Statistical Analysis Plan

STUDY FULL TITLE	A pre-post intervention study to investigate the effectiveness of diabetes specific online therapist delivered cognitive behavioural therapy for patients with Type 2 diabetes and with a comorbid axis I mental health disorder
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1 Abbreviations and Definitions

ADDQoL	Audit of Diabetes Dependent Quality of Life
ADSM	Anxiety Disorder Specific Measure
BABCP	British Association for Behavioural and Cognitive Psychotherapies
CBT	Cognitive Behavioural Therapy
DDS	Diabetes Distress Scale
DNA	Did not attend
GAD-7	Generalized Anxiety Disorder questionnaire
HAI	Health Anxiety Inventory
IAPT	Improving Access to Psychological Therapy
IES-R	Impact of Events Scale Revised
MI	Agoraphobia Mobility Inventory
OCI	Obsessive-Compulsive Inventory
PAM	Patient Activation Measure
PDSS	Panic Disorder Severity Scale
PHQ-9	Patient Health Questionnaire
PTSD	Post-traumatic Stress Disorder
SAQ	Self-assessment questionnaire
SPIN	Social Phobia Inventory

2 Introduction

2.1 Preface

People with diabetes are more likely to experience issues with their mental health. Prevalence of depression has been reported at around 25% in people with diabetes, with rates of around 40% for anxiety. As well as the impact that living with depression and diabetes has on quality of life, there is also an associated decrease in lifespan. Reports show that despite the acknowledgment of these risks, people with diabetes are unable to access the support services that they require.

Cognitive Behavioural Therapy (CBT) has been shown to be effective for people with type 2 diabetes experiencing depression. However, as noted, resources are stretched and not everyone has access to the appropriate support. Digital support may be able to bridge this provision gap by reaching a greater number of individuals. Online and telephonic coaching interventions to support people with diabetes have been trialled.

These studies also observed changes in the Patient Activation Measure (PAM), a validated measure of confidence, skills and motivation relating to any condition. PAM has been demonstrated to predict certain health outcomes such as cholesterol and blood pressure in patients with diabetes. Despite the relatively large number of studies looking at PAM in diabetes (up to 80), there are very few focused on PAM, mental health and diabetes.

2.2 Purpose of the analyses

There is a proposed link between PAM and mental health disorders however this is not well established within a specific diabetes cohort. These analyses will further our understanding of the

link between PAM and mental health, potentially leading to the development of new therapy pathways.

3 Study Objectives and Outcomes Measures

3.1 Study Objectives

The primary aim of this study is to evaluate a new online therapy service tailored for people with diabetes. The secondary aim of this study is to explore the relationship between patient motivation and engagement (as measured by the PAM score), anxiety and depression, and diabetes distress.

3.2 Outcomes

Primary:

The following will be measured at baseline, before each therapy session and at a 6-month follow-up call: PHQ-9 (depression) and GAD-7 (anxiety). If appropriate, ADSM (anxiety-disorder specific measure e.g. for post-traumatic stress disorder, health anxiety etc) will be measured at baseline and before the 3rd and 6th therapy sessions.

Secondary:

The following will be measured at baseline, before each therapy session and at a 6-month follow-up call: PAM (patient activation measure), DDS (Diabetes Distress Scale). The ADDQoL (Audit of Diabetes Dependent Quality of Life) will be measured at baseline and before the 3rd and 6th therapy sessions.

4 Study Methods

4.1 General Study Design and Plan

This study will use a pre-post treatment comparison design to determine the efficacy of a newly developed, diabetes-specific, online CBT programme. Participants will be recruited in England and as the therapy will be delivered online, this will be at a location convenient to the participant. There will be no formal control group, but a comparison data set will be evaluated in order to provide a reference for clinical outcomes in depression and anxiety in people with a long-term physical condition (including, but not exclusively diabetes). Such data will be obtained from NHS mental health services providing psychological therapy in primary care. Although it will not be possible to use a comparison dataset comprising patients with Type 2 diabetes only, such a comparison will, however, enable us to say whether the therapy modality being studied is broadly equivalent to the standard care received by people with a long term physical condition.

People with Type 2 diabetes, who have been diagnosed for at least a year, will be informed about this study either by a health care professional (GP, specialist nurse, psychological therapist), via a recruitment leaflet placed in their GP's surgery, on the Roche Diabetes Care internet site, or on the Roche or Ieso blog or Facebook pages. This evaluation will aim to include 500 participants within the

therapy pathway. This will ensure that people with a range of mental health conditions and symptom severity are represented.

On recruitment, participants will have time to read detailed study information before consenting to take part. Participants will be asked to complete a commitment contract detailing the study procedure and therapy duration. It will also explain the next steps if someone is not suitable for the therapy pathway.

All patients who meet the initial criteria will be directed to the therapy triage process to determine caseness of depression, anxiety or both. This will be done via completion of a self-assessment questionnaire and questionnaires to identify depression and anxiety (PHQ-9 and GAD-7). If patients do not meet caseness thresholds on the PHQ-9 or GAD-7, but there is reason to believe that there is a mental health problem, patients will be asked to complete an anxiety disorder specific measure (ADSM) e.g. for PTSD, health anxiety etc to see if caseness threshold is reached on one of these measures. This will be the baseline measurements and this information will form the basis of triage for treatment suitability. The triage process will be carried out by a junior clinician at Ieso Digital Health, supervised by one of the clinical supervisors. All responses will be recorded securely on a specific study database.

Participants who are eligible for the full online therapy will be allocated to a BABCP-accredited CBT therapist who has undertaken additional training in diabetes-specific CBT. Participants will be asked to complete the Patient Activation Measure (PAM), the full Diabetes Distress Scale (DDS) and the Audit of Diabetes Dependent Quality of Life (ADDQoL) immediately before the first treatment session to obtain baseline measurements.

People who do not exhibit “caseness” at the triage stage will be called to discuss their results with a trained therapist. It is widely recognised that people with a long-term condition, including diabetes, can commonly experience symptoms such as low mood, worry and general distress. These commonly occurring symptoms can sometimes be misinterpreted as signs of a more severe mental health disorder. It is anticipated that some people with diabetes will misinterpret these symptoms and apply to the study; they will be provided with appropriate psycho-education and reassured that they do not have an anxiety disorder or diagnosable depression and will be signposted to more appropriate support services where necessary. These individuals will not go on to receive further treatment or follow-up in this study.

If the participant has provided consent to inform their GP, a letter will be sent to alert them of their study interest and involvement if applicable.

If the study identifies people who are at-risk to themselves they would not be suitable for the online CBT intervention. These patients would be immediately sign-posted to the most appropriate service and GP would be contacted. Ieso Digital Health has robust risk and safeguarding management protocols.

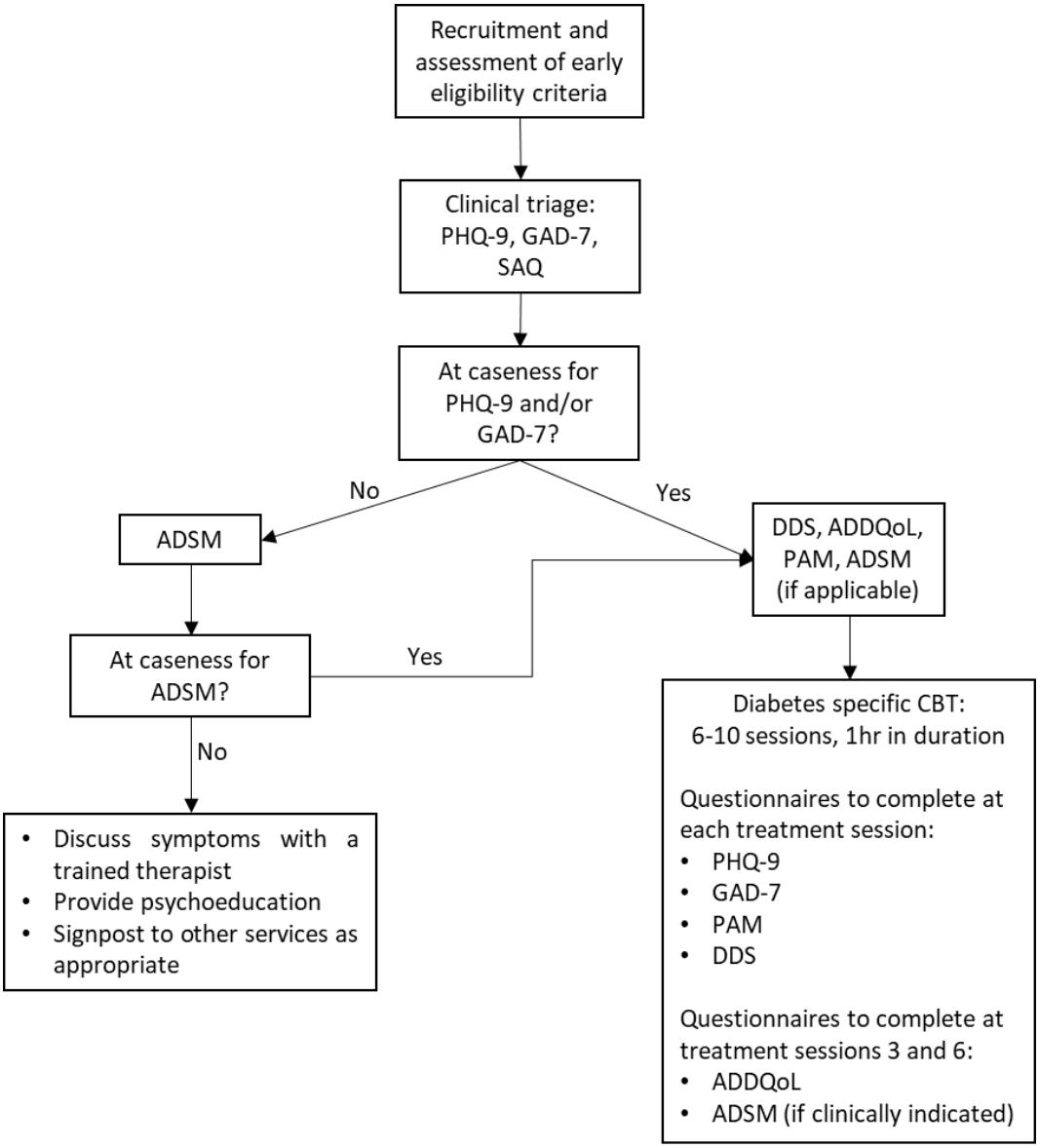

Figure 1 – Flowchart of recruitment and study design

4.2 Inclusion-Exclusion Criteria and General Study Population

The following inclusion/exclusion criteria, assessed on recruitment and initial screening, will apply:

Inclusion criteria:

- Diagnosed with Type 2 diabetes at least 1 year ago
- Over 18 years of age at the time of recruitment
- Able and willing to sign a consent prior to the study

- Therapy will be provided based on set criteria, which define if a patient is a clinical case of depression (based on PHQ-9 score), anxiety (based on GAD-7 score) or an appropriate Anxiety Disorder Specific Measure.

Exclusion criteria:

- People who are not suitable for CBT, e.g. patients with cognitive deficits from brain damage or dementia.
- People who are already receiving psychological therapy.
- People who do not have access to an Internet enabled device or have access to an Internet connection.
- People who have a low level of literacy; those who cannot write or read emails or texts will be excluded from this study because they will be unable to utilise the intervention.
- People who are visually impaired and are unable to write on or read from a computer and do not have access to appropriate assistive technology for the visually impaired.
- People who do not speak English.
- People who become unsuitable for treatment within the service. The normal IAPT (Improving Access to Psychological Therapies) exclusion criteria will be applied whereby someone who becomes actively suicidal or presents as a risk to others requires a referral on to a more specialised, secondary care service. In addition people who are experiencing symptoms of psychosis, hyper-mania, severe cognitive impairment, severe personality disorder or severe learning disability are also deemed as being unsuitable for an IAPT service. These individuals will be excluded from this study and referred on to more specialised services.

4.3 Study Variables

	Before the first treatment session	At each treatment session	At treatment sessions 3 and 6	Follow-up at 6 months
ADDQoL	x		x	x
ADSM	x (if indicated)		x (if indicated)	x (if indicated)
DDS	x	x		x
GAD-7	x	x		x
PAM	x	x		x
PHQ-9	x	x		x
SAQ	x			

- **ADDQoL (Audit of Diabetes Dependent Quality of Life)**; 19-item measure assessing quality of life in relation to the impact of diabetes on different domains of every day life; range -9 to +3, with -9 indicating maximum negative impact, and +3 maximum positive impact on quality of life.
- **ADSM (Anxiety Disorder Specific Measure)**; questionnaires designed to measure symptoms for specific anxiety disorders:
    - **MI (Agoraphobia Mobility Inventory);** 26-item scale assessing symptoms of agoraphobia; caseness threshold: 2.3; reliable change threshold: 0.73;
    - **HAI (Health Anxiety Inventory)**; 14-item questionnaire assessing symptoms of health anxiety; caseness threshold: 18; reliable change threshold: 4;
    - **IES-R (Impact of Events Scale Revised);** 22-item scale assessing post-traumatic stress disorder symptoms; caseness threshold: 33; reliable change threshold: 9;
    - **Obsessive Compulsive Inventory (OCI);** 42-item scale assessing obsessive-compulsive symptoms; caseness threshold: 40; reliable change threshold: 32;
    - **Panic Disorder Severity Scale (PDSS);** 7-item scale assessing panic disorder symptoms; caseness threshold: 8; reliable change threshold: 5;
    - **Social Phobia Inventory (SPIN);** 17-item measure assessing social anxiety symptoms; caseness threshold: 19; reliable change threshold: 10;
- **DDS (Diabetes Distress Scale);** 17-item scale aimed at measuring symptoms of diabetes related distress. Total score greater than 2 is considered as clinically significant moderate distress.
- **GAD-7 (Generalized Anxiety Disorder);** 7-item questionnaire aimed at measuring symptoms of anxiety; caseness threshold: 8; reliable change threshold: 4;
- **PAM (Patient Activation Measure);** 13-item questionnaire aimed at measuring patient activation with regards to their own health, specifically their diabetes; Scores smaller than or equal to 47 indicate the lowest level of activation (level 1), while scores higher than or equal to 67.1 indicate the highest level of activation (level 4); previous research demonstrates that a change in PAM of 10 points or more represents a large effect size (Moljord et al, 2015).
- **PHQ-9 (Patient Health Questionnaire);** 9-item questionnaire aimed at measuring depressive symptoms; caseness threshold: 10; reliable change threshold: 6;
- **SAQ (Self-assessment Questionnaire);** free text self-reported questionnaire, where the patient is given the opportunity to describe their current mental health problem as well as mental health history;

5 Sample Size

The aim is to recruit 500 patients into the study. This number is needed to demonstrate an effect of the treatment, given that patients will be recruited in a real-world setting, and hence will show high diversity in terms of presentation of their mental health disorder, severity of the

disorder, demographics etc. High numbers will also be needed to enable us to carry out post-hoc group analyses, for example comparing patients with high vs low PAM scores at baseline, different mental illness diagnoses (eg depression, anxiety, PTSD, social anxiety etc), or different demographics (eg male vs female, older adults vs younger adults).

6 General Considerations

6.1 Timing of Analyses

- A first interim analysis will be performed when 100 engaged patients (i.e. attending two or more therapy sessions) are discharged from treatment.
- A final analysis will be performed when 500 engaged patients are discharged from treatment or alternatively when the last patient completes treatment.
- A follow-up analysis will be performed after the 6-month follow-up of the 500 patients completing the study.

6.2 Analysis Populations

6.2.1 Full Analysis Population

- All patients who fulfil inclusion criteria and are deemed eligible to receive therapy following clinical triage.

6.2.2 Per Protocol Population

- All patients who engage with therapy (i.e. complete two or more treatment sessions).

6.3 Demographics and treatment variables

The following variables have been shown in previous research to have an effect on clinical outcomes (primary outcome measures), and will be used in the final analyses to compare the study group to the control group.

- Patient age
- Presence of long-term physical comorbidities (in addition to diabetes)
- Presence of a physical disability
- Symptom severity at the start of treatment (as measured by PHQ-9, GAD-7 and/or ADSM)
- Work and Social Adjustment Scale (WSAS) score at the start of treatment
- Depression sub-type (if primary diagnosis of depression)
- Total number of treatment sessions
- Total number of sessions the patient did not attend (DNAs)

An exploratory analysis will also assess the impact of these variables on secondary outcome metrics (PAM, DDS, ADDQoL).

6.4 Missing Data

When analysing the full analysis population, missing data for primary and secondary outcome measures will be treated as missing not at random. In this case, data from all patients will be analysed, working under the assumption that missing data may indicate patient attrition, either during treatment or at follow-up appointment. Missing covariate data will be treated as missing at random, and a pairwise deletion approach will be used when exploring the effect of covariates on primary and secondary outcome measures.

For per protocol analysis, missing data for primary and secondary outcome measures, as well as covariates, will be treated as missing at random. A last observation carried forward approach will be used for primary and secondary outcome measures. A pairwise deletion approach will be used when exploring the effect of covariates on primary and secondary outcome measures. Covariate variables with more than 60% observations missing will be dropped from the analysis.

6.5 Interim Analyses and Data Monitoring

6.5.1 Purpose of Interim Analyses

The purpose of the interim analyses will be to assess ongoing recruitment procedures (e.g. suitability of the patient sample targeted), patient engagement, safety and effectiveness of the clinical intervention.

6.5.2 Planned Schedule and Scope of Interim Analyses

An interim analysis will be performed when 100 engaged patients (i.e. attending two or more therapy sessions) are discharged from treatment. In this analysis, patient recruitment and conversion rates, patient engagement rates, and safety aspects of the intervention will be assessed, as well as initial efficacy of the intervention. If there is evidence that the intervention is not leading to a significant decrease in PHQ-9, GAD-7 and/or ADSM scores over time, or it is significantly less effective than standard care, a deeper quantitative and qualitative analysis will be conducted to investigate the root cause and inform any changes to therapeutic protocol or procedures. If changes are made to the therapeutic protocol or procedures, recruitment for the study will re-start, and data acquired thus far will be discarded from future analyses. Patient recruitment procedures may also be revised at this stage if patient conversion rate (i.e. from a patient beginning the registration process to fulfilling the eligibility criteria and being enrolled in the study) is lower than 40%. Changes to patient recruitment procedures will not lead to the study being re-started.

A final analysis will be conducted when 500 engaged patients are discharged from treatment, or alternatively when the last patient completes treatment. In this analysis, the effectiveness of the clinical intervention will be fully assessed.

6.5.3 Practical Measures to Minimise Bias

Interim analyses will be conducted by a clinical scientist within Ieso. The results of these analyses will be shared internally with other stakeholders within the project, but will not be shared with therapists responsible for providing the therapy, therapist supervisors, or patient services team, unless a decision is made by the project manager to do so.

Snapshots of the data available at each interim analysis will be preserved, as well as documentation of analysis plans, programming code and reporting provided at each interim.

7 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation and median. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by diagnosis and patient, and when appropriate by therapy session number within patient. All summary tables will be structured with a column for each outcome metric (e.g. recovery, reliable improvement) and will be annotated with the total population size relevant to that table/diagnosis, including any missing observations.

7.1 Patient Recruitment

Patient engagement will be defined as a patient attending two or more therapy sessions, and having two or more primary outcome measures available (i.e. PHQ-9, GAD-7 and/or an appropriate ADSM). Following IAPT convention, this is the minimum dose of therapy a patient must receive such that pre- and post-treatment scores are collected and clinical change can be estimated.

The project aims to collect data for 500 engaged patients over a period of 14 months. Assuming a conversion rate (from recruitment to enrolment) of approximately 50%, and an engagement rate (from enrolment to engagement) of approximately 65%, this translates as an average recruitment rate of 110 patients per month.

7.2 Derived variables

Clinical outcome metrics such as caseness, recovery and improvement will be calculated based on symptom metrics collected during the course of therapy, namely PHQ-9, GAD-7 and/or ADSM.

A reduction in score on any of these scales which equals or surpasses the reliable change threshold for that scale is indicative of statistically reliable improvement in symptom severity. If a patient shows reliable improvement in one of these scales, while not showing reliable deterioration (an increase in score which equals or surpasses the reliable change threshold) in any of the other scales, they will be classed as improved.

Inclusion criteria for the study states that all patients taking part in the study must be at caseness at baseline. This means they must score above the caseness threshold for at least one of the scales referenced above. Patients who move from above caseness at baseline, to below caseness on all scales at the last treatment session will be classed as recovered.

Patients who simultaneously meet the criteria for improvement and recovery will be classed as reliably recovered.

7.3 Demographic and Baseline Variables

The IAPT programme mandates the collection of a minimum data set across all services providing psychological therapy for NHS patient in England. Ieso Digital Health operates within the IAPT

framework, and will therefore be collecting these data for patients recruited for this study. This data set includes information on patient demographics such as gender, age, ethnicity, religion, sexual orientation and disabilities) as well as mental health diagnosis.

8 Analyses

Summary statistics will be produced separately for all patients enrolled in the study and patients completing a course of treatment per protocol. Additionally, for patients completing a course of treatment data will also be summarised by mental health diagnosis. Summary statistics for continuous variables will include N, mean, standard deviation and median. Tests for normality of the distribution will also be conducted. Summary statistics for categorical variables will include number and percent. Efficacy analyses will be conducted for engaged patients only.

Where appropriate continuous predictor variables will be scaled and centred to the mean. Multicollinearity analyses will be performed to investigate potential correlations between independent variables. Statistical significance will be defined as $p<.05$ two-tailed, uncorrected.

8.1 Primary analyses on primary endpoints

Primary analysis on primary endpoints will be conducted on PHQ-9, GAD-7 and/or ADSM scores. These analyses will also be conducted on variables derived from primary endpoint metrics, as described in section 7.2 (i.e. recovery, improvement and reliable recovery).

For continuous variables (PHQ-9, GAD-7 and/or ADSM scores), repeated-measures analyses of variance (ANOVA) will be conducted, with questionnaire score as the dependent measure and time (pre- vs post-treatment) as a within-subjects variable. These analyses will test the hypothesis that psychological therapy is efficacious in reducing symptoms of mental disorder in patients with type 2 diabetes.

The variables described in section 7.3 have been shown to have a significant effect on clinical outcomes. Final analyses will explore any differences in demographic variables between the study and control groups.

Growth curve modelling will be used to assess rate of change in primary endpoint metrics over time, and calculate the mean number of treatment sessions needed to reach the thresholds for the derived variables described in section 7.2 (i.e. mean number of sessions needed to reach recovery, improvement or reliable recovery). Descriptive statistics for the mean recovery rate, improvement rate and reliable recovery rate for the group will also be presented.

8.2 Primary analyses on secondary endpoints

Primary analyses on secondary endpoints will be conducted using the procedures described in section 8.1 (excluding growth curve modelling), with PAM, DDS and ADDQoL as dependent variables. The aim of these analyses is to test the hypothesis that a psychological intervention in patients with type 2 diabetes will result in a significant reduction of diabetes distress, and an increase of quality of life and patient engagement with the management of their diabetes.

8.3 Secondary analyses

For primary endpoint variables (PHQ-9, GAD-7 and/or ADSM scores) collected in both treatment and control groups, a mixed model analysis of variance (ANOVA) will be conducted with time (pre- vs post-treatment) as a within-subject variable, and treatment group (control vs study treatment group) as a between-subjects variable. This secondary analysis will test the hypothesis that the diabetes-specific therapy protocol used in the proposed study is significantly more efficacious at decreasing symptoms of mental health conditions in patients with type 2 diabetes than standard care.

If the treatment groups are not matched for demographic variables (described in section 7.3), treatment group (control vs study treatment group) will also be included as a between-subjects variable in a secondary ANCOVA analysis, with the variables listed in section 7.3 included as covariates, time (pre- vs post-treatment) included as a within-subject variable, and treatment group (control vs study treatment group) included as a between-subjects variable. This will allow us to compare primary endpoint variables between the two treatment groups, while controlling for differences in demographic variables.

For categorical variables derived from primary endpoint variables (i.e. recovery, improvement, reliable recovery), a chi-square analysis comparing study treatment group to the control group will be performed, to test the hypothesis that the diabetes-specific therapy protocol used in the proposed study is significantly more efficacious at decreasing symptoms of mental health conditions in patients with type 2 diabetes than standard care. To control for the effect of covariate variables on categorical outcome metrics, a logistic regression with covariate variables and treatment group as independent variables will also be conducted.

9 Technical Details

All analyses will be performed in R. Any outputs will include: the date and time of the analysis; the name of the code file that produced the analysis; the author; a log capturing the version of the software and any external add-on code used.

At the start of any code file there will be a set of comments that include: the author; the date and time of writing; references to inputs and outputs; reference to any parent code file that runs the child code file.

10 Summary of Changes to the Protocol

Date	Author	Summary of change
13/07/2020	Ana Catarino	Incorporated changes suggested by Michael Ewbank, including removing the use of demographic variables as covariates in the analyses, as these are not the main focus of the study and including these will reduce statistical power. Demographic variables will be compared between treatment groups, and if

		the groups are not matched then these variables will be included as covariates in secondary analyses.
24/11/2020	Ana Catarino	Updated Chief Investigator and control group to include historical patients with any long-term physical condition, not just diabetes.