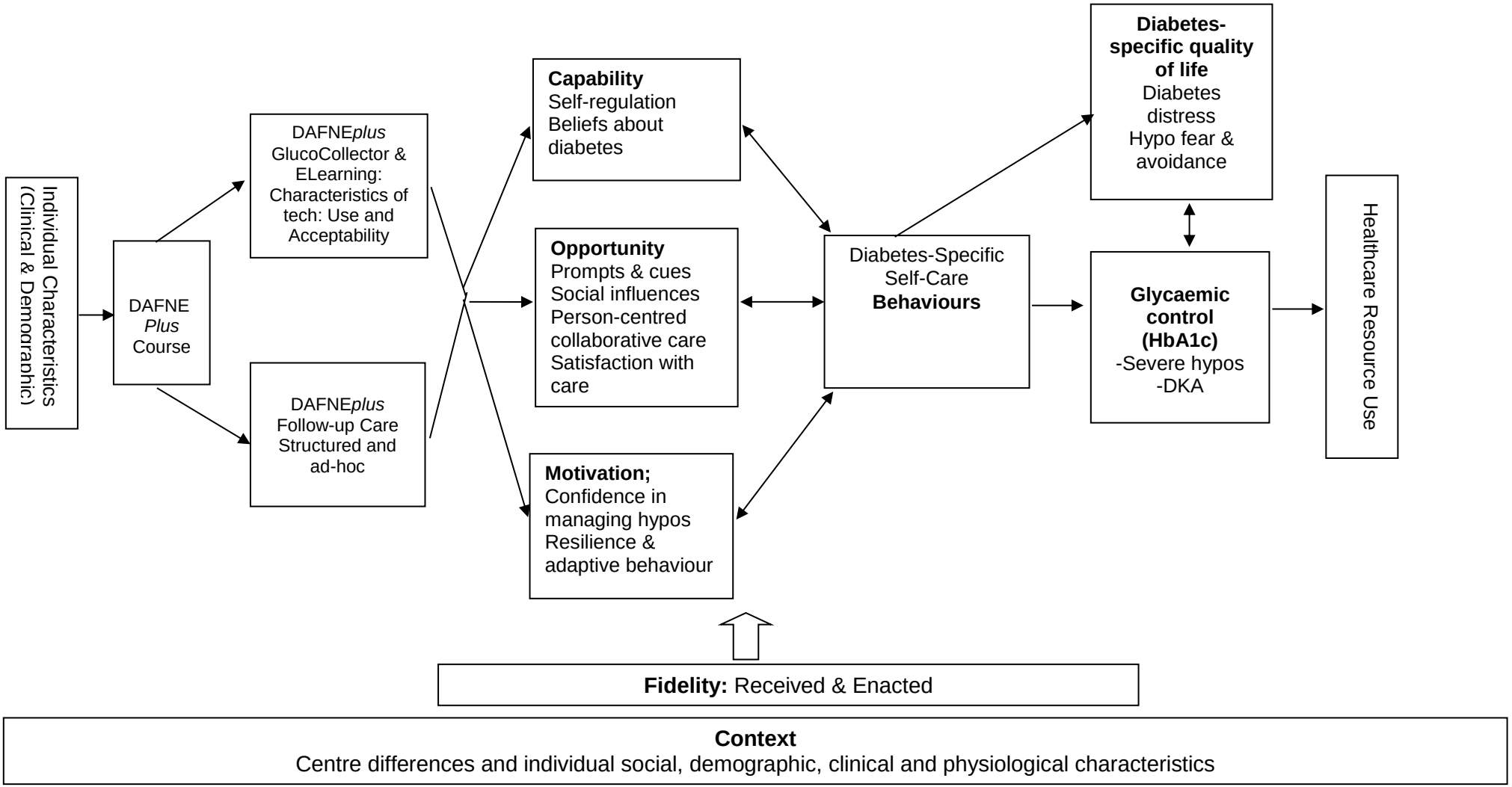
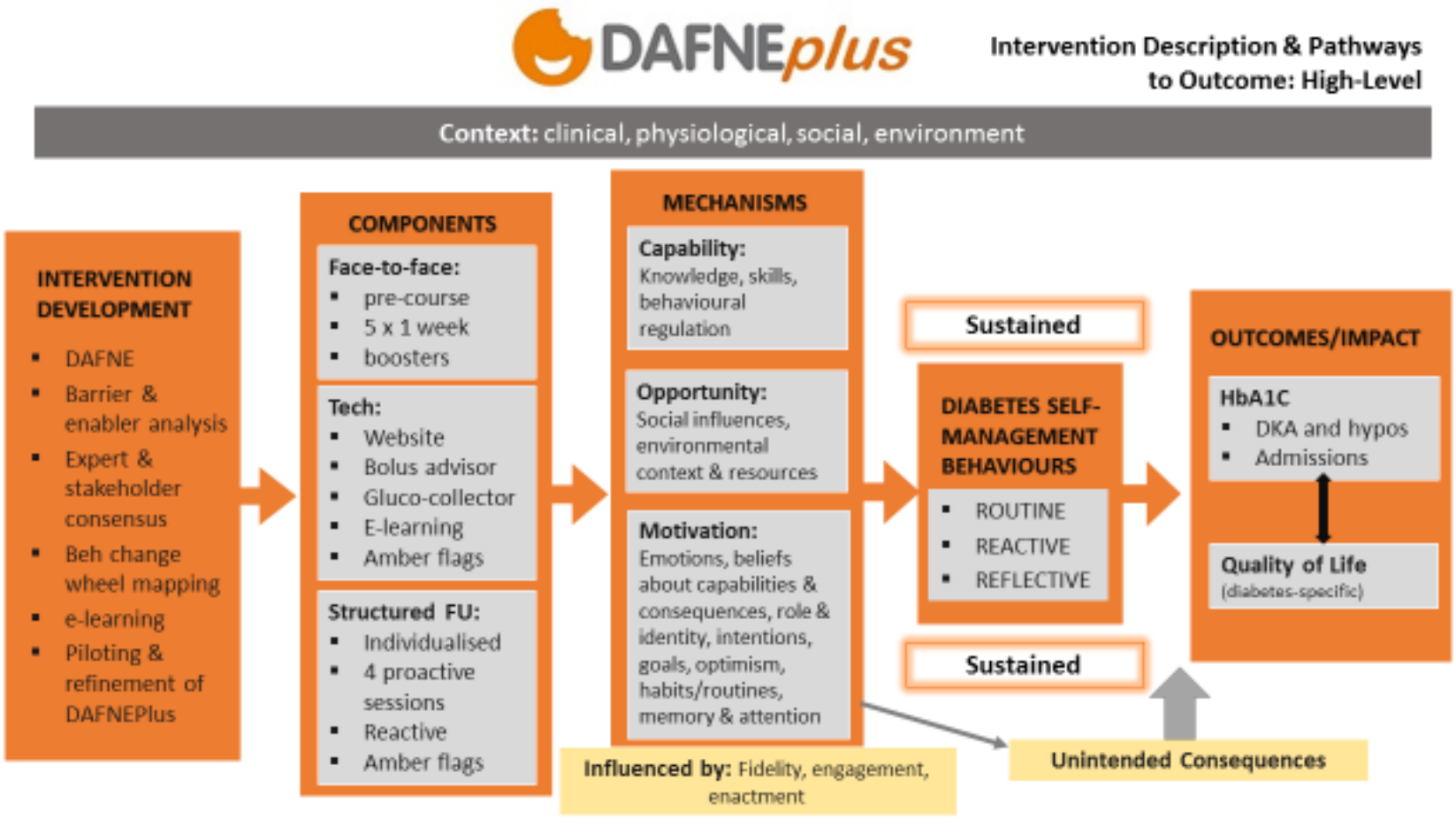
Appendix 1: DAFNEplus: Conceptual Model



Appendix 2: Intervention Description and pathways to outcome: high level



Appendix 3: Modified Patient Reported Outcomes

Confidence in Diabetes Scale (CIDS)

This scale assesses the extent to which an individual believes they can engage in particular behaviours related to their type 1 diabetes treatment regimen (self-efficacy). The scale was published in 2003 and Dr Cooke contacted Prof Snoek, the senior author on the original validation paper to seek permission to amend item 3 on the scale (*I believe I can perform the prescribed number of daily insulin injections*). He gave his permission for the team to make the following amendment to reflect the more flexible approach to multiple daily insulin treatment regimens, advocated by courses like DAFNE and DAFNE*plus* (*I believe I can perform the number of daily insulin injections I need to*).

Self-Regulation Questionnaire for Type 1 Diabetes (SRQ-T1D)

This questionnaire is an adaptation of the Self-Regulation Questionnaire (Brown, Miller, & Lawendowski, 1999). Self-regulation is the ability to develop, implement, and flexibly maintain planned behaviour in order to achieve one's goals. The SRQ and our adaptation of this builds on the work of Frederick Kanfer and two researchers who formulated a seven-step model of self-regulation (Brown, 1998; Miller & Brown, 1991). Although this model was developed specifically to study addictive behaviours, the self-regulatory processes it describes are meant to be general principles of behavioural self-control. In this model, people may have problems managing certain behaviours (behavioural self-regulation) because of challenges at any of these seven steps:

1.**Receiving** relevant information
2.**Evaluating** the information and comparing it to norms
3.**Triggering** change
4.**Searching** for options
5.**Formulating** a plan
6.**Implementing** the plan
7.**Assessing** the plan's effectiveness (which recycles to steps 1 and 2)

The original SRQ has demonstrated reliability, concurrent and discriminant validity in community samples (Aubrey, Brown & Miller, 1994). It consists of 63 items which was too long for our team to use in the DAFNE*plus* questionnaire pack, when this is one of several process measures. This measure was reviewed by 3 members from the DAFNE*plus* PPI group and by our process evaluation team consisting of clinicians, behavioural scientists, psychologists and social anthropologists, two of whom also have type 1 diabetes. The PPI group strongly recommended altering the wording of the individual items slightly so that these were all framed to be diabetes-specific in focus, rather than generic. Dr Cooke, in discussion with two members of the PPI group amended the wording of some of these items to ensure that they were clear and made sense. The process evaluation team and PPI group selected their top 2-3 items from each of the seven categories (above), rank ordering them. Dr Cooke then reviewed these to select the items from each category which the majority had agreed should be included within the final questionnaire.

Beliefs about Consequences of Diabetes Self-Care Behaviours; Diabetes Support and Routines

The DAFNE*plus* revisions to the original DAFNE curriculum were structured around the Theoretical Domains Framework (Atkins et al, 2017) hence it is very important to the process evaluation team to assess the constructs that are being targeted within individuals through the content and delivery of the DAFNE*plus* course; to assess whether participants in the DAFNE*plus* and standard DAFNE groups respond differently on these measures but also whether these constructs explain any differences in outcomes (HbA1c and diabetes-specific quality of life). Three of these constructs are 'social influences', 'beliefs about consequences of diabetes self-care' and 'environmental cues and prompts'. The research team have generated 11 diabetes-specific items to assess these constructs and have piloted them with our PPI group. These are unvalidated but once we have collected data at two timepoints (course completion and 3-months follow-up), if these measures are shown not to be psychometrically robust, we will remove these items from the 9-month follow-up point. Please note that we are only collecting these process measures at 3 timepoints.

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Appendix 4: RCT Gantt Chart:

Project Year	**Year 3**			**Year 4**				**Year 5**				**Year 6**				**Year 7**				**Year 8**	
Project month	31	32-34	35-37	38-40	41-43	44-46	47-49	50-52	53-55	56-58	59-61	62-64	65-67	68-70	71-73	74-76	77-79	80-82	83-85	86-88	89-90
	Sept 18	Q3 18/19	Q4 18/19	Q1 19/20	Q2 19/20	Q3 19/20	Q4 19/20	Q1 20/21	Q2 20/21	Q3 20/21	Q4 20/21	Q1 21/22	Q2 21/22	Q3 21/22	Q4 21/22	Q1 22/23	Q2 22/23	Q3 22/23	Q4 22/23	Q1 23/24	Q2 23/24
Workstream 4: Cluster RCT																					
Site recruitment																					
Governance approvals (continued from period 1)																					
Site initiations (continued from period 1)																					
Educator Training (4 training courses)		1st	2nd	3rd	4th																
Recruitment	**M5**	**M5**									**M6**										
Baseline Assessment (first patient first observed value)																					
DAFNE/DAFNEplus Courses (5 days each)																					
Post-course data collection upon course completion																					
6 month data collection (assessments/questionnaires)																					
12 month data collection(assessments/questionnaires)																					
Database lock																	**M7**				
Qualitative interviews																					
Qualitative analysis and write-up																					
Fidelity data collection & analysis																					
Close out, analysis, report write-up (includes Process - PROMS, Qual & Fidelity - synthesis)																				**M8**	
End of main programme grant																					
24 month data collection																					
Additional analysis and reporting - 24 month outcomes																					

Milestones

5. 1st ppt recruited to RCT, month 32
6. Ppt recruitment complete, month 60
7. Database final lock, month 78
8. Final report month 87 ,submission date 14.05.23

24 month f-up data submission, 31.08.23, month 90

Colour key

Original GANTT

Agreed extension