



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

## **Research Procedures Training Manual**

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## Baseline Visit

2 weeks

## Pre-Course Assessment

2 weeks

## Course

5 weeks

## Course Completion

3 months

## 3 Month Point

## 6 Month Point

6 months

## 12 Month Point

12 months

## 24 Month Point

- Face-to-face meeting with patient in clinic
- Take informed consent
- Fill out baseline case report form
- Take blood (HbA1c, renal function and lipids) and urine samples
- Give participant baseline questionnaire

- Participant will be emailed questionnaire from central team
- Complete THE POST COURSE DATA FORM re changes to insulin

- Participant will be emailed questionnaire from central team

- Face-to-face meeting with patient in clinic
- Fill out 6-month case report form
- Take blood sample for HbA1c only (no renal function, lipids or urine sample)
- Measure height and weight
- Ask about instances of DKA/severe hypos since /baseline/adverse events
- Participant will be emailed questionnaire from central team

- Face-to-face meeting with patient in clinic
- Fill out 12-month case report form
- Take blood and urine samples
- Participant will be emailed questionnaire from central team

- HbA1c and severe hypoglycaemic episodes will be collected from patient notes, after the main study has closed and been reported.

# 1. Background

Existing evidence suggests that an educational intervention (DAFNE) is effective in helping individuals with diabetes manage their disease through managing and adjusting their insulin doses. However, there is also evidence that improved management is not sustained in the long term following completion of the DAFNE course, and so a new course has been developed (DAFNE*plus*) which aims to improve upon the existing course. Rigorous evaluation is the essential next step in the development of the DAFNE*plus* intervention.

The DAFNE*plus* cluster randomised controlled trial aims to compare 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 6 and 12 months

## **The secondary objectives are:**

- To assess the effects of the intervention on diabetes-specific quality of life.
- 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, renal function 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 undertake a health economic analysis to determine the cost-effectiveness of DAFNE*plus* versus standard DAFNE.
- To assess fidelity of delivery of the DAFNE*plus* intervention.

This is a cluster randomised controlled trial (RCT). This differs from a traditional RCT in which individual study participants are randomly allocated to a treatment. In a cluster RCT it is the

site that is randomised, so of the 14 sites included in the study 7 are allocated before the start of the study to deliver the intervention (DAFNE*plus*) and seven are allocated to deliver the control (Standard DAFNE). All participants in the study at any given site will receive the same version of the course. This avoids 'contamination' as theoretically nobody in the control sites is exposed to the new intervention and therefore cannot, consciously or unconsciously, include aspects of the new intervention in their delivery of the control.

Alongside the cluster RCT a process evaluation will be conducted. This is in recognition that the interventions under consideration (DAFNE and DAFNE*plus*) are complex in nature and so the style of delivery and context, as well as the content, could all influence the effectiveness or otherwise of the intervention. Researchers will therefore investigate some of these factors using a variety of techniques:

- A fidelity assessment will be conducted in two parts. After each session facilitators will complete a checklist (figure 1.) to record whether they delivered key aspects of the session as specified for DAFNE or DAFNE*plus*. Additionally, six sites will be selected to audio record sessions for later transcription and analysis; selected sites will be provided with a laptop and encrypted digital audio recorder. Audio files and checklists will be uploaded via Google Drive where they will be accessed by the Central (Sheffield) CTRU team. Separate instructions on these processes will be provided (appendix A).
- Qualitative interviews will be conducted by researchers from the University of Edinburgh with a selected sample of participants and clinicians in the intervention (DAFNE*plus*) arm of the trial. It is anticipated that twenty participants (2-3 from each site) will be selected at baseline to participate and interviews will be conducted over the telephone at baseline, course completion and 3 and 12 months post course with the same participants. Interviews will be audio recorded and transcribed. University of Edinburgh researchers will have access to some research and clinical data via the research (PROSPECT) and DAFNE*plus* (Glucollector) websites but will need additional clinical data to be uploaded via Google drive. Facilitators involved in the delivery of DAFNE*plus* sessions to those participants selected for interview will also be invited to participate in interviews.

Prompts will be incorporated into the CTRU database (PROSPECT) to remind site staff of the actions required related to the process evaluation, but the process of transferring and storing data will be managed independently of PROSPECT.

Figure 1. Example of fidelity checklist

FACILITATOR CHECKLIST WEEK 1 – SESSION 1: INTRODUCTION TO <u>DAFNEplus</u>			Please tick:		
Site ID:	Facilitator ID:	Date:	Done	To some extent	Not done
Outlined the DAFNE hypo guidelines and pointed out the box where recommended hypo treatment will be kept for the week					
Explained the benefits of following DAFNE for BG levels and other clinical outcomes					
Explained that the course is to introduction to the skills, which will require further practice, and that active participation is essential					
Presented the messy cupboard visual and facilitated discussion about expected feelings during and after course participation					
Explained the DAFNE approach to managing diabetes and expected benefits of the approach					
Introduced participant resources and demonstrated the two parts of the <u>DAFNEplus</u> website, including how to log on, and explained its purpose					
Facilitated discussion of the total number of years of diabetes experience in the group and its value					
Facilitated discussion of participants’ hopes and expectations (discussed at PCA) for the DAFNE course					
Emphasised that perfect control is not achievable					
Explained individual differences in BG control, and that there would be no judgement around BG levels					
Facilitated discussion about participants’ feelings about diabetes using emotions cards					
Set group agreements					
Showed video of previous DAFNE graduate(s)’ testimonial					
Explained that facilitator support would be available after the course at individual follow-up appointments					
<b>If anything was not done, or was done to some extent, please give a brief reason (e.g. ran out of time, forgot, a problem arose):</b>					
<b>If you did not feel confident or able to deliver any part fully, give further details (e.g. training did not cover it adequately, didn’t feel comfortable):</b>					
<b>If you added anything extra to the session, please explain further (e.g. found additional resources):</b>					

## **1.1 Intervention (DAFNEplus)**

Following informed consent, participants who are in sites allocated to the intervention arm will attend the DAFNEplus course one day per week, over five consecutive weeks. The course includes the use of technology to transmit and display blood glucose data to support pattern recognition and interpretation. Participants will receive a bolus calculator to support insulin dose calculations and a Withcare+ box, which can be used to download and display data from the study participant's blood glucose meter. The Withcare+ box can also transfer this information to the Glucollector website, which can be accessed by study participant and their health care professional. The Glucollector website has the facility to display participants' data in a number of ways to facilitate understanding and recognition of patterns, it can also act as a medium for two-way communication between participant and healthcare professional.

**Following completion of the five full days participants attend up to five structured follow-up appointments in the 12 months after the course.**

## **1.2 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 (Aviva Accucheck Expert Meter) 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.**

## **1.3 Site files**

A Working folder containing all the blank Case Report Forms (CRF) required for use in the trial will be supplied by the Clinical Trials Research Unit (CTRU), in addition to the Investigator Site File. The Site File should be maintained in accordance with research governance and the study protocol. The Working folder like the Site File(s) should be stored in a locked, secure area when not in use. It is important to store the consent and contact details forms separate from the completed case report forms; these can be managed according to local policy or a separate file for each study participant could be used. Please do not store any identifiable participant information in the Site File(s).

## 1.4 Site File updates

If any updates are made to CTRU Standard Operating Procedures (SOPs) throughout the duration of the study, these will be sent to sites. You may be asked to read these and sign a declaration once complete. Any updates to study documents will also be disseminated to sites. You will be required to acknowledge receipt of these documents, file them in the site file, and supersede any old versions.

# 2. Recruitment

## 2.1 Identification of participants

### **Key Document: Identification Log**

Participants will usually be identified from current caseloads of adults with type 1-diabetes at 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 attend a baseline research visit where the study can be discussed in detail and consent to participation can be obtained- no study related activity can be conducted before informed consent is obtained. 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. It is important to note that in the control arm, it is not possible to combine research and non-research patients in a course. 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. Where potential participants are not able to join the courses as planned, patients from the reserve list will be invited to participate, where necessary and/or feasible.



**Tasks:**

- After issuing invitation letters please telephone potential participants to discuss the study and find out if they are interested in taking part. It's anticipated that most participants will initially be contacted by post with an aim to follow up via telephone between 1 and 3 weeks after the date of posting of the participant information sheet (PIS). Where potential participants are approached face-to-face, for instance in clinic, they must be given time to consider the information contained in the PIS before informed consent is obtained.
- Record date(s) contacted and if they are interested on the identification log
- Also record details of those not contacted if they are
  1. Not contactable
  2. Not needed i.e. all courses are fully booked
  3. Any other reason
- For interested participants discuss the eligibility criteria and check they are available for the course dates
- Arrange a baseline assessment appointment to take informed consent and collect baseline data. Baseline appointments can be arranged up to 4 weeks prior to their DAFNE course. Please note that this is a baseline research appointment which is separate to the initial DAFNE pre-course assessment. These two visits will sometimes be combined and happen on the same day, but they could have a couple of weeks between them (with the research baseline visit happening first – the participant must give informed consent prior to any research activity).
- If a baseline appointment is not scheduled, please use the identification log (figure 2.) to record the reason why

Figure 2. Identification log - Enter all details on identification log on the Prospect database.



## Identification log

Study ID	Initials	Age	Sex (M/F)	Postcode <small>excluding final two letters e.g. AA99 9</small>	Date invited	Contacted to discussP			InterestedP		Baseline assessment scheduledP		
						Y/N	Date (if Y)	Reason * (if N)	Y/N	Reason † (if N)	Y/N	Date (if Y)	Reason † (if N)
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\* **NO** Not contactable  
**NN** Not needed  
**O** Other

† **I** Illness  
**T** Lack of time  
**NS** Prefers not to say  
**O** Other (specify)

‡ **NI** Not Interested  
**NE** Not eligible (specify why)  
**I** Illness  
**T** Lack of time  
**NS** Prefers not to say  
**O** Other (specify)

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## 2.2 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 ( $\geq 18$  years);
2. Diagnosis of type 1 diabetes for at least 6 months, or post-honeymoon;<sup>1</sup>
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% (Investigators can use their judgement, informed by standard DAFNE guidelines and in agreement with the trial team, to include participants with HbA1c >12%).
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

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<sup>1</sup> 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.

## 2.3 Documentation of initial contact

Potential participant names can be stored in a local document to monitor attempts to contact. Sheets (either paper or electronic) should be filed securely in accordance with Information Governance and GCP. Avoid using any identifiable participant information in written correspondence (e.g. emails with the central CTRU team).

# 3. Baseline visit

## Key Documents: Baseline Assessment, Eligibility, Consent, Contact Details, Case Report Forms Booklet

At the baseline visit, it will usually be the case that the potential participant has received the participant information sheet (PIS) by post from the site team, and has had a chance to discuss any concerns over the phone or in person. However, it is still important to ensure that they have read and fully understood the PIS. This is also a key time to offer them the opportunity to ask any further questions about the trial. There are several things to keep in mind during this initial visit, which are outlined in this section.

### 3.1 Communicating clinical equipoise

**Equipoise:** *A state of uncertainty regarding whether alternative arms of a clinical trial would be therapeutically superior for a patient, including the balance of benefits and harms.*

Put plainly we have two interventions and although the people involved in developing the new intervention (DAFNE<sub>plus</sub>) hope that it is more effective than the existing intervention (DAFNE) as they have committed considerable time and resources into its development, we do not, and cannot, know that this is the case until there has been a rigorous and unbiased comparison in the form of an RCT. It is important for all those involved in the evaluation of the intervention at this stage to keep an open mind and to communicate this uncertainty to potential participants.

It is possible that the potential participant may voice concerns over the effectiveness of DAFNE<sub>plus</sub> over standard DAFNE, particularly if they are in a site that has been randomised to the control arm, perhaps assuming that the new intervention is likely to be more effective than the old. As there is genuine uncertainty about the comparative effectiveness of the two arms, it is of fundamental importance that all research and clinical staff involved in the study are in

clinical equipoise about the relevant treatments, and that this is then accurately relayed to prospective participants.

While members of the clinical team may have personal preferences or opinions, this study is based on the basic principle that there is currently no direct comparative clinical evidence in relation to whether either of these courses should be deemed superior to the other.

On this basis it is essential that all in the clinical team who interact with the patients believe that everyone 'gets a good deal', and that there is no 'inferior' course to be enrolled into. As far as we know, both could be totally equivalent with regards to their effectiveness.

When explaining this to participants, it can be useful to use phrases such as: *"it is not known whether one course is better than the other, that's why we need to do this study to find out"* or *"being in the original DAFNE course doesn't mean you are getting inferior treatment to others, as far as we know they could both be equally effective"*.

It is also interesting to note that clinicians truly uncertain about which is the best treatment in other RCTs have been shown to have the highest recruitment rates.

### **3.2 Informed consent**

If the patient is eligible to participate in the trial (*see Section 2.2*), and is interested in taking part, proceed with obtaining written informed consent. Check that the participant has read through the correct version of the **Participant Information Sheet (PIS)**, allow them to read or re-read it if they wish, allow them time to ask any questions, and answer them fully to the participant's satisfaction.

Written informed consent must 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. Individuals taking informed consent must have completed GCP training

When completing the consent form:

- Ensure the participant **initials (do not tick)** all mandatory statements (All are mandatory except for the optional statements)
- Ensure the participant signs and dates the consent form
- The local clinician taking consent must also sign the consent form

If the participant decides not to consent, put them on the waiting list for a future (non-research) DAFNE course.

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.

### **3.3 Allocating a participant ID**

Every participant in the study will be allocated a unique identifying number. This enables researchers to deal with patient data without the introduction of different biases, such as which arm of the study they are in, or their demographic data.

In this study, the participant ID and will take the form of: ABC/0001

The first 3 letters refers to your site - every site will already have a unique 3 letter DAFNE site code. The second 4-digit number refers to the participant and will be allocated sequentially as per the usual procedure at your site.

After the participant has given their informed consent please allocate their number, and use this on all of the study forms pertaining to that participant.

### **3.4 Baseline data collection**

Once the participant has signed the consent form, you can proceed with completing the case report form with the participant. Ensure that the following are completed:

- Take blood pressure
- Measure weight and height
- Take blood and urine sample as per local procedure, ensure blood sample is tested for the following:
  1. HbA1c – For the primary outcome measure this will be analysed at a central lab in Newcastle. We will send sites full instructions regarding this procedure, and will provide the relevant equipment e.g. sample boxes and pre-paid envelopes. Please see

*Section 3.5* for further information. Please also take a second sample of blood for analysis of HbA1c locally.

2. Lipids and eGFR– this will be measured locally at your site's lab facilities

- Record medical history

### **3.5 Bloods process**

- As we are using a central lab (Newcastle laboratories) to analyse HbA1c, there are a number of procedures to be aware of. The central lab will provide sites with equipment such as the following:
- Pre-paid packaging
- Blood sample bottles & holder

Other key points to consider are:

- Samples don't need to be refrigerated, but need to be posted as soon as possible
- Timescales for the central lab to receive samples (within 7 days)
- Lipid and eGFR samples must be taken (except at 6 months), but these will not be analysed by the central lab and so must be processed locally
- HbA1c should also be analysed locally

### **3.6 Post Baseline visit**

Inform the participant's GP of their participation in the study using the GP letter template (check participant has consented to the relevant statement on the consent form i.e. agree to my GP being informed)

1. Take two photocopies of the consent form
2. The original copy is to be kept at your site with the site file (see below)
3. File one photocopy in the participant's clinical notes
4. Give one photocopy to the participant
5. Also file a copy of the PIS and letter to GP in the clinical notes
6. Enter details of consented participant on attendance log for courses (the attendance log will be used to log those recruited and their subsequent attendance to the course). This will start the clock to generate your contact reminders on Prospect
7. Give the participant a copy of the Participant Questionnaire – it is important that you tell the participant to **bring this completed questionnaire with them** on the first day of their course. Also, please inform them that they will be emailed a link to complete future questionnaires online, but they **will not be as lengthy** as the first one.

Enter the following data onto the Prospect database:

- Eligibility checklist
- Contact details form
- Consent record form
- Baseline CRF
- Baseline participant questionnaire
- Course attendance log

Please aim to enter data from paper forms onto the database within 24 hours, and at the latest within one week.

File the following forms along with the site file (they can be in a separate folder, as long as they are in a locked cupboard/drawer in the same locked room as the site file, as per GCP guidelines):

- Consent form
- Contact details form

Create a separate file for the completed case report forms to file the following forms by participant:

- Eligibility checklist
- Consent record form
- Baseline CRF
- Course attendance log

This means you will have a “pack” of forms for each participant for easy reference.



## 4. DAFNE courses – DAFNEplus or DAFNE 2018 5x1

### 4.1 Fidelity assessment

#### Sites being audio-recorded:

- Every day of ALL courses to be recorded.
- Identify each recording - Site, course and day e.g. NOT/1<sup>st</sup> course/day 1
- Save each recording to provided laptop.
- Upload to Google drive
- Instructions to do this are provided separately

#### ALL Sites:

- Complete day-appropriate checklist for the course you are providing
- Every day of ALL courses to have a checklist completed
- Scan and email completed checklists to [becky.brown@sheffield.ac.uk](mailto:becky.brown@sheffield.ac.uk)

### 4.2 Qualitative interviews - DAFNEplus ONLY

#### For those 2-3 participants identified for qualitative interviews:

##### *Weeks 1-5*

- Compile all 5 weeks' worth of the participants 'Plan for action' and 'Review of Plan' forms
- Scan and email the copied 'Plan for action' and 'Review of Plan' to David Rankin [david.rankin1@nhs.net](mailto:david.rankin1@nhs.net)
- *Week 5* -Scan and email the copied 'Rainy Day Plan and 'DAFNEplus Takeaway' to David

### 4.3 Health Economics

We are asking all sites to complete a resource usage questionnaire at the time of their 3<sup>rd</sup> and 4<sup>th</sup> courses. The central team at CTRU will email you this form prior to the start of your 3<sup>rd</sup> course. Please complete this form and enter the information onto Prospect.

## 5. After the course

### 5.1 Course completion

After the participant has completed the 5 week DAFNE or DAFNE*plus* course, they will be sent a postal questionnaire with a pre-paid envelope, or emailed a link to an online version of the same questionnaire. The delivery of the questionnaires and management of resulting data will be managed by the central team at Sheffield CTRU. This will also be the case at all subsequent time-points where questionnaire completion is required (course completion, 3, 6, 9, and 12 months).

It is important to schedule the first face-to-face follow-up appointment in advance- the Prospect database will prompt you when to do this.

### 5.2 Follow ups

All follow-ups will be timed from course completion (defined as the last planned full day of attendance). Follow up visits will be prompted by the Prospect database. Follow-up visits fall into two categories:

- Those associated with the DAFNE and DAFNE*plus*, which will be conducted according to standard practice (DAFNE) or as per the training provided as part of the DAFNE*plus* intervention training respectively.
- Research appointments which are scheduled at 6 and 12 months and which involve the collection of outcome data such as HbA1C, lipids, blood pressure, height and weight, and episodes of hypoglycaemia and ketoacidosis.

The following sections detail the research appointments only. For information related to standard DAFNE please follow usual procedure at your site, for DAFNE*plus* please refer to the guidance given as part of the intervention training.

### 5.3 6 months

6 months after the participant has completed the course, they will need to attend the clinic again for a face-to-face visit. At this visit, only the following measurements need to be taken:

- Blood sample to be tested for HbA1c by the central lab (see *Section 3.5*) with a second sample taken for local analysis.
- Measure weight and height

At this visit you need to complete the 6-month participant CRF booklet, which compared to the CRF booklet completed at baseline is relatively short.

## 5.4 12 months

At the 12-month visit (12-months post-course), the primary outcome measure (HbA1c) will be recorded. At this visit, the same measures will be taken and the same data collected as the baseline visit. This will be the participant's final face-to-face visit, and for the majority of participants, this marks the end of their completion in the study. It is important to remind participants who have consented to be contacted for future research about this possibility at this time.

## 6. 24 months

At the 24-month point, a separate analysis of glycaemic control, episodes of severe hypoglycaemia and DKA will take place. This will be in the form of a case note review, and this data will be analysed after the main study has closed and been reported.

## 7. Serious Adverse Events (SAEs)

### Adverse Events

Study centres should report any episodes of diabetic ketoacidosis or severe hypoglycaemia (severe cognitive impairment requiring external assistance for recovery) which do not require admission to hospital as adverse events. No other events are categorised as adverse (rather than 'serious' adverse events) in this trial.

To report adverse events, enter details onto the CRF and the Prospect database at routine research appointments at 6 and 12 months; there is no requirement to report DKA or severe

hypoglycaemia that does not meet the criteria of 'serious' (see below) in between these time-points.

### **Serious Adverse Events**

Study centres are required to report Serious Adverse Events (SAEs) in conjunction with the CTRU SOP PM004 (adverse events and serious adverse events) which will be forwarded separately. The definition of an SAE is any event that:

- Results in death
- Is life threatening\* (subject at immediate risk of death)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation\*\*
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- 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.

### **Recording**

- If you become aware of an SAE e.g. admission to hospital of a participant, complete a paper copy of the serious adverse event form
- The Principal Investigator should assess the adverse event for:
  1. Seriousness e.g. any of the above categories
  2. Expectedness e.g. DKA/severe hypos expected in this population
  3. Relationship to intervention (DAFNE or DAFNEplus programme)

- The PI is required to sign the SAE form and the information from the form should also be entered on the database

## Reporting

It is not anticipated that there will be many SAEs related to the DAFNE*plus* or standard DAFNE programmes.

- For any SAEs that are unexpected e.g. admission for infections, or deemed related to the DAFNE*plus* programme, the site will email the form to the CTRU within 24 hours of the event being discovered.
- For exceptions to this rule, see the paragraph below.
- A copy of the SAE form must be kept with the Site File.
- SAEs will be reported by CTRU in the periodic safety reports to the REC and the TSC.

Episodes of severe hypoglycaemia and diabetic ketoacidosis are expected to occur in some adults with T1D. **Therefore, any of these episodes, defined as SAEs e.g. admission to hospital with severe hypoglycaemia, will be exempt from immediate reporting to the sponsor.** In these instances, the Principal Investigator, or delegated staff, will email the SAE form to the Sheffield Clinical Trials Research Unit (as delegated by the Sponsor) within 4 weeks 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.

The central CTRU team will provide sites with blank paper copies of SAE forms.

Email completed Serious Adverse Event forms to [ctr-u-saes-group@sheffield.ac.uk](mailto:ctr-u-saes-group@sheffield.ac.uk)

# 8. Non-compliance

## 8.1 Non-compliance with the protocol

All DAFNE*plus* study procedures should be conducted in compliance with the study protocol which has been reviewed and approved by the REC. You should not undertake any activity which you know, in advance, will breach the protocol. Your site will be required to comply with specified CTRU SOPs, as well as the standards set out in your GCP training. Any non-compliances will be reported to the study Sponsor (Sheffield Teaching Hospitals) as well as

any other relevant committees. There are various common non-compliances, for example if the process of informed consent has not been followed correctly, or if a participant is recruited despite not meeting all of the eligibility criteria.

All study documents used should be the current approved version. Any new documents or procedures should **not** be implemented until the REC has provided a favourable opinion, and approval has been received from the appropriate NHS Research & Development department. Please note that the process for updating documents and procedures will be done centrally by the CTRU. We will then inform your site that there is an update, and will send out instructions of how to implement this.

## 8.2 Protocol non-compliance form

For any suspected protocol or GCP non-compliance, a **protocol non-compliance form** should be completed. This must provide as much detail as possible about the non-compliance, including any immediate action that was taken. The form must be signed by the PI to acknowledge that they have been informed. Once page 1 of the form has been completed, this should be returned to Sheffield CTRU who will inform the Sponsor and/or REC as appropriate. Once assessed, the non-compliance form will be returned to the site for filing in the site file. Further action may be required.

The study manager will liaise with the CI and Sponsor to assess the non-compliance as:

- **Major Non-compliance:** serious non-compliance with the protocol due to error, misconduct or fraud (e.g. not consented)
- **Minor Non-compliance:** less serious non-compliance. Usually occurs to cope with unforeseen circumstances. Often referred to as minor, technical or non-serious deviation (e.g. failure to correctly document consent)
- **Serious breach:** breach, of either the conditions or principles of GCP in connection with that study/trial; or the protocol relating to that trial, which is **likely** to effect to a significant degree
  - the safety or physical or mental integrity of the subjects of the study; or
  - the scientific value of the study.

The inclusion/exclusion criteria and the consent process of the DAFNE*plus* trial are outlined in the study protocol. Below are some pre-specified events that may occur in the study and how they will be categorised:

### **Pre-Specified Major Non-Compliances:**

- Finding out that participants are ineligible following recruitment. All incidents should be reported to the Sponsor and the participant should be withdrawn.
- If the consent procedure or GCP is not followed correctly (e.g. patient not consented). All incidents should be reported to the Sponsor and the participant may need to be re-consented.
- Consent taken by person not appropriately trained in GCP or DAFNEplus study procedures.

### **Pre-Specified Minor Non-Compliances:**

- Minor errors on the consent form (e.g. participant ticks statements on the consent form rather than initialling) – this would only be a minor non-compliance if this occurred persistently.
- A member of site staff carried out a task that they have not been delegated on the delegation log e.g. Taking consent, CRF completion etc.

Participants withdrawn or lost to follow up should be recorded on the appropriate case report form and not logged as a non-compliance. Repeated instances of a particular minor non-compliance will be upgraded to a major non-compliance. Note that this list is not exhaustive, there will be other events that can be classed as non-compliances.

The Minor Non-Compliances listed above, and similar incidences will be reported as aggregate data to the Sponsor periodically; action will normally involve staff training, though a specific response may be required e.g. protocol amendment.

## **9. 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).



## Example of Intervention Withdrawal Form

**DAFNEplus** Study ID   /

---

### Intervention withdrawal

Date of withdrawal request        
d d m m y y y y

Request logged by   
name

Date of last session       OR  Did not attend any sessions  
d d m m y y y y

Type of withdrawal

Patient request

Main reason:  
(please tick one box only)

No longer wanting to participate in research  Illness  
 No longer comfortable with DAFNEplus technology  Lack of time  
 Other (provide details below)

Additional details  
 No reason given

Clinician decision

Reason   
specify

Clinician   
name

Other (provide details below)

Additional details

---

**Future involvement**

Has the participant agreed to continued follow-up?

Yes – full participation  
 Yes – partial participation (please complete the 'Participation preferences' form if participant requests reduced follow-up)  
 No (please complete the 'Study completion / discontinuation' form)

---

**Signature**

name signature d d m m y y y y

**DAFNEplus** Study ID   /

---

### Participation preferences

Date of request to change level of data collection        
d d m m y y y y

Request logged by   
name

Which elements of the study is the participant continuing?<sup>\*</sup>  
 (Tick all that apply)

Face-to-face visits  
 Questionnaire completion  
 Contact for interview

\* Note: where a participant only agrees to the 24 month case note review this should be documented on the 'Study completion / discontinuation' form

## 9.1 Withdrawal procedure

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.

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.

## 10. Prospect database

CTRU Prospect is the system used to store data relating to all trials managed by the Clinical Trials Research Unit. All data collected from screened patients and participants for the DAFNE<sup>plus</sup> trial must be entered on to Prospect. This data should be entered from the CRF to ensure that there is a complete record both on paper and electronically.

## Individual Details

Study ID: NOT/0247

<b>Dataset</b>	Core
<b>Study ID</b>	NOT/0247
<b>Site</b>	Nottingham (010)
<a href="#">Back to Study Overview</a>	

### Screening

Forms				
Identification	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>
Baseline assessment	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>
Eligibility	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>

### Consent

Forms				
Consent	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>
Contact details	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>

### Baseline

Forms				
CRF completion	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>
Demographics	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>
Measurements & Labs	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>
Medical history	<a href="#">Edit</a>	<a href="#">View</a>	<a href="#">History</a>	<a href="#">Delete</a>
Questionnaire booklet completion	<a href="#">New</a>	<a href="#">Unavailable</a>	–	–

### *Example of an individual participant in Prospect*

If the database is updated for any reason, the paper copy should also be updated. Any corrections on paper forms or the database should have a reason given, and this should be initialled and dated on the paper version.

Access to the DAFNEplus Database on Prospect is restricted. Activity is logged so do not share your username and password with anyone else.

Access to the database is via: <https://www.ctru-prospect.shef.ac.uk/>

A user guide for the Prospect database will be provided separately, but If you have any questions or need any assistance with using Prospect please contact the DAFNEplus Study Manager (Elaine Scott: [elaine.scott@sheffield.ac.uk](mailto:elaine.scott@sheffield.ac.uk) / 0114 222 5158), Research Assistant (Ellen Bradley: [e.bradley@sheffield.ac.uk](mailto:e.bradley@sheffield.ac.uk) / 0114 222 0843) or the Data Management Team [dafne-plus-dm-group@sheffield.ac.uk](mailto:dafne-plus-dm-group@sheffield.ac.uk)

## 10.1 Data entry

- Data should be entered into the database as soon as possible and ideally within 1 week to minimise the possibility of data loss and ensure timely central reporting. CRFs can be entered into the database in batches.
- Use the field annotation function (see Prospect user guide) to document or explain data entered into the database. For numerical fields, the data should be entered exactly as recorded on the CRF even when there are obvious errors. Where the data cannot be entered (e.g. a non-numeric character in a numeric field) these queries will be followed up when data discrepancy reports are run from the database.
- The CTRU will provide a list of discrepancies and provide support to help you resolve these in the database. Once a participant's 12-month follow-up visit is complete, data entry and resolution of discrepancies should be completed as soon as possible to ensure timely database lock.

## 11. Site monitoring

Trial monitoring is necessary part of the research process to ensure the standards and guidelines applicable to the trial are met. As part of this process the CTRU are required to review a percentage of the data collected and input by sites. Most of the monitoring we will be undertaking for the DAFNEplus trial will be remote (telephone discussions and review of copied documents and CRFs), however we may also undertake some site visits. As part of the monitoring process the CTRU will:

- Arrange telephone calls with you to review the site study file and discuss any potential protocol non-compliance issues your site may have identified
- Randomly identify a number of Consent and Case Review Forms (CRFs) such as the Baseline Assessment Visit form, 6-month Assessment form for review. You will need to scan and email these documents to Elaine Scott, Trial Manager at a secure NHS email address (this will be sent to you)
- Check that you have all the consumables (e.g. *blood packs, Withcare boxes, course materials, blank CRFs etc*) you require
- Compile a report which will be sent to the site and will be reported to the appropriate trial management committee

## 12. Contact Details

The DAFNE $plus$  Core Team:

Please use the group email address below as the primary method of contact:

[dafneplus@sheffield.ac.uk](mailto:dafneplus@sheffield.ac.uk)

**Study Manager:**

Elaine Scott



[elaine.scott@sheffield.ac.uk](mailto:elaine.scott@sheffield.ac.uk)

0114 222 5158

**Research Assistant:**

Jose Schutter



[j.schutter@sheffield.ac.uk](mailto:j.schutter@sheffield.ac.uk)

0114 2221726

**Trial Support Officer:**

Becky Brown



[becky.brown@sheffield.ac.uk](mailto:becky.brown@sheffield.ac.uk)

0114 222 9186

**Senior Study Manager:**

Liz Cross



[e.a.cross@sheffield.ac.uk](mailto:e.a.cross@sheffield.ac.uk)

0114 222 0762

More Information can also be found at:

[www.sheffield.ac.uk/scharr/sections/dts/ctru/dafneplus](http://www.sheffield.ac.uk/scharr/sections/dts/ctru/dafneplus)

**Thank you all for taking part in the DAFNE $plus$  Trial, we look forward to working with you!**

## Appendix A

### **Uploading Audio Files to Google Drive**

#### *Audio Files*

Some sites will be selected to audio record sessions for later transcription and analysis. An encrypted digital audio recorder and laptop will be provided to sites for this purpose. Instructions for using the audio recorder will be provided along with the device - please note that these devices will be password protected. The use of this device will also be addressed in the Technology Checklist phonecall.

Once the session has finished and the recording is complete, the recorder should be plugged into the laptop provided. The folder containing the most recent files should open automatically, and the decryption software on the laptop (if applicable) will decrypt the files to a readable format.

The files should then be uploaded to Google Drive, using the link provided by CTRU. As with the fidelity checklists, it is important to name the files in an identifiable format:  
(Site\_CourseNumber\_SessionNumber\_Date)

Please also fill out the audio recordings paper log once this has been done.

**A separate document with detailed instructions on this procedure will also be sent to relevant sites.**