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An effectiveness-implementation hybrid type 2 trial evaluating two psychoeducational programmes for severe hypoglycaemia in type 1 diabetes: Implementation study protocol

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Abstract

Introduction: Two of the most acute and feared complications in type 1 diabetes (T1D) are hypoglycaemia and severe hypoglycaemia (SH). While impaired awareness of hypoglycaemia (IAH) can lead to SH with cognitive and motivational barriers implicated, the available education does not integrate behaviour change techniques to address these. A novel Hypoglycemia Awareness Restoration Programme despite optimised care (HARPdoc) is currently being tested against an established Blood Glucose Awareness Training (BGAT) within a parallel, two-arm, group randomised, blinded trial (with its own protocol; NCT02940873) with adults with T1D whose problems with hypoglycaemia and SH have persisted despite otherwise optimised insulin management. While both programmes are aimed at reducing hypoglycaemia, SH and IAH, it is the former that integrates behavior change techniques.

The aim of the current (implementation) study is to evaluate delivery of both HARPdoc and BGAT and explore associations between implementation outcomes and trial endpoints; as well as to develop an evidence-based implementation blueprint to guide implementation, sustainment and scale-up of the effective programmes.

Methods and analysis: Stakeholder engagement has underpinned study design and materials to maximise relevance, feasibility, and impact. Guided by the implementation science tools, frameworks, methods and principles, the current study was thus designed through a series of focus groups (N=11) with the key intervention stakeholders (N=28) - including (i) individuals with lived experience of T1D, IAH and a pilot version of the HARPdoc (n=6), and (ii) diabetes healthcare professionals (n=22). A mixed methods approach will be utilised throughout.

Ethics and dissemination: The protocol has been reviewed and received ethical approval by the Harrow Research Ethics Committee (18/LO/1020; 240752) on October 01, 2018.

Strengths

- Study design driven by the intervention stakeholders including people with lived experience and the health care professionals
- Study design driven by implementation science theories, models and principles
- Mixed method approach

Limitations

- Assessments will not be conducted prior to intervention implementation

Introduction

Type 1 diabetes and hypoglycaemia

Type 1 diabetes (T1D) is a condition of deficiency of endogenous insulin secretion characterised by hyperglycaemia (blood glucose *above* normal), requiring administration of exogenous insulin for regulation of blood glucose levels.[1] However, one of the most acute and feared complications of the insulin therapy in T1D is *hypoglycaemia* (blood glucose *below* normal), and in particular severe hypoglycaemia (SH), whereby blood glucose is so low that an individual may lose consciousness, or become acutely cognitively impaired to the degree that they are unable to take appropriate glucose treatment to raise their blood glucose and so require someone else to give treatment to them.[2-3] Each year, 22-46% of people with T1D experience SH[4-5] with common presentations including confusion, coma, and seizure.[6-8] SH can lead to mortality: 4-10% of adults with T1D under the age of 40 die as a result of SH.[9-11] In England and Wales alone, this equates to 500-1391 deaths annually,[12-13] as well as 14,387 hospital admissions, 660 day cases and 65,601 bed days (between 2012 and 2013).[14]

A significant factor affecting the successful management of hypoglycaemia in adults with T1D is *impaired awareness of hypoglycaemia* (IAH), that is, reduction in intensity or delayed onset of the physiological symptoms (e.g. dizziness, sweating, palpitations) that serve a vital function of prompting an individual to ingest glucose to raise blood glucose to normal limits. Not surprisingly, thus, IAH is a significant risk factor for SH, and linked to a 6-8-fold increase in the frequency of SH events.[3] Evidence shows that 25-40% of adults with T1D have IAH.[15-16]

C*ognitive and motivational* factors have been found to be associated with *IAH* in a subset of individuals who express low concern for hypoglycaemia and SH, yet they are at high risk of such events.[17-18] Certain cognitions or beliefs, such as normalising the presence of IAH or underestimating the consequences of hypoglycaemia, excessive concern about the possible

consequences of hyperglycaemia, and wanting to avoid the sick role have been identified as barriers to avoiding hypoglycaemia and regaining awareness of associated symptoms.[17-19] The presence of such beliefs are thought to explain why one third of people with T1D continue to experience SH and IAH, despite receiving optimal education in insulin self-management.[16]

Several education programmes[20] such as the German Diabetes Teaching and Training Programme (DTTP),[21] and the UK's Beta Cell Education Resources for Training (BERTIE)[22] and Dose Adjustment for Normal Eating (DAFNE),[23] aim to provide a foundation of knowledge and skills in flexible and safe insulin management, and in the UK, these are offered to all adults with T1D. While these programmes do not explicitly focus on IAH or SH, they provide more general training in diabetes self-management and include information for the general treatment and prevention of hypoglycaemia.[20] However, improvement in glycaemic outcomes following completion of such programmes is unclear. For instance, individuals that have completed DAFNE[23] do not always experience improved or sustained glycaemic outcomes, indicating that a more targeted approach may be required for individuals who continue to experience problematic hypoglycaemia despite education on the general principles.[24]

Structured education with specific focus on hypoglycaemia management and avoidance has therefore been developed, such as, for instance, Blood Glucose Awareness Training (BGAT)[25-30] and self-management-oriented education programme (PRIMAS),[31] which seem to have similar benefit on hypoglycaemia risk as the more generic programmes, where these have been specifically compared.[20] Another programme is DAFNE - Hypoglycaemia Awareness Restoration Training (DAFNE-HART),[32] which was specifically designed to address the on-going needs of people with T1D who continued to experience severe hypoglycaemia and IAH after completing DAFNE.[23]

DAFNE-HART was based on the research identifying abnormal activation of cortical brain regions in response to hypoglycaemia in people with IAH and the research identifying low concern, and unhelpful cognitions about hypoglycaemia among people with IAH.[33] It sought to address cognitive and motivational barriers associated with IAH and SH, especially in adults with T1D who continue to experience severe hypoglycaemia despite optimal previous insulin regimens and educational programmes.[33] However, to further enhance diabetes education, it has been argued that future programmes should incorporate behaviour change and other psychologically informed techniques to address cognitive and motivational barriers associated with IAH and SH.[17,19,20,23]

To address this goal, a novel education programme has been further developed from DAFNE-HART, namely, Hypoglycaemia Awareness Restoration Programme despite optimised care (HARPdoc), which is currently being tested against the BGAT programme within a parallel, two-arm, group randomised, blinded clinical trial (with its own detailed protocol; NCT02940873; aka HARPdoc trial).[33] Both HARPdoc and BGAT are group therapies aimed at reducing hypoglycaemia, SH and IAH in adults with T1D who are continuing to experience SH and are being tested in the trial only in people whose problems with hypoglycaemia have persisted despite otherwise optimised management of their insulin treatment regimens and educational programmes. For more detail on the two education programmes tested with the trial and evaluated as part of the implementation, please see the Methods section.

Aim and objectives

The aim of the study is to assess the way in which HARPdoc and BGAT are delivered in the context of the clinical trial sites, facilitating understanding of the potential link between the delivery of the programmes under investigation and the expected improvements in SH rates. This will be achieved in a qualitative, but also quantitative manner which will allow us to

explore the relationship between the implementation of the programmes and the clinical trial's outcomes. Ultimately, this will enable the development of an implementation blueprint to facilitate future implementation after the trial is completed.

The study will address the following research questions for both education programmes from the perspectives of the intervention stakeholders (including adults with T1D with problematic hypoglycaemia, their relatives, as well as diabetes physicians, educators, psychologists, and support staff):

1. To what extent are the programmes **acceptable, appropriate** and **feasible**?
2. To what extent were the programmes **delivered as intended** *(fidelity of delivery)*?
3. To what extent were the programmes **received as intended** *(fidelity of receipt)*?
4. How willing are key stakeholders to **adopt** the programmes, and what are the anticipated facilitators and barriers to adoption?
5. What are the anticipated facilitators **and barriers to sustainment** of the programmes long-term (i.e. after the trial is completed)?
6. What are the **costs** associated with implementing the programmes?
7. What are **unintended consequences** (positive/negative) associated with programmes?
8. What are the **contextual enablers and barriers** associated with the **implementation** of the programmes?
9. What **implementation strategies** were used within individual sites to improve implementation of the programmes?
10. Is there a **relationship between implementation and effectiveness outcomes**?

Methods

Design

The design of our study is an effectiveness-implementation hybrid type 2,[34] placing equal focus on investigating the effectiveness of the two education programmes as part of the HARPdoc trial,[33] while simultaneously investigating the implementation of the programmes as part of the current protocol. We plan to apply a mixed-methods approach incorporating a variety of qualitative and quantitative data collection techniques, including surveys, structured interviews and psychometrically established measurement scales.

The study design was (1) *shaped* by implementation science concepts and frameworks, (2) *refined and informed* by the intervention stakeholders, and (3) *guided* by a tool specifically developed to guide the design of implementation research. In what follows, we describe the design process in more detail.

Firstly, the design was *shaped* by a number of complementary implementation science frameworks that have been selected in light of the aims and objective of the study:

- Medical Research Council (MRC) framework for evaluating complex interventions[35-38] to guide and inform the study design and processes (questions 1 to 10),
- Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework[39] to guide selection of implementation outcomes in conjunction with Proctor et al[41] definitions of these outcomes (questions 1 to 7),
- Consolidated Framework for Implementation Research (CFIR)[41-42] to develop semi-structured interview topic guides (see Methods) and subsequently guide the coding and analysis of barriers and facilitators to programme implementation (question 8), and
- Implementation strategies compendium reported by Powel et al[44] (question 9)

Second, the design was *refined* by the key intervention stakeholders, including (a) individuals with lived experience of T1D, hypoglycaemia unawareness and an earlier version of the HARPdoc, namely, DAFNE-HART (this is the patient and public involvement group for the study or PWD group), and (b) health care professionals (HCPs) involved in the delivery of the interventions under investigation. The stakeholders critically reviewed for relevance, feasibility and clarity a selection of (a) factors commonly assessed and reported in implementation science research,[39-43] and (b) qualitative and quantitative assessment tools and methods (e.g. surveys and interview topic guides described in more detail in the *data collection plan* below), and their measurement time points. Figure 1 shows stakeholder groups involved in the research design process.

Figure 1: Stakeholder groups involved in the design of the study

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Specifically, the outcome measures and materials were presented and reviewed, within an iterative process of continuous development and refinement, to the key stakeholders (*N*=28), including the people with lived experience of T1D, IAH and education courses (*n*=6), as well as the HCPs (*n*=22) across participating diabetes centres (UK=4; US=1) in a series of focus groups (*N*=11) between October and December 2017. Two 1.5h long sessions were conducted with same group of representatives of people with T1D, and nine 1h long sessions with different HCPs. Following each meeting, stakeholders' feedback was incorporated, and the final versions of the study materials further co-designed and refined. The final selection of the stakeholder-driven outcome measures, materials and methods (e.g. surveys and interview topic guides) proposed in this protocol was thus a result of an iterative development process where feedback from stakeholders fed directly into the development and refinement of the study design (see Table 1 presented in the *data collection plan* below).

Lastly, the Implementation Science Research Development (ImpRes) tool and guide[44] was used to *guide* the study design and the stakeholder-driven planning process. ImpRes is a newly developed instrument that helps researchers to design high-quality implementation research, based on best evidence and expert recommendations. ImpRes is theory-agnostic in that it does not advocate or require use of a specific implementation framework; rather, ImpRes guides research teams through the various elements that a well-designed implementations study should consider, based on current literature and expert inputs. These include: choice of appropriate frameworks, articulation of patient, service and implementation outcomes and how they are to be assessed, articulation of the stakeholders of a study, a proforma for the definition of implementation costs and other elements. Using ImpRes, we were able to:

- *establish* a set of most relevant and feasible implementation outcome measures (drawing on Implementation Outcomes taxonomy,[40] implementation strategies,[43] and RE-AIM framework,[39]
- *identify the* most relevant and feasible validated surveys for the study,
- *formulate* instructions to participants for the selected validated pragmatic surveys,
- *develop* a set of interview topic guides drawing on implementation science frameworks, including the Implementation Outcomes taxonomy,[40] implementation strategies taxonomy,[43] RE-AIM framework,[39] and CFIR,[41-42]
- *identify* appropriate and most relevant participant groups for the study, and
- *develop* stakeholder-centred participant information sheets and consent forms.

Using the ImpRes tool and guide[45] ensured that the study design was (1) informed by implementation science frameworks, concepts and measures, and (2) informed by key stakeholders. This process was conducted within the context of a highly intricate study design of a parallel, two-arm, group randomised, blinded clinical trial where pragmatic considerations for the current study had to be made (e.g., timelines for evaluating implementation outcomes).

Setting

This is an international, multisite study based in the UK and US. In the UK, participants will be recruited from 4 diabetes centres, across 4 National Health Service (NHS) Trusts in England – two in the greater London area, one in Dorset and one in South Yorkshire, while in the US from a single diabetes centre in Massachusetts.

Participants

Stakeholders of the HARPdoc trial[33] and the two educational programmes under investigation (described in detail below) form the participant group of the current study. They include course participants who are people with T1D with problematic hypoglycaemia, relatives of people enrolled in the trial (HARPdoc arm only since it encompasses relative session in Week 6), as well as the diabetes health care professionals (HCPs). People with T1D include participants who were found eligible for the trial and have either (a) fully, or (b) partially attended either one of the two programmes, or (c) have declined and not attended either one of the programmes. The HCPs comprise diabetes educators, physicians, psychologists, and support staff.

Patient and public involvement

Patient and public involvement group i.e. people with diabetes (PWD) group for the study (as described under the *Design* and in Figure 1) was involved in the development of the study presented in this protocol from the very conception through to the selection of outcomes, design of measures including topic guides, and formulating documents for ethical approval (incl. information sheets and consent forms), as well as this protocol itself. A detailed description of how the PWD group for the study has shaped the design of this study is outlined under the Design section, and in Figure 1. The group will also be actively involved in the analysis, write up and subsequent dissemination of the study findings, going forward.

Trialled educational programmes

The clinical trial testing the effectiveness of the programmes is currently ongoing and blinded (NCT02940873)[33] and therefore, in what follows, we provide only a high-level overview of the programmes (see also Table 1) with detailed information on the curricula purposefully omitted to prevent contamination.

The trial is testing two group programmes – HARPdoc[32-33] and BGAT.[25-30] The former incorporates structured education relevant to hypoglycaemia management, avoidance and strategies to restore hypoglycaemia awareness with behaviour change and psychologically informed techniques aimed to address the cognitive barriers to hypoglycaemia avoidance associated with IAH. It also involves family members in the final session. The curriculum is delivered over 6 weeks in a combination of group and individual sessions facilitated by two experienced diabetes educators, trained to deliver the intervention and supported in its delivery by the study clinical psychologist. The programme was piloted in the DAFNE-HARP study and amended in the light of the experience of that study.[32] A significant and substantial reduction of SH from 10 to 0.5 episodes per year was document in the pilot study, as well as a significant reduction in worry and improved behavioural avoidance of hyperglycaemia.[32]

The latter is a UK's National Institute for Health and Care Excellence (NICE)[25] recommended programme focused on recognising and reducing both, hypo and hyperglycaemia and empowering people with T1D to anticipate, detect, treat and prevent extremes in blood glucose levels.[25-30] The curriculum is delivered by one experienced diabetes educator, trained in its delivery by one of the clinical psychologists who originally designed it. For the purposes of the trial, the BGAT timetable has been modified to be delivered in the same time frame as the HARPdoc, with the original eight 2 hour sessions delivered over 6 weeks, and as two sessions in one day in weeks 1,2,3 and 6. While BGAT has proved successful in improving glycaemic control, hypoglycaemia awareness,[27] fear of hypoglycaemia,[29] as well as in reducing SH

episodes[27-28] from 1.78 to 0.13 as assessed at one-year post-intervention,[28] it has not yet been tested specifically in people whose SH persists despite exposure to structured education.[27,29]

Table 1: The structure and delivery of courses

Data collection plan

All data collected will be conducted with the view of developing an implementation blueprint after the trial is completed. As previously described, all implementation outcomes, measures and methods presented in this protocol have been reviewed for relevance and feasibility and co-designed with key stakeholders. In what follows, we describe our data collection plan in relation to the questions we are seeking to address, while in Table 2 below, we provide the final set of stakeholder-driven implementation outcomes, study design and methods.

Table 2: Stakeholder-driven data collection plan

Question 1: To what extent are the programmes **acceptable, appropriate** and **feasible** to key intervention stakeholders?

Previously validated pragmatic surveys[45] will be used to assess the acceptability, appropriateness and feasibility of HARPdoc and BGAT. The surveys will be completed by key stakeholders, i.e. people with T1D, relatives of people enrolled on HARPdoc and diabetes HCPs who will assess the degree to which they perceive the programmes acceptable, feasible and appropriate for diabetes and hypoglycaemia management. In addition, one-to-one semi-structured interviews with stakeholders will also be conducted. The interviews will complement the survey data and explore in more detail stakeholders' perceptions and experiences of HARPdoc and BGAT in terms of acceptability, appropriateness and feasibility. Both surveys and interviews will occur at one-time point, after the programme completion.

Question 2: To what extent were programmes **delivered as intended** by diabetes educators *(fidelity of delivery)*?

Relevant sections of audiotapes from both the BGAT and HARPdoc group sessions across each of the sites will be assessed; this will form the fidelity of delivery part of the study that will be led by the clinical study team. An observational assessment tool has been adapted and refined by the clinical study team from the AMIGOS.[43] Two trained and experienced independent raters will use the tool to assess the delivery of the programmes by the diabetes educators from the audio recordings of individual sessions across each site.

Question 3: To what extent were programmes **received as intended** by adults with T1D *(fidelity of receipt)*?

Literature acknowledges patients as active participants in health interventions with the fidelity of receipt focused on the way the intervention is received by the individuals as highly important although seldom addressed in health research.[46] We will therefore explore the fidelity of receipt, i.e. fidelity with which the content of HARPdoc and BGAT is received by the adults with T1D, as part of the one-to-one semi-structured interview (which will also explore acceptability, appropriateness and feasibility of the programmes as described above). The participants who have had a useful exposure to the programmes and have either fully or partly (at least the first 3 days attended) completed one of the programmes will be recruited. We will explore their views and experience of the programme in relation to the extent they feel able to:

- *engage* with the programme content and their group,
- *understand* the content delivered to them by the diabetes educators, and
- *acquire and apply* the programme skills to their everyday management of hypoglycaemia.

This will help advance our knowledge of the programmes in terms of how easy or difficult it is for individuals to engage with the content, as well as to understand and apply the skills acquired as part of HARPdoc and BGAT to manage hypoglycaemia.

Question 4: How willing are key stakeholders to **adopt** the programmes?

As part of the interviews with the key stakeholders (described above in detail), we will explore the intention to adopt HARPdoc and BGAT from two very specific standpoints. Firstly, from the perspective of the provider or diabetes HCPs (which is commonly explored in health research),[40] where the interview will explore the extent to which the provider intends to adopt the programme (e.g. deliver the programme again or refer people onto such programme) after the trial is completed.

Secondly, we will explore the intention to adopt from the perspective of adults with T1D who are at the receiving end and active participants in the intervention (far less commonly explored in research).[40] We plan to explore the extent to which adults with T1D intend to (a) use the intervention skills in their everyday diabetes management, and (b) use such a programme again or recommend it to other individuals with T1D and problematic hypoglycaemia.

In addition, we plan to interview participants who, although eligible, chose not to take part in HARPdoc and BGAT. This will allow us to explore reasons that may potentially prevent adults with T1D and problematic hypoglycaemia in participating in such programmes in future. This is important in terms of exploring the reach[30] of both interventions (i.e. the absolute number, proportion, and representativeness of individuals who are willing to participate in a given initiative).[30]

Question 5: What are the potential **facilitators and barriers to sustainment** of the programmes long-term after the trial is complete and an effective programme identified?

As part of the one-to-one interview with the key stakeholders (described above in detail), we will explore potential facilitators and barriers to sustained use of HARPdoc and BGAT after the trial is completed from the perspectives of providers (i.e. diabetes HCPs) as well as the

course participants who are adults with T1D and the relatives of people in the HARPdoc arm of the trial who attended the last week of the programme.

With the providers, the focus will be on understanding the potential facilitators and barriers to the implementation of HARPdoc and BGAT into the local services after the trial is completed. In contrast, with the adults with T1D who have either fully or partially completed one of the programmes as well as the relatives, the focus will be on exploring the potential and experienced facilitators and barriers to sustained use of knowledge and skills gained in long-term hypoglycaemia management.

Question 6: What are the **costs** associated with implementing the programmes to the key stakeholders?

One-to-one interviews with the key stakeholders will also explore costs, in terms of time and money, associated with implementing HARPdoc and BGAT. With the HCPs, the focus will be on costs incurred as a result of the delivery, preparation and training in relation to the programme, while with adults with T1D and the relatives, the focus will be on the costs incurred attending and completing the programme.

Question 7: Are there any **unintended consequences** associated with either one of the programmes?

One-to-one interviews with the key stakeholders will also explore any unintended consequences, both positive and negative, associated with HARPdoc and BGAT. Unintended consequences will be explored from the perspectives of the HCPs, adults with T1D and their relatives, in relation to how the programme has impacted on them and the people around them.

Question 8: What are the **contextual enablers and barriers** associated with the **implementation** of the programmes?

The contextual enablers and barriers to intervention implementation that stakeholders have experienced will be explored and assessed in two ways: interviews with the key stakeholders and meeting minutes between HCPs involved in the trial.

One-to-one interviews with the key stakeholders (described above) will explore context of HARPdoc and BGAT in more detail from the perspectives of the HCPs, adults with T1D and the relatives. They will focus on exploring the factors that facilitated delivery or present a particular challenge to delivery.

Minutes from meetings taking place with the HCPs as part of the trial management processes will be assessed for contextual factors affecting delivery of interventions using qualitative content analysis. This will help us identify any potential barriers or facilitators to post-trial adoption, implementation and sustained use of the successful programme.

Question 9: What **implementation strategies** were used within individual sites to improve the implementation of the programmes?

As part of the one-to-one interviews with the diabetes HCPs (described above), we will explore and identify implementation strategies (i.e. methods or techniques used to enhance and promote adoption, implementation and sustainability of an intervention)[43] used within individual sites during the trial in order to improve delivery and implementation of the programmes. In addition, we will also explore any potential strategies that may be important to consider by the local sites wishing to implement HARPdoc and BGAT in future after the trial is completed.

Question 10: What is the **relationship between the implementation and effectiveness outcomes** of the trial?

Clinical outcome data contain information on the primary outcome i.e., the number of SH events over the preceding year, as well as at 12 and 24 months' post-course (as recorded in the anonymised SH recall form), and the secondary outcomes (e.g. hypoglycaemia awareness

score) in people with T1D taking part in the programmes. These data will be examined in relation to the pragmatic implementation outcome (acceptability, feasibility and appropriateness) survey data. This assessment will enable us to explore the relationship between the implementation and the effectiveness of the two arms of the trial.

Data Analysis

Data will be analysed using quantitative and qualitative approaches.

Quantitative analysis

Descriptive statistics of survey and clinical trial data will be provided. Parametric and nonparametric tests will be employed to compare the survey responses between the two arms of the trial. Random intercept linear, logistic and Poisson regression models (depending on the distribution of the outcome*)* will be used to explore the relationship between implementation data and clinical trial outcome data. Mediation analysis with the use of Structural Equation Models will also be employed to understand the potential pathways in which implementation has an impact on the effectiveness of the two suggested education programmes. An implementation by treatment interaction will be included to allow the effect of implantation to differ at each arm of the trial. All our models will be controlled for a variety of demographic and socioeconomic variables. All analyses will be conducted in STATA 14.1.

Qualitative analysis

Interviews with course participants and HCPs as well as trial's meeting minutes will be analysed qualitatively, using inductive and deductive content analysis approach until saturation is reached.[50] We will use the CFIR[40-41] to guide the coding and analysis (i.e. framework analysis) of interview data to identify barriers and facilitators to the implementation and sustainment of HARPdoc and BGAT. This approach has been used previously i.e. CFIR has been applied post-implementation to investigate facilitators and barriers to implementation

among stakeholders who had already adopted and implemented an innovation, thus identifying determinants of implementation post hoc.[40-41] Whilst we are aware that this approach is not entirely consistent with Damschroder's guidance stipulating that CFIR should be applied pre-implementation to investigate facilitators/barriers to implementation,[40-41] given the constraints of conducting the effectiveness-implementation hybrid type 2 where equal focus is placed on both, implementation and effectiveness, it is not possible to follow this guidance. However, we strongly believe that our approach is of value in identifying *actual*, rather than *anticipated*, facilitators and barriers to the implementation and sustainment of HARPdoc and BGAT.

In line with Damschroder et al's guidance,[41-42] we plan to link determinants of implementation to implementation outcomes as part of the quantitative analyses described above where we propose to link the pragmatic implementation outcome survey data with the trial outcome data with the logistic and Poisson regression models.

Discussion

This is a stakeholder-driven, mixed-methods, multi-site, international project aimed at assessing the way in which two education programmes, HARPdoc and BGAT, implemented within an effectiveness-implementation hybrid type 2 trial are delivered in participating diabetes centres based in the UK and US. Such evaluation will facilitate understanding of the association between programme implementation and the trial's end points. In the process, we will address a specific set of implementation objectives:

- *understand* the extent to which the programmes are perceived to be acceptable, appropriate and feasible to key stakeholders,
- *understand* the extent to which the programmes *are delivered and received as intended,*
- *identify* contextual enablers and facilitators to the implementation of the programmes,

- *identify* potential barriers and facilitators to sustainment and intention to adopt the programmes long-term after the trial is completed,
- *identify* any unintended consequences and *understand* implementation costs associated with the programmes,
- *identify* strategies used to implement the programmes within the trial, and
- *Identify* potential links between implementation and clinical effectiveness of the programmes.

Such evaluation will also enable us to develop an evidence-based implementation blueprint to help guide the implementation, sustainment and scale up of HARPdoc and/or BGAT after the trial is completed.

The study in this protocol depicts a complex research landscape. It is concerned with evaluating implementation of two educational programmes (i.e., HARPdoc and BGAT) introduced and currently being tested within a parallel, two-arm, group randomised, blinded clinical trial, from the perspectives of multiple key intervention stakeholders (including, the adults with T1D, their relatives, as well as diabetes physicians, educators, psychologists and support staff). Within such a complex landscape, continuous stakeholder engagement is essential to the design of a meaningful implementation project. It is also critical in adequately addressing potential challenges and operational issues early on, thus helping maximise feasibility and relevance, in particular, in relation to the methodological approach and measures, as well as the subsequent data collection.

One such challenge was encountered in relation to the potential pre-intervention assessments. The complexity of assessing programme delivery within a parallel, two-arm, group randomised, blinded trial design means that the opportunity to assess course participants just before the start of the programme when they are fully aware of the arm that they are assigned to is small and dependant on the receipt of the ethical approval (for the implementation). This

is further compounded by the methodological issues around surveying or interviewing programme participants about their views of the programmes while they are being randomly assigned to one or the other; something that could potentially contaminate the trial. Hence, the pre-intervention assessments in the current study were not feasible and the primary focus has been placed on post-intervention measurements.

Nonetheless, the current study offers a stakeholder-driven approach to evaluating the implementation of interventions. It uses mixed methods to assess implementation outcomes and the delivery of the programmes. The findings will inform the development of an implementation blueprint and the identification of specific implementation strategies for the post-trial scale-up of the programme/s into routine services. The findings will also form the basis for a further trial (likely a hybrid type 3 effectiveness-implementation trial)[34] focused on evaluating implementation success of a number of different implementation strategies in scaling up and sustaining the clinically effective intervention following the current trial. Such developments will in turn contribute to the scientific understanding of methods for evaluating and implementing complex interventions within a complex organisational structure of a health care system, thus addressing the gaps on many important methodological and practical issues.

Ethics approval and consent to participate

The study described in this protocol has been reviewed and given favourable opinion by the Harrow Research Ethics Committee (18/LO/1020; 240752) on October 01, 2018. Informed consent will be sought from all participants. The study will be conducted in accordance with the Good Clinical Practice and recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

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Competing interests

NS is the Director of London Safety & Training Solution ltd, which provides advisory and training services on safety and quality improvement to hospitals and training programs internationally. TS serves as a consultant to F. Hoffmann-La Roche Ltd Diagnostics providing advisory research services in relation to innovations for multidisciplinary tumor boards. The remaining authors declare that they have no competing interests.

Authors' contributions

As per International Committee of Medical Journal Editors guidelines, to qualify as an author one should have:	
• made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;	TS, LH, IB, AH, NS, SA, ES, PWD Group
• been involved in drafting the manuscript or revising it critically for important intellectual content;	TS, LH, IB, AH, NS, SA, ES, PWD Group
• given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and	TS, LH, IB, AH, NS, SA, ES, PWD Group
• agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.	TS, LH, IB, AH, NS, SA, ES, PWD Group

List of abbreviations

BERTIE = Beta Cell Education Resources for Training

BGAT = Blood Glucose Awareness Training

CFIR = Consolidated Framework for Implementation Research

DAFNE = Dose Adjustment for Normal Eating

DAFNE HART = Dose Adjustment for Normal Eating Hypoglycaemia Awareness Restoration Training

HARPdoc = Hypoglycaemia Awareness Restoration Programme despite optimised care

HCP – Health Care Professional

IAH = Impaired Awareness of Hypoglycaemia

MRC = Medical Research Council

NICE = National Institute for Health and Care Excellence

PWD = People With Diabetes

RE-AIM = Reach Effectiveness Adoption Implementation Maintenance

SH = Severe Hypoglycaemia

T1D = Type 1 Diabetes

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Figure Captions

Figure 1. Stakeholder groups that informed the design of the study

Table 1. Differences and similarities between HARPdoc and BGAT structure and delivery within the trial

Structure & delivery	HARPdoc	BGAT
Programme duration	6 weeks	6 weeks
Programme structure	4 weekly full-day group sessions, weeks 1, 2, 3 and 6 1 weekly one-to-one telephone session in weeks 4 and 5	8 x 2hr group sessions delivered as 2 sessions delivered in one day in weeks 1, 2, 3 and 6 1 optional one-to-one telephone session in either week 4 or 5
Group size	5-10	5-10
Diabetes centres	4	4
Number of courses per diabetes centre	2 - 4	2 – 4
Sample size (overall 96 course participants)	Total of 48 course participants 4-8 participants per course	Total of 48 course participants 4-8 participants per course
Educator training	3-day workshop (1 day to standardise training in hypoglycaemia prevention, and 2 days to train in behaviour change and psychologically informed strategies) 1-day refresher course after first courses; Scheduled supervision by clinical psychologist	3-day workshop (1 day to standardise training in hypoglycaemia prevention, and 2 days to review and update the curriculum with the clinical psychologist 1-day refresher course after first courses; supervision optional (on request)
Educators per course	2 educators per course	1 educator per course
Programme structure	4 weekly group sessions in weeks 1, 2, 3 and 6 2 one-to-one telephone sessions in weeks 4 and 5	4 weekly group sessions in weeks 1, 2, 3 and 6 1 optional one-to-one telephone session in week 4 or 5
Follow-ups	2h group sessions delivered at 3, 6, and 12 months after the course	None
Programme adherence	First 3 group sessions, and 1 one-to-one session	First 3 group sessions

Note. BGAT = Blood Glucose Awareness Training (comparator). HARPdoc = Hypoglycaemia Awareness Restoration Programme despite optimised care.

Table 2. Data collection plan for the implementation study: assessment objectives, data, instruments, timeline and participants

#	Study outcomes	Definition of the study outcome	Data type	Data collection method	Measurement time-point	Stakeholder groups*
IMPLEMENTATION OUTCOMES:						
1.	Acceptability[41]	Extent to which programme is perceived to be agreeable and acceptable for hypoglycaemia and diabetes management.	Quantitative	AIM† survey [47]	Post-intervention	HCPs, people with T1D and their relatives
			Qualitative	Interview	Post-intervention	
2.	Appropriateness[41]	Extent to which programme is perceived to be fit and relevant for hypoglycaemia and diabetes management.	Quantitative	IAM‡ survey[47]	Post-intervention	HCPs, people with T1D and their relatives
			Qualitative	Interview	Post-intervention	
3.	Feasibility[41]	Extent to which programme can be successfully used or carried out to reduce incidents of severe hypoglycaemia.	Quantitative	FIM§ survey[47]	Post-intervention	HCPs, people with T1D and their relatives
			Qualitative	Interview	Post-intervention	
4.	Fidelity of delivery[41]	Extent to which programme is delivered as intended.	Quantitative	Checklist[49]	Post-intervention	Diabetes educators and psychologists
5.	Fidelity of receipt[41]	Extent to which programme is received as intended.	Qualitative	Interview	Post-intervention	People with T1D
6.	Adoption[31]	Intention to adopt and use the knowledge and skills learned in the programme in everyday hypoglycaemia and diabetes management.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
7.	Sustainability[41,45-46]	Facilitators and barriers to sustained use of the programme.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
8.	Implementation costs[41,45-46]	Costs associated with prospective implementation of the programme.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
OTHER OUTCOMES:						
9.	Unintended consequences of programmes[43,45-46]	Positive or negative consequences that are not anticipated at the time of programme implementation.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
10.	Contextual factors[43,45-46]	Facilitators and barriers to the implementation of the programme.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
11.	Implementation strategies[44]	Strategies used to deliver and implement the programme; they refer to methods or techniques to enhance and promote adoption, implementation and sustainability of the programme.	Qualitative	Interview	Post-intervention	HCPs

Note. *HCPs = Health Care Professionals incl. diabetes educator, physician, psychologist, and administrative support. †AIM = Acceptability of Intervention Measure; ‡IAM = Intervention Appropriateness Measure; §FIM = Feasibility of Intervention Measure.[47]

Stakeholder groups that informed the design of the study

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An effectiveness-implementation hybrid type 2 trial evaluating two psychoeducational programmes for severe hypoglycaemia in type 1 diabetes: Implementation study protocol

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An effectiveness-implementation hybrid type 2 trial evaluating two psychoeducational programmes for severe hypoglycaemia in type 1 diabetes: Implementation study protocol

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Abstract

Introduction: Two of the most acute and feared complications in type 1 diabetes (T1D) are hypoglycaemia and severe hypoglycaemia (SH). While impaired awareness of hypoglycaemia (IAH) can lead to SH with cognitive and motivational barriers implicated, the available education does not integrate behaviour change techniques to address these. A novel Hypoglycemia Awareness Restoration Programme despite optimised care (HARPdoc) is currently being tested against an established Blood Glucose Awareness Training (BGAT) within a parallel, two-arm, group randomised, blinded trial (with its own protocol; NCT02940873) with adults with T1D whose problems with hypoglycaemia and SH have persisted despite otherwise optimised insulin management. While both programmes are aimed at reducing hypoglycaemia, SH and IAH, it is the former that integrates behavior change techniques.

The aim of the current (implementation) study is to evaluate delivery of both HARPdoc and BGAT and explore associations between implementation outcomes and trial endpoints; as well as to develop an evidence-based implementation blueprint to guide implementation, sustainment and scale-up of the effective programmes.

Methods and analysis: Guided by the implementation science tools, frameworks, methods and principles, the current study were designed through a series of focus groups (N=11) with the key intervention stakeholders (N=28) - including (i) individuals with lived experience of T1D, IAH and a pilot version of the HARPdoc (n=6), and (ii) diabetes healthcare professionals (n=22). A mixed methods approach will be utilised throughout. Stakeholder engagement has underpinned study design and materials to maximise relevance, feasibility, and impact.

Ethics and dissemination: The protocol has been reviewed and received ethical approval by the Harrow Research Ethics Committee (18/LO/1020; 240752) on October 01, 2018. The findings will be submitted to a peer-reviewed journal and presented at scientific meetings.

Strengths

- Study design driven by the intervention stakeholders including people with lived experience and the health care professionals
- Study design driven by implementation science theories, models and principles
- Mixed method approach

Limitations

- Assessments will not be conducted prior to intervention implementation

Introduction

Type 1 diabetes and hypoglycaemia

Type 1 diabetes (T1D) is a condition of deficiency of endogenous insulin secretion characterised by hyperglycaemia (blood glucose *above* normal), requiring administration of exogenous insulin for regulation of blood glucose levels.[1] However, one of the most acute and feared complications of the insulin therapy in T1D is *hypoglycaemia* (blood glucose *below* normal), and in particular severe hypoglycaemia (SH), whereby blood glucose is so low that an individual may lose consciousness, or become acutely cognitively impaired to the degree that they are unable to take appropriate glucose treatment to raise their blood glucose and so require someone else to give treatment to them.[2-3] Each year, 22-46% of people with T1D experience SH[4-5] with common presentations including confusion, coma, and seizure.[6-8] SH can lead to mortality: 4-10% of adults with T1D under the age of 40 die as a result of SH.[9-11] In England and Wales alone, this equates to 500-1391 deaths annually,[12-13] as well as 14,387 hospital admissions, 660 day cases and 65,601 bed days (between 2012 and 2013).[14]

A significant factor affecting the successful management of hypoglycaemia in adults with T1D is *impaired awareness of hypoglycaemia* (IAH), that is, reduction in intensity or delayed onset of the physiological symptoms (e.g. dizziness, sweating, palpitations) that serve a vital function of prompting an individual to ingest glucose to raise blood glucose to normal limits. Not surprisingly, thus, IAH is a significant risk factor for SH, and linked to a 6-8-fold increase in the frequency of SH events.[3] Evidence shows that 25-40% of adults with T1D have IAH.[15-16]

C*ognitive and motivational* factors have been found to be associated with *IAH* in a subset of individuals who express low concern for hypoglycaemia and SH, yet they are at high risk of such events.[17-18] Certain cognitions or beliefs, such as normalising the presence of IAH or underestimating the consequences of hypoglycaemia, excessive concern about the possible

consequences of hyperglycaemia, and wanting to avoid the sick role have been identified as barriers to avoiding hypoglycaemia and regaining awareness of associated symptoms.[17-19] The presence of such beliefs are thought to explain why one third of people with T1D continue to experience SH and IAH, despite receiving optimal education in insulin self-management.[16]

Several education programmes[20] such as the German Diabetes Teaching and Training Programme (DTTP),[21] and the UK's Beta Cell Education Resources for Training (BERTIE)[22] and Dose Adjustment for Normal Eating (DAFNE),[23] aim to provide a foundation of knowledge and skills in flexible and safe insulin management, and in the UK, these are offered to all adults with T1D. While these programmes do not explicitly focus on IAH or SH, they provide more general training in diabetes self-management and include information for the general treatment and prevention of hypoglycaemia.[20] However, improvement in glycaemic outcomes following completion of such programmes is unclear. For instance, individuals that have completed DAFNE[23] do not always experience improved or sustained glycaemic outcomes, indicating that a more targeted approach may be required for individuals who continue to experience problematic hypoglycaemia despite education on the general principles.[24]

Structured education with specific focus on hypoglycaemia management and avoidance has therefore been developed, such as, for instance, Blood Glucose Awareness Training (BGAT)[25-30] and self-management-oriented education programme (PRIMAS),[31] which seem to have similar benefit on hypoglycaemia risk as the more generic programmes, where these have been specifically compared.[20] Another programme is DAFNE - Hypoglycaemia Awareness Restoration Training (DAFNE-HART),[32] which was specifically designed to address the on-going needs of people with T1D who continued to experience severe hypoglycaemia and IAH after completing DAFNE.[23]

DAFNE-HART was based on the research identifying abnormal activation of cortical brain regions in response to hypoglycaemia in people with IAH and the research identifying low concern, and unhelpful cognitions about hypoglycaemia among people with IAH.[33] It sought to address cognitive and motivational barriers associated with IAH and SH, especially in adults with T1D who continue to experience severe hypoglycaemia despite optimal previous insulin regimens and educational programmes.[33] However, to further enhance diabetes education, it has been argued that future programmes should incorporate behaviour change and other psychologically informed techniques to address cognitive and motivational barriers associated with IAH and SH.[17,19,20,23]

To address this goal, a novel education programme has been further developed from DAFNE-HART, namely, Hypoglycaemia Awareness Restoration Programme despite optimised care (HARPdoc), which is currently being tested against the BGAT programme within a parallel, two-arm, group randomised, blinded clinical trial (with its own detailed protocol; NCT02940873; aka HARPdoc trial).[33-34] Both HARPdoc and BGAT are group therapies aimed at reducing hypoglycaemia, SH and IAH in adults with T1D who are continuing to experience SH and are being tested in the trial only in people whose problems with hypoglycaemia have persisted despite otherwise optimised management of their insulin treatment regimens and educational programmes. For more detail on the two education programmes tested with the trial and evaluated as part of the implementation, please see the Methods section.

Aim and objectives

The aim of the study is to assess the way in which HARPdoc and BGAT are delivered in the context of the clinical trial sites, facilitating understanding of the potential link between the delivery of the programmes under investigation and the expected improvements in SH rates. This will be achieved in a qualitative, but also quantitative manner which will allow us to

explore the relationship between the implementation of the programmes and the clinical trial's outcomes. Ultimately, this will enable the development of an implementation blueprint to facilitate future implementation after the trial is completed.

The study will address the following research questions for both education programmes from the perspectives of the intervention stakeholders (including adults with T1D with problematic hypoglycaemia, their relatives, as well as diabetes physicians, educators, psychologists, and support staff):

1. To what extent are the programmes **acceptable, appropriate** and **feasible**?
2. To what extent were the programmes **delivered as intended** *(fidelity of delivery)*?
3. To what extent were the programmes **received as intended** *(fidelity of receipt)*?
4. How willing are key stakeholders to **adopt** the programmes, and what are the anticipated facilitators and barriers to adoption?
5. What are the anticipated facilitators **and barriers to sustainment** of the programmes long-term (i.e. after the trial is completed)?
6. What are the **costs** associated with implementing the programmes?
7. What are **unintended consequences** (positive/negative) associated with programmes?
8. What are the **contextual enablers and barriers** associated with the **implementation** of the programmes?
9. What **implementation strategies** were used within individual sites to improve implementation of the programmes?
10. Is there a **relationship between implementation and effectiveness outcomes**?

Methods

Design

The design of our study is an effectiveness-implementation hybrid type 2,[35] placing equal focus on investigating the effectiveness of the two education programmes as part of the HARPdoc trial,[33-34] while simultaneously investigating the implementation of the programmes as part of the current protocol. We plan to apply a mixed-methods approach incorporating a variety of qualitative and quantitative data collection techniques, including surveys, structured interviews and psychometrically established measurement scales.

The study design was (1) *shaped* by implementation science concepts and frameworks, (2) *refined and informed* by the intervention stakeholders, and (3) *guided* by a tool specifically developed to guide the design of implementation research. In what follows, we describe the design process in more detail.

Firstly, the design was *shaped* by a number of complementary implementation science frameworks that have been selected in light of the aims and objective of the study:

- Medical Research Council (MRC) framework for evaluating complex interventions[36-39] to guide and inform the study design and processes (questions 1 to 10),
- Reach Effectiveness Adoption Implementation Maintenance (RE-AIM) framework[40] to guide selection of implementation outcomes in conjunction with Proctor et al[41] definitions of these outcomes (questions 1 to 7),
- Consolidated Framework for Implementation Research (CFIR)[42-43] to develop semi-structured interview topic guides (see Methods) and subsequently guide the coding and analysis of barriers and facilitators to programme implementation (question 8), and
- Implementation strategies compendium reported by Powel et al[44] (question 9)

Second, the design was *refined* by the key intervention stakeholders, including (a) individuals with lived experience of T1D, hypoglycaemia unawareness and an earlier version of the HARPdoc, namely, DAFNE-HART (this is the patient and public involvement group for the study or PWD group), and (b) health care professionals (HCPs) involved in the delivery of the interventions under investigation. The stakeholders critically reviewed for relevance, feasibility and clarity a selection of (a) factors commonly assessed and reported in implementation science research,[40-44] and (b) qualitative and quantitative assessment tools and methods (e.g. surveys and interview topic guides described in more detail in the *data collection plan* below), and their measurement time points. Figure 1 shows stakeholder groups involved in the research design process.

Figure 1: Stakeholder groups involved in the design of the study

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Specifically, the outcome measures and materials were presented and reviewed, within an iterative process of continuous development and refinement, by the key stakeholders (*N*=28), including the people with lived experience of T1D, IAH and education courses (*n*=6), as well as the HCPs (*n*=22) across participating diabetes centres (UK=4; US=1) in a series of focus groups (*N*=11) between October and December 2017. Two 1.5h long sessions were conducted with same group of representatives of people with T1D, and nine 1h long sessions with different HCPs. Following each meeting, stakeholders' feedback was incorporated, and the final versions of the study materials further co-designed and refined. The final selection of the stakeholder-driven outcome measures, materials and methods (e.g. surveys and interview topic guides) proposed in this protocol was thus a result of an iterative development process where feedback from stakeholders fed directly into the development and refinement of the study design (see Table 1 presented in the *data collection plan* below).

Lastly, the Implementation Science Research Development (ImpRes) tool and guide[45-46] was used to *guide* the study design and the stakeholder-driven planning process. ImpRes is a newly developed instrument that helps researchers to design high-quality implementation research, based on best evidence and expert recommendations. ImpRes is theory-agnostic in that it does not advocate or require use of a specific implementation framework; rather, ImpRes guides research teams through the various elements that a well-designed implementations study should consider, based on current literature and expert inputs. These include: choice of appropriate frameworks, articulation of patient, service and implementation outcomes and how they are to be assessed, articulation of the stakeholders of a study, a proforma for the definition of implementation costs and other elements. Using ImpRes, we were able to:

- *establish* a set of most relevant and feasible implementation outcome measures (drawing on Implementation Outcomes taxonomy,[41] implementation strategies,[44] and RE-AIM framework,[40]
- *identify the* most relevant and feasible validated surveys for the study,
- *formulate* instructions to participants for the selected validated pragmatic surveys,
- *develop* a set of interview topic guides drawing on implementation science frameworks, including the Implementation Outcomes taxonomy,[41] implementation strategies taxonomy,[44] RE-AIM framework,[40] and CFIR,[42-43]
- *identify* appropriate and most relevant participant groups for the study, and
- *develop* stakeholder-centred participant information sheets and consent forms.

Using the ImpRes tool and guide[45-46] ensured that the study design was (1) informed by implementation science frameworks, concepts and measures, and (2) informed by key stakeholders (Figure 1). This process was conducted within the context of a highly intricate study design of a parallel, two-arm, group randomised, blinded clinical trial where pragmatic

considerations for the current study had to be made (e.g., timelines for evaluating implementation outcomes).

Setting

This is an international, multisite study based in the UK and US. In the UK, participants will be recruited from 4 diabetes centres, across 4 National Health Service (NHS) Trusts in England – two in the greater London area, one in Dorset and one in South Yorkshire, while in the US from a single diabetes centre in Massachusetts between July 2018 and December 2019. The participating sites are specialist care diabetes centres that (i) provide structured education for type 1 diabetes and therefore have on-site diabetes educators, (ii) contain the necessary clinical capability and expertise in the hypoglycaemia management, and (iii) routinely receive tertiary referrals for problematic hypoglycaemia and therefore act as a channel for recruiting this very niche group of adults with type 1 diabetes and problematic hypoglycaemia.

Participants

Stakeholders of the HARPdoc trial[33-34] and the two educational programmes under investigation (described in detail below) form the participant group of the current study. They include course participants who are people with T1D with problematic hypoglycaemia, relatives of people enrolled in the trial (HARPdoc arm only since it encompasses relative session in Week 6), as well as the diabetes health care professionals (HCPs). People with T1D include participants who were found eligible for the trial and have either (a) fully, or (b) partially attended either one of the two programmes, or (c) have declined and not attended either one of the programmes. The HCPs comprise diabetes educators, physicians, psychologists, and support staff. For the quantitative part of data collection, a census approach will be used, and the entire available population will be approached i.e. all patients (N=96) participating in the trialled interventions and all HCPs (N=28) involved in the delivery of these

interventions. For the qualitative part, availability sampling will be used within the subgroups of the recruited population according to the site and course i.e. those HCPs and patients within the participating hospitals recruited into or delivering one of the two programmes who are available and willing to partake in the interview. The latter will culminate in sample of approx. 32 patients in total (4 sites x 2 patients x 2 types of courses x 2 sets of courses per site), and 28 HCPs. A convenience sampling will be used to recruit people who declined to take part in the programme.

Patient and public involvement

Patient and public involvement group i.e. people with diabetes (PWD) group for the study (as described under the *Design* and in Figure 1) was involved in the development of the study presented in this protocol from the very conception through to the selection of outcomes, design of measures including topic guides, and formulating documents for ethical approval (incl. information sheets and consent forms), as well as this protocol itself. A detailed description of how the PWD group for the study has shaped the design of this study is outlined under the Design section, and in Figure 1. The group will also be actively involved in the analysis, write up and subsequent dissemination of the study findings, going forward.

Trialled educational programmes

The clinical trial testing the effectiveness of the programmes is currently ongoing and blinded (NCT02940873)[33-34] and therefore, in what follows, we provide only a high-level overview of the programmes (see also Table 1) with detailed information on the curricula purposefully omitted to prevent contamination.

The trial is testing two group programmes – HARPdoc[34] and BGAT.[25-30] The former incorporates structured education relevant to hypoglycaemia management, avoidance and strategies to restore hypoglycaemia awareness with behaviour change and psychologically

informed techniques aimed to address the cognitive barriers to hypoglycaemia avoidance associated with IAH. It also involves family members in the final session. The curriculum is delivered over 6 weeks in a combination of group and individual sessions facilitated by two experienced diabetes educators, trained to deliver the intervention and supported in its delivery by the study clinical psychologist. The programme was piloted in the DAFNE-HARP study, and amended in the light of the experience of that study.[32] A significant and substantial reduction of SH from 10 to 0.5 episodes per year was document in the pilot study, as well as a significant reduction in worry and improved behavioural avoidance of hyperglycaemia.[32]

The latter is a UK's National Institute for Health and Care Excellence (NICE)[25] recommended programme focused on recognising and reducing both, hypo and hyperglycaemia and empowering people with T1D to anticipate, detect, treat and prevent extremes in blood glucose levels.[25-30] The curriculum is delivered by one experienced diabetes educator, trained in its delivery by one of the clinical psychologists who originally designed it. For the purposes of the trial, the BGAT timetable has been modified to be delivered in the same time frame as the HARPdoc, with the original eight 2 hour sessions delivered over 6 weeks, and as two sessions in one day in weeks 1,2,3 and 6. While BGAT has proved successful in improving glycaemic control, hypoglycaemia awareness,[27] fear of hypoglycaemia,[29] as well as in reducing SH episodes[27-28] from 1.78 to 0.13 as assessed at one-year post-intervention,[28] it has not yet been tested specifically in people whose SH persists despite exposure to structured education.[27,29]

Table 1: The structure and delivery of courses

Data collection plan

All data collected will be conducted with the view of developing an implementation blueprint after the trial is completed. As previously described, all implementation outcomes, measures

and methods presented in this protocol have been reviewed for relevance and feasibility and co-designed with key stakeholders. In what follows, we describe our data collection plan in relation to the questions we are seeking to address, while in Table 2 below, we provide the final set of stakeholder-driven implementation outcomes, study design and methods.

Table 2: Stakeholder-driven data collection plan

Question 1: To what extent are the programmes **acceptable, appropriate** and **feasible** to key intervention stakeholders?

Previously validated pragmatic surveys[47] will be used to assess the acceptability, appropriateness and feasibility of HARPdoc and BGAT. The surveys will be completed by key stakeholders, i.e. people with T1D, relatives of people enrolled on HARPdoc and diabetes HCPs who will assess the degree to which they perceive the programmes acceptable, feasible and appropriate for diabetes and hypoglycaemia management. In addition, one-to-one semi-structured interviews with stakeholders will also be conducted. The interviews will complement the survey data and explore in more detail stakeholders' perceptions and experiences of HARPdoc and BGAT in terms of acceptability, appropriateness and feasibility. Both surveys and interviews will occur at one-time point, after the programme completion.

Question 2: To what extent were programmes **delivered as intended** by diabetes educators *(fidelity of delivery)*?

Relevant sections of audiotapes from both the BGAT and HARPdoc group sessions across each of the sites will be assessed; this will form the fidelity of delivery part of the study that will be led by the clinical study team. An observational assessment tool has been adapted and refined by the clinical study team from the AMIGOS.[48] Two trained and experienced independent raters

will use the tool to assess the delivery of the programmes by the diabetes educators from the audio recordings of individual sessions across each site.

Question 3: To what extent were programmes **received as intended** by adults with T1D *(fidelity of receipt)*?

Literature acknowledges patients as active participants in health interventions with the fidelity of receipt focused on the way the intervention is received by the individuals as highly important although seldom addressed in health research.[49] We will therefore explore the fidelity of receipt, i.e. fidelity with which the content of HARPdoc and BGAT is received by the adults with T1D, as part of the one-to-one semi-structured interview (which will also explore acceptability, appropriateness and feasibility of the programmes as described above). The participants who have had a useful exposure to the programmes and have either fully or partly (at least the first 3 days attended) completed one of the programmes will be recruited. We will explore their views and experience of the programme in relation to the extent they feel able to:

- *engage* with the programme content and their group,
- *understand* the content delivered to them by the diabetes educators, and
- *acquire and apply* the programme skills to their everyday management of hypoglycaemia.

This will help advance our knowledge of the programmes in terms of how easy or difficult it is for individuals to engage with the content, as well as to understand and apply the skills acquired as part of HARPdoc and BGAT to manage hypoglycaemia.

Question 4: How willing are key stakeholders to **adopt** the programmes?

As part of the interviews with the key stakeholders (described above in detail), we will explore the intention to adopt HARPdoc and BGAT from two very specific standpoints. Firstly, from the perspective of the provider or diabetes HCPs (which is commonly explored in health research),[41] where the interview will explore the extent to which the provider intends to adopt

the programme (e.g. deliver the programme again or refer people onto such programme) after the trial is completed.

Secondly, we will explore the intention to adopt from the perspective of adults with T1D who are at the receiving end and active participants in the intervention (far less commonly explored in research).[41] We plan to explore the extent to which adults with T1D intend to (a) use the intervention skills in their everyday diabetes management, and (b) use such a programme again or recommend it to other individuals with T1D and problematic hypoglycaemia.

In addition, we plan to interview participants who, although eligible, chose not to take part in HARPdoc and BGAT. This will allow us to explore reasons that may potentially prevent adults with T1D and problematic hypoglycaemia in participating in such programmes in future. This is important in terms of exploring the reach[30] of both interventions (i.e. the absolute number, proportion, and representativeness of individuals who are willing to participate in a given initiative).[30]

Question 5: What are the potential **facilitators and barriers to sustainment** of the programmes long-term after the trial is complete and an effective programme identified?

As part of the one-to-one interview with the key stakeholders (described above in detail), we will explore potential facilitators and barriers to sustained use of HARPdoc and BGAT after the trial is completed from the perspectives of providers (i.e. diabetes HCPs) as well as the course participants who are adults with T1D and the relatives of people in the HARPdoc arm of the trial who attended the last week of the programme.

With the providers, the focus will be on understanding the potential facilitators and barriers to the implementation of HARPdoc and BGAT into the local services after the trial is completed. In contrast, with the adults with T1D who have either fully or partially completed one of the programmes as well as the relatives, the focus will be on exploring the potential and experienced

facilitators and barriers to sustained use of knowledge and skills gained in long-term hypoglycaemia management.

Question 6: What are the **costs** associated with implementing the programmes to the key stakeholders?

One-to-one interviews with the key stakeholders will also explore costs, in terms of time and money, associated with implementing HARPdoc and BGAT. With the HCPs, the focus will be on costs incurred as a result of the delivery, preparation and training in relation to the programme, while with adults with T1D and the relatives, the focus will be on the costs incurred attending and completing the programme.

Question 7: Are there any **unintended consequences** associated with either one of the programmes?

One-to-one interviews with the key stakeholders will also explore any unintended consequences, both positive and negative, associated with HARPdoc and BGAT. Unintended consequences will be explored from the perspectives of the HCPs, adults with T1D and their relatives, in relation to how the programme has impacted on them and the people around them.

Question 8: What are the **contextual enablers and barriers** associated with the **implementation** of the programmes?

The contextual enablers and barriers to intervention implementation that stakeholders have experienced will be explored and assessed in two ways: interviews with the key stakeholders and meeting minutes between HCPs involved in the trial.

One-to-one interviews with the key stakeholders (described above) will explore context of HARPdoc and BGAT in more detail from the perspectives of the HCPs, adults with T1D and the relatives. They will focus on exploring the factors that facilitated delivery or present a particular challenge to delivery.

Minutes from meetings taking place with the HCPs as part of the trial management processes will be assessed for contextual factors affecting delivery of interventions using qualitative content analysis. This will help us identify any potential barriers or facilitators to post-trial adoption, implementation and sustained use of the successful programme.

Question 9: What **implementation strategies** were used within individual sites to improve the implementation of the programmes?

As part of the one-to-one interviews with the diabetes HCPs (described above), we will explore and identify implementation strategies (i.e. methods or techniques used to enhance and promote adoption, implementation and sustainability of an intervention)[44] used within individual sites during the trial in order to improve delivery and implementation of the programmes. In addition, we will also explore any potential strategies that may be important to consider by the local sites wishing to implement HARPdoc and BGAT in future after the trial is completed.

Question 10: What is the **relationship between the implementation and effectiveness outcomes** of the trial?

Clinical outcome data contain information on the primary outcome i.e., the number of SH events over the preceding year, as well as at 12 and 24 months' post-course (as recorded in the anonymised SH recall form), and the secondary outcomes (e.g. hypoglycaemia awareness score) in people with T1D taking part in the programmes. These data will be examined in relation to the pragmatic implementation outcome (acceptability, feasibility and appropriateness) survey data. This assessment will enable us to explore the relationship between the implementation and the effectiveness of the two arms of the trial.

Data Analysis

Data will be analysed using quantitative and qualitative approaches.

Quantitative analysis

Descriptive statistics of survey and clinical trial data will be provided. Parametric and nonparametric tests will be employed to compare the survey responses between the two arms of the trial while controlling for a variety of demographic and socioeconomic variables, including the diabetes centres. Random intercept linear, logistic and Poisson regression models (depending on the distribution of the outcome*)* will be used to explore the relationship between implementation data and clinical trial outcome data. Mediation analysis with the use of Structural Equation Models will also be employed to understand the potential pathways in which implementation has an impact on the effectiveness of the two suggested education programmes. An implementation by treatment interaction will be included to allow the effect of implantation to differ at each arm of the trial and across different diabetes centres. All analyses will be conducted in STATA 14.1.

Qualitative analysis

Interviews with course participants and HCPs as well as trial's meeting minutes will be analysed qualitatively, using inductive and deductive content analysis approach until saturation is reached.[50] Analysis will be conducted according to the intervention (BGAT and HARPdoc), and the diabetes centre, especially UK versus US due to differences in the healthcare systems. We will use the CFIR[41-42] to guide the coding and analysis (i.e. framework analysis) of interview data to identify barriers and facilitators to the implementation and sustainment of HARPdoc and BGAT. This approach has been used previously i.e. CFIR has been applied post-implementation to investigate facilitators and barriers to implementation among stakeholders who had already adopted and implemented an innovation, thus identifying determinants of implementation post hoc.[41-42] Whilst we are aware that this approach is not entirely consistent with Damschroder's guidance stipulating that CFIR should be applied pre-implementation to investigate facilitators/barriers to implementation,[41-42] given the constraints of conducting the

effectiveness-implementation hybrid type 2 where equal focus is placed on both, implementation and effectiveness, it is not possible to follow this guidance. However, we strongly believe that our approach is of value in identifying *actual*, rather than *anticipated*, facilitators and barriers to the implementation and sustainment of HARPdoc and BGAT.

In line with Damschroder et al's guidance,[42-43] we plan to link determinants of implementation to implementation outcomes as part of the quantitative analyses described above where we propose to link the pragmatic implementation outcome survey data with the trial outcome data with the logistic and Poisson regression models.

Discussion

This is a stakeholder-driven, mixed-methods, multi-site, international project aimed at assessing the way in which two education programmes, HARPdoc and BGAT, implemented within an effectiveness-implementation hybrid type 2 trial are delivered in participating diabetes centres based in the UK and US. Such evaluation will facilitate understanding of the association between programme implementation and the trial's end points. In the process, we will address a specific set of implementation objectives:

- *understand* the extent to which the programmes are perceived to be acceptable, appropriate and feasible to key stakeholders,
- *understand* the extent to which the programmes *are delivered and received as intended,*
- *identify* contextual enablers and facilitators to the implementation of the programmes,
- *identify* potential barriers and facilitators to sustainment and intention to adopt the programmes long-term after the trial is completed,
- *identify* any unintended consequences and *understand* implementation costs associated with the programmes,
- *identify* strategies used to implement the programmes within the trial, and

- *Identify* potential links between implementation and clinical effectiveness of the programmes.

Such evaluation will also enable us to develop an evidence-based implementation blueprint to help guide the implementation, sustainment and scale up of HARPdoc and/or BGAT after the trial is completed.

The study in this protocol depicts a complex research landscape. It is concerned with evaluating implementation of two educational programmes (i.e., HARPdoc and BGAT) introduced and currently being tested within a parallel, two-arm, group randomised, blinded clinical trial, from the perspectives of multiple key intervention stakeholders (including, the adults with T1D, their relatives, as well as diabetes physicians, educators, psychologists and support staff). Within such a complex landscape, continuous stakeholder engagement is essential to the design of a meaningful implementation project. It is also critical in adequately addressing potential challenges and operational issues early on, thus helping maximise feasibility and relevance, in particular, in relation to the methodological approach and measures, as well as the subsequent data collection.

One such challenge was encountered in relation to the potential pre-intervention assessments. The complexity of assessing programme delivery within a parallel, two-arm, group randomised, blinded trial design means that the opportunity to assess course participants just before the start of the programme when they are fully aware of the arm that they are assigned to is small and dependant on the receipt of the ethical approval (for the implementation). This is further compounded by the methodological issues around surveying or interviewing programme participants about their views of the programmes while they are being randomly assigned to one or the other; something that could potentially contaminate the trial. Hence, the

pre-intervention assessments in the current study were not feasible and the primary focus has been placed on post-intervention measurements.

Nonetheless, the current study offers a stakeholder-driven mixed methods approach to evaluating the implementation of two novel psychoeducational programmes in adults with T1D and problematic hypoglycaemia within the UK and US healthcare systems. While the difference in the two healthcare systems is fundamental, i.e. public versus private provision of care, it provides an important insight into the breadth of potential barriers and facilitators to the implementation of such complex programmes, including any delivery adaptations potentially needed to achieve population coverage and scale up; ultimately, enabling more people with T1D and problematic hypoglycaemia to benefit from the trialled programmes worldwide. Due to the complexity of the trialled interventions and the niche patient group that they are designed for, the inclusion of the specialist UK and US sites was pragmatically critical since they are leading tertiary referral centres with world renowned expertise in hypoglycaemia management, recognition and treatment.

The findings will thus inform the development of an implementation blueprint and the identification of specific implementation strategies for the post-trial scale-up of the programme/s into routine services. The findings will also form the basis for a further international trial (likely a hybrid type 3 effectiveness-implementation trial)[35] focused on evaluating implementation success of a number of different implementation strategies in scaling up and sustaining the clinically effective intervention in different healthcare systems, following the current trial. Such developments will in turn contribute to the scientific understanding of methods for evaluating and implementing complex interventions within a complex organisational structure of a health care system, and within two different modes of

care provision, i.e. private/US versus public/UK, thus addressing the gaps on many important methodological and practical issues.

Ethics and dissemination

The study described in this protocol has been reviewed and given favourable opinion by the Harrow Research Ethics Committee (18/LO/1020; 240752) on October 01, 2018. Informed consent will be sought from all research participants for this study. The study will be conducted in accordance with the Good Clinical Practice and recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. The study will produce key information to the stakeholders on planning, funding and implementation of the interventions under investigation. Hence, the findings will be disseminated through peer-reviewed journals, relevant national and international meetings, as well as educational events within the individual hospitals to ensure that they are brought to the appropriate stakeholders. We will report to people with diabetes and their carers through publications of the Juvenile Diabetes Research Foundation, study website, and by the presentation to patient groups.

Data sharing statement

After the completion of the study, the anonymised dataset that supports published results will be deposited in a secure data repository (e.g. Zenodo) so that it is accessible for future reuse.

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The funding agreements ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Competing interests

NS is the Director of London Safety & Training Solution ltd, which provides advisory and training services on safety and quality improvement to hospitals and training programs internationally. TS serves as a consultant to F. Hoffmann-La Roche Ltd Diagnostics providing advisory research services in relation to innovations for multidisciplinary tumor boards. The remaining authors declare that they have no competing interests.

Authors' contributions

As per International Committee of Medical Journal Editors guidelines, the co-authors have contributed as following:

- made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; TS, LH, IB, AH, NS, SA, ES, Mike Kendall for PWD Group
- been involved in drafting the manuscript or revising it critically for important intellectual content; TS, LH, IB, AH, NS, SA, ES, Mike Kendall for PWD Group
- given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; TS, LH, IB, AH, NS, SA, ES, Mike Kendall for PWD Group
- agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; TS, LH, IB, AH, NS, SA, ES, Mike Kendall for PWD Group

List of abbreviations

BERTIE = Beta Cell Education Resources for Training

BGAT = Blood Glucose Awareness Training

CFIR = Consolidated Framework for Implementation Research

DAFNE = Dose Adjustment for Normal Eating

DAFNE HART = Dose Adjustment for Normal Eating Hypoglycaemia Awareness Restoration Training

HARPdoc = Hypoglycaemia Awareness Restoration Programme despite optimised care

HCP – Health Care Professional

IAH = Impaired Awareness of Hypoglycaemia

MRC = Medical Research Council

NICE = National Institute for Health and Care Excellence

PWD = People With Diabetes

RE-AIM = Reach Effectiveness Adoption Implementation Maintenance

SH = Severe Hypoglycaemia

T1D = Type 1 Diabetes

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Figure Captions

Figure 1. Stakeholder groups that informed the design of the study

Table 1. Differences and similarities between HARPdoc and BGAT structure and delivery within the trial

Structure & delivery	HARPdoc	BGAT
Programme duration	6 weeks	6 weeks
Programme structure	4 weekly full-day group sessions, weeks 1, 2, 3 and 6 1 weekly one-to-one telephone session in weeks 4 and 5	8 x 2hr group sessions delivered as 2 sessions delivered in one day in weeks 1, 2, 3 and 6 1 optional one-to-one telephone session in either week 4 or 5
Group size	5-10	5-10
Diabetes centres	4	4
Number of courses per diabetes centre	2 - 4	2 – 4
Sample size (overall 96 course participants)	Total of 48 course participants 4-8 participants per course	Total of 48 course participants 4-8 participants per course
Educator training	3-day workshop (1 day to standardise training in hypoglycaemia prevention, and 2 days to train in behaviour change and psychologically informed strategies) 1-day refresher course after first courses; Scheduled supervision by clinical psychologist	3-day workshop (1 day to standardise training in hypoglycaemia prevention, and 2 days to review and update the curriculum with the clinical psychologist 1-day refresher course after first courses; supervision optional (on request)
Educators per course	2 educators per course	1 educator per course
Programme structure	4 weekly group sessions in weeks 1, 2, 3 and 6 2 one-to-one telephone sessions in weeks 4 and 5	4 weekly group sessions in weeks 1, 2, 3 and 6 1 optional one-to-one telephone session in week 4 or 5
Follow-ups	2h group sessions delivered at 3, 6, and 12 months after the course	None
Programme adherence	First 3 group sessions, and 1 one-to-one session	First 3 group sessions

Note. BGAT = Blood Glucose Awareness Training (comparator). HARPdoc = Hypoglycaemia Awareness Restoration Programme despite optimised care.

Table 2. Data collection plan for the implementation study: assessment objectives, data, instruments, timeline and participants

#	Study outcomes	Definition of the study outcome	Data type	Data collection method	Measurement time-point	Stakeholder groups*
IMPLEMENTATION OUTCOMES:						
1.	Acceptability[41]	Extent to which programme is perceived to be agreeable and acceptable for hypoglycaemia and diabetes management.	Quantitative	AIM† survey [47]	Post-intervention	HCPs, people with T1D and their relatives
			Qualitative	Interview	Post-intervention	
2.	Appropriateness[41]	Extent to which programme is perceived to be fit and relevant for hypoglycaemia and diabetes management.	Quantitative	IAM‡ survey[47]	Post-intervention	HCPs, people with T1D and their relatives
			Qualitative	Interview	Post-intervention	
3.	Feasibility[41]	Extent to which programme can be successfully used or carried out to reduce incidents of severe hypoglycaemia.	Quantitative	FIM§ survey[47]	Post-intervention	HCPs, people with T1D and their relatives
			Qualitative	Interview	Post-intervention	
4.	Fidelity of delivery[41]	Extent to which programme is delivered as intended.	Quantitative	Checklist[48]	Post-intervention	Diabetes educators and psychologists
5.	Fidelity of receipt[41]	Extent to which programme is received as intended.	Qualitative	Interview	Post-intervention	People with T1D
6.	Adoption[31]	Intention to adopt and use the knowledge and skills learned in the programme in everyday hypoglycaemia and diabetes management.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
7.	Sustainability[41,45-46]	Facilitators and barriers to sustained use of the programme.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
8.	Implementation costs[41,45-46]	Costs associated with prospective implementation of the programme.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
OTHER OUTCOMES:						
9.	Unintended consequences of programmes[43,45-46]	Positive or negative consequences that are not anticipated at the time of programme implementation.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
10.	Contextual factors[43,45-46]	Facilitators and barriers to the implementation of the programme.	Qualitative	Interview	Post-intervention	HCPs, people with T1D and their relatives
11.	Implementation strategies[44]	Strategies used to deliver and implement the programme; they refer to methods or techniques to enhance and promote adoption, implementation and sustainability of the programme.	Qualitative	Interview	Post-intervention	HCPs

Note. *HCPs = Health Care Professionals incl. diabetes educator, physician, psychologist, and administrative support. †AIM = Acceptability of Intervention Measure; ‡IAM = Intervention Appropriateness Measure; §FIM = Feasibility of Intervention Measure.[47]

Stakeholder groups that informed the design of the study

338x190mm (96 x 96 DPI)