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**Helping Urgent Care Users Cope with Distress about Physical Complaints: A randomized Controlled Trial**

Statistical Analysis Plan

Version 0.2 (27 Mar 18)

Based on Protocol version **4 (24.11.17)**

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**Abbreviations**

|  |  |
| --- | --- |
| **Abbreviation** | **Description** |
| AE | Adverse Event |
| AHSN | Academic Health Science Network |
| CI | Chief Investigator overall |
| CLAHRC EM | Collaboration for Leadership in Applied Health Research and Care  for the East Midlands |
| CBT | Cognitive Behavioural Therapy |
| CRF | Case Report Form |
| GCP | Good Clinical Practice |
| HAI | Short form Health Anxiety Inventory |
| IAPT | Improving Access to Psychological Therapies |
| ICF | Informed Consent Form |
| NHS | National Health Service |
| PI | Principal Investigator at a local centre |
| PIS | Participant Information Sheet |
| REC | Research Ethics Committee |
| R&D | Research and Development department |
| RCT | Randomised Controlled Trial |
| SAE | Serious Adverse Event |
| TAU | Treatment As Usual |
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# 1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from a randomised controlled trial titled Helping Urgent Care Users Cope with Distress about Physical Complaints: A Randomised Controlled Trial. The study is investigating the clinical and cost effectiveness of remotely delivered CBT for people who repeatedly access unscheduled/urgent care. The study was funded by NIHR CLAHRC East Midlands.

**The purpose of the plan is to:**

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

# 2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

## 2.1. Trial aims and objectives

The primary purpose of the trial is to determine the cost and clinical effectiveness of offering 6-12 sessions of remotely delivered cognitive behaviour therapy (CBT) via video calling or over the telephone for health anxiety in repeated utilisers of unscheduled/urgent care versus treatment as usual. A study protocol has been published1. The trial is registered: NCT02298036).

Alongside the RCT, an implementation analysis will also be carried out to determine the barriers and enablers to delivering remote CBT and how such treatment might fit into a wider care pathway to enhance patient experience of care.

### 2.1.1. Primary objective

The primary objective of the study will be to investigate longitudinal change on the short form 14 item Health Anxiety Inventory (HAI) from baseline to 6 months [2](#_ENREF_1). This measure was the primary outcome for the CHAMP study 3,4.

**2.1.2. Secondary objectives**

Secondary objectives will be any change in the following measures from baseline to 12 months.

* Short form 14 item Health Anxiety Inventory (HAI) 5;
* 7 item Generalised Anxiety Disorder for anxiety (GAD-7) 6;
* 15 item Patient Health Questionnaire for somatic distress (PHQ-15)7;
* 9 item Patient Health Questionnaire for depression (PHQ-9)8;
* 8 item Work and Social Adjustment Scale for social function (WSAS)9;
* 5 item quality of life on the EQ5D-5L 10;
* 36 item Short Form Health Survey (SF-36) 11;
* Change in number of contacts with unscheduled or emergency care established through an adapted and stylised Client Service Receipt Inventory (CSRI) 12.

## 2.2. Trial design and configuration

A multi-centre longitudinal mixed methods study will be undertaken in primary and secondary care centres across the East Midlands in the United Kingdom; Nottinghamshire, Leicestershire, Derbyshire, Northamptonshire and Lincolnshire. In addition two sites from outside of the East Midlands wishing to be involved in the study were also invited to participate. Participants will be recruited from unscheduled primary and secondary care services in each centre. This includes Emergency Departments, GP practices providing same day urgent appointments, walk in centers and outpatient clinics. A pragmatic RCT; intention to treat analysis of a remotely delivered CBT intervention versus treatment as usual will be conducted. Participants randomised to the trial will be allocated to one of two arms:

1. In the remote CBT intervention arm participants will receive 6-12 sessions of CBT delivered remotely, this will be via video calling or over the telephone in addition to the usual care they receive.
2. In the TAU arm participants continue to consult with their general practitioner and other health providers they would normally approach.

Referring clinicians approached patients meeting eligibility criteria. Potential participants who provide written or verbal consent to be contacted by the research team will be telephoned by a researcher. Information will be provided about the study and an eligibility screening completed. A person will be deemed eligible if they have had two or more consultations with any provider of unscheduled services in the last twelve months and a score of 18 or more on the Health Anxiety Inventory (HAI) 13. If eligible, the researcher will arrange an assessment interview with the potential participant. At the interview, oral and written consent will be sought and the baseline assessment conducted. The baseline assessment will consist of the primary and secondary outcome measures. At the baseline assessment only, the participant will also be interviewed using the research version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID 5) psychiatric interview14. This will determine if people have mental disorders that exclude participation in the study and record the absence or presence of somatisation disorders, depressive disorders and anxiety disorders.

Participants in both arms will be followed up 3, 6, 9 and 12 months after the baseline assessment by study researchers. All outcome data will be collected single blind at 3, 6, 9 and 12 months from randomisation except for the SF-36 which will be collected at 6 and 12 months only. All the outcome measures in the study except the EQ5D-5L, PHQ15, SF-36 and the CSRI are routinely given by IAPT services to all patients at all assessments on a routine basis in the NHS. All baseline assessments will be carried out face-to-face or over the telephone (if requested by the participant) by the study researchers. All the measures have established reliability, validity and history of use in Clinical NHS settings. Follow up assessments will be carried out over the phone, email, via video calling or by post at all-time points depending on the participant’s preference.

## 2.3. Trial centres

The following sites agreed to participate in the study.

Nottinghamshire County and Nottingham City CCGs

Nottingham University Hospitals NHS Trust

Sherwood Forest Hospitals NHS Foundation Trust

Nene and Corby CCGs

Lincolnshire CCGs

Derby City and Derbyshire County CCG

Leicester City and Leicestershire CCGs

Bradford Districts CCG

Staffordshire & Stoke on Trent Partnership NHS Trust

Bradford Districts CCG did not recruit any participants to the study.

## 2.4. Eligibility criteria

### 2.4.1. Inclusion criteria

The pragmatic nature of this study requires that inclusion/exclusion criteria must reflect everyday criteria that NHS clinicians use and would be used by specialist psychological therapies services14.

* ≥ 2 consultations, referrals or hospital admissions with any provider of unscheduled or emergency care (including urgent same day appointment at their general practice) in last 12 months for symptoms such as cardiac, respiratory, neurological, gastrointestinal or genitourinary problems not attributed to identified pathology.
* Scores above the threshold for severe health anxiety of 18 or more on the 14 item short form of the Health Anxiety Inventory (HAI) 12.
* Age 18 years and over. There will be no maximum age limit.
* Sufficient understanding of English (spoken and written) to enable full engagement in the intervention. We are only recruiting participants who have a good understanding of English, as the questionnaires and session by interview assessments are primarily validated in English. Furthermore, it is unclear how language difficulties could impact on the effectiveness of the intervention. Therefore, understanding of English is required to maintain the fidelity of the intervention.
* Able and willing to give oral and written informed consent to participate in the study.

### 2.4.2. Exclusion criteria

* Pathological medical condition requiring further assessment or acute management, or pregnancy.
* Other severe mental illness (schizophrenia, bipolar disorder, severe major depressive episode, eating disorder) ascertained by the Structured Clinical Interview for DSM-IV Disorders (SCID)13 or anyone at immediate risk of harm to themselves or other people through their mental state
* Organic mental disorder (dementia, delirium, substance use disorder, organic mood disorder).
* They are already receiving specialist mental health intervention (or have done within the last six months), including psychological treatment as part of specialist medical care e.g. pain clinic.
* Significant learning disability (moderate to severe or to the extent that engagement in the intervention is not possible).

All of the above require a different clinical approach to the treatments being tested in the study. Unipolar mild to moderate depressive episodes, other anxiety disorders or stable physical illness are not exclusions to the study as they are readily addressed by the intervention and are necessary to include if the study is pragmatic and going to generalise to clinical practice.

**2.5. Description of interventions**

Following baseline assessment and confirmation of eligibility, participants will be randomly allocated to one of two treatment arms; 1) remote CBT intervention (in addition to usual treatment) or 2) treatment as usual only.

*Remotely delivered CBT intervention*

Participants allocated to the remote CBT intervention will be provided with a detailed information sheet about the remote CBT intervention and contacted by a CBT practitioner within ten days of randomisation. A team of experienced CBT practitioners will deliver CBT for health anxiety remotely using a treatment manual developed from the CHAMP study15. Clinical supervision will be facilitated by the lead therapist from the CHAMP study (HT) trained and experienced in the engagement of high service utilisers and delivery of CBT for health anxiety. The Cognitive Therapy Rating Scale Revised (CTSR)16 will be used to assess therapist competence and treatment integrity. It will also be used to maintain the standard of therapy provided, as assessment results will inform supervision. Two randomly selected sessions will be assessed for each therapist by the supervisor (HT) and feedback given for areas of strength and areas for development. Six to 12 sessions will be offered, with the addition of follow-up sessions if required. The number of sessions will be dependent on the pace of engagement with the participant and in line with client need. The intervention will address the symptoms of health anxiety from a cognitive-behavioural perspective. This will include undoing patterns of thought and behaviour that maintain health anxiety. For example, safety- seeking behaviours such as reassurance seeking or phobic avoidance aim to reduce worry, but can often fuel health anxiety.

The CBT intervention will be delivered remotely via video-calling or over the telephone depending on the participant’s preference. Participants’ may also receive SMS/email reminders of CBT sessions. The system used for video calling was deemed to offer a secure connection and user-friendly inter-face following a pilot review of available services. A contingency management plan has been put in place to address all potential failures in the technology. Permission will be sought to audio/video record treatment sessions. These will be made available to all participants as a means of consolidating learning from each session. They will also be used for assessments of therapeutic quality and reflection in clinical supervision meetings. Supervisory records will also help establish any adjustments required for effective remote delivery of therapy.

Participants will be free to continue to consult clinicians and other healthcare providers other than the CBT therapist throughout the intervention and after treatment completion. A discharge plan will be developed prior to treatment completion. A summary of the discharge plan will be distributed to the participant, their GP and any other relevant healthcare providers with the participant’s consent. Outcome data will continue to be collected after the CBT sessions are completed until the end of the follow up period.

*Treatment as usual*

Usual treatment will constitute a care plan decided by the patient and any healthcare providers involved in their care, including their GP. Treatment as usual will be unconstrained other than it will not be provided by the treatment intervention therapists.

**2.6. Randomisation procedures**

## RANDOMIZATION AND BLINDING

Following eligibility screening and baseline assessment the researcher will enter the service user participants details onto a web-based randomisation system (set up by University of Nottingham Clinical trial Unit; CTU).

The treatment to which a participant is assigned will be determined by a computer generated pseudo-random code using random permuted blocks of varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure and held on a secure server. Participants will be allocated with equal probability to each treatment arm with stratification by region. Only the trial coordinator, or their nominee, will have password access to the randomisation data. The CI, statistician and researchers will be blind to treatment allocation.

The trial coordinator will contact the CBT practitioners to inform them which participants have been allocated to the remote CBT intervention. The researchers responsible for collecting the baseline and outcome data will remain blind to randomisation until data collection has been completed. Participants themselves and the CBT practitioners will not be blind to treatment group. Participants will be advised by the CBT practitioners and also by the researchers when collecting outcome data not to specify which treatment arm they are in. Interviews conducted for the second doctoral research with participants who remain in the study will only be conducted after the twelve month follow up assessments have been completed to prevent un-blinding.

### Maintenance of randomisation codes and procedures for breaking code

Investigators may identify the treatment of participants through password protected access; however, this will only be done at the end of the trial or in the event of a medical emergency or SAE. Participants may also accidentally reveal to the researcher when obtaining outcome data that they have been receiving the remote CBT intervention. If this occurs then any case of un-blinding will be reported within 48 hours, as practicable in person or by phone or fax to the Clinical Trials Manager who will record the date, reason and whether follow up assessments will continue. A written account of the reason for un-blinding will also be made. If the Clinical Trials Manager is unavailable the CLAHRC theme manager will be informed. Following data collection an analysis will be completed to determine if incidences of un-blinding were equal in the two treatment groups.

## 2.7. Sample size and justification

The sample size justification was Based on the CHAMP study results15 which showed the mean HAI score for CBT and TAU group were 24.9 (SD 4.2) and 25.1 (SD 4.5) respectively at baseline and 17.7 (SD 8.0) and 22.6 (SD 6.8) respectively at 6 months, 114 participants are required to detect such a difference in HAI score at 6 months for a 90% power at 2 tailed significance 0.05 level, assuming equal SD (8.0) for both groups and null correlation between baseline and follow up measures for the purpose of being conservative. After taking into account 20% loss to follow up; rate a sample size of 144 is required. Given previous studies have shown that intra-class correlation coefficients from individual practices or primary care organisations in primary care studies of MUS are extremely small (10-7), even when interventions are delivered by GPs, there will be no need to account for intra-class correlation provided more than two patients are not recruited by each GP because there can be a more substantial intra-GP correlation17,18. We therefore will assume the possible trivial centre heterogeneity will unlikely influence the sample size calculation in our study. Stata 13 was used to run power analysis.

However in September 2016 we observed that our follow up rate for the primary outcome measure was 75%. Thus in order to detect a difference the sample size was increased to 152. Sponsor and ethical approval was gained to recruit additional participants resulting in a sample size of 156 participants.

## 2.8. Blinding and breaking of blind

Following eligibility screening and baseline assessment the researcher will enter the service user participants details onto a web-based randomisation system (set up by University of Nottingham Clinical trial Unit; CTU).

The treatment to which a participant is assigned will be determined by a computer generated pseudo-random code using random permuted blocks of varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure and held on a secure server. Participants will be allocated with equal probability to each treatment arm with stratification by region. Only the trial coordinator, or their nominee, will have password access to the randomisation data. The trial coordinator will contact the CBT practitioners to inform them which participants have been allocated to the remote CBT intervention. The researchers responsible for collecting the baseline and outcome data will remain blind to randomisation until data collection has been completed. Participants themselves and the CBT practitioners will not be blind to treatment group. Participants will be advised by the CBT practitioners and also by the researchers when collecting outcome data not to specify which treatment arm they are in. Interviews conducted for the second doctoral research with participants who remain in the study will only be conducted after the twelve month follow up assessments have been completed to prevent un-blinding. Investigators may identify the treatment of participants through password protected access; however, this will only be done at the end of the trial or in the event of a medical emergency or SAE. Participants may also accidentally reveal to the researcher when obtaining outcome data that they have been receiving the remote CBT intervention. If this occurs then any case of un-blinding will be reported within 48 hours, as practicable in person or by phone or fax to the Clinical Trials Manager who will record the date, reason and whether follow up assessments will continue. A written account of the reason for un-blinding will also be made. If the Clinical Trials Manager is unavailable the CLAHRC theme manager will be informed. Following data collection an analysis will be completed to determine if incidences of un-blinding were equal in the two treatment groups.

**2.9. Trial committees**

The independent CLAHRC Scientific Committee will monitor progress with the project annually, receiving quarterly progress reports on progress against project milestones and a report on the progress of the study from the research team. The members of the committee are drawn externally from outside the institutions that the research team currently work with to ensure its independence from the research team. It will serve the function of a Trial Steering Committee and a Data Monitoring Committee. It consists of an independent statistician, lay representative, a previous CLAHRC Director and Director of a Research Design Service. The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator.

**2.10. Outcome measures**

### 2.10.1. Primary outcome

The primary clinical outcome will be longitudinal change on the short form 14 item Health Anxiety Inventory (HAI) from baseline to 6 months [2](#_ENREF_1). This is a self-reported measure.

### 2.10.2. Secondary outcomes

The secondary endpoints will be to examine a significant difference in change in any of the secondary objective measures between the two groups. All of measures are self-reported.

**2.11. Interim analysis**

There is no planned interim analysis. All analysis will be backed up to the UoN servers.

# 3. GENERAL ANALYSIS CONSIDERATIONS

**3.1. Analysis samples**

All analysis will be performed on an intention-to-treat basis, i.e. all participants will be included in the analysis at their originally randomized status. Nevertheless, as part of sensitivity analysis to check results robustness under various assumptions, we will run similar modeling with observed data only for all outcome variables.

**3.2. Derived variables**

Participant’s age will be calculated as time between date of randomization and birthday:

Age= date of randomization - DOB

**3.3. Procedures for missing data**

Missing values in all outcomes will be checked and reported across treatment group and follow up time. As the outcome will be repeatedly measured, a two level logistic regression with patients as level 2 unit will be performed to test the influence of treatment status and baseline measures on outcome missingness. The missing value patterns and the results from multilevel logistic regression modelling will be used to inform missing value imputation under Missing At Random (MAR) assumption19. The missing values will be imputed using multilevel modelling20. Because multilevel modelling will be used to test treatment effects for all outcome variables that will be repeatedly measured, missing values could be automatically taken into account under MAR assumption to give sensible results21, the analysis with observed data will be used as sensitivity analysis22. STATA 15 and REALCOM-IMPUTE software will be used to impute missing values by means of Markov Chain Monte Carlo (MCMC) approach for multilevel data20. Twenty Imputed datasets would be generated for each outcome variables.

# 4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

**4.1. Participant flow**

30 lost to follow-up at 3 months

1 withdrew

29 unable to collect data

22 lost to follow-up at 6 months

2 withdrew

20 unable to collect data

28 lost to follow-up at 9 months

1 withdrew

27 unable to collect data

31 lost to follow-up at 12 months

0 withdrew

31 unable to collect data

6 excluded as met exclusion criteria

78 allocated to Treatment as usual (TAU)

524 Patients referred

78 allocated to Remote CBT intervention

56 completed or had 5 or more sessions

156 randomised

48 males and 108 females

135 unable to contact

163 declined to participate

48 not eligible

16 did not attend baseline assessment

Xx d

Total 3 months received = 48 (60%)

Total 6 months received = 56 (72%)

Total 9 months received = 50 (64%)

Total 12 months received = 47 (60%)

Total 3 months received = 53 (68%)

Total 6 months received = 56 (72%)

Total 9 months received = 47 (60%)

Total 12 months received = 47 (60%)

1 withdrawn from study after randomisation due to high suicide risk

162 consented and completed baseline assessments

25 lost to follow-up at 3 months

2 withdrew

23 unable to collect data

22 lost to follow-up at 6 months

0 withdrew

22 unable to collect data

31 lost to follow-up at 9 months

0 withdrew

31 unable to collect data

31 lost to follow-up at 12 months

0 withdrew

31 unable to collect data

**4.2. Baseline characteristics**

Patients demographic and baseline measures will be summarized by treatment arms. The descriptive statistics will present mean standard deviation, median, minimum, maximum and number of observation for normally distributed data; the minimum, lower quantile, median, upper quantile and number of observation will be presented for skewed data; the categorical data will be summarized with frequency (percentage) for each observed level. Trial center level background information will be summarized in similar manor.

Table template: Summary of Participant demographic background information

Table template: number of children per group for each site

|  |  |  |
| --- | --- | --- |
| Site name | TAU | treatment |
| Age: mean (SD, range) |  |  |
| Gender, female: n (%) |  |  |
| HAI mean (SD, range) |  |  |
| Other outcome continuous |  |  |

# 5. ASSESSMENT OF STUDY QUALITY

**5.1. Randomisation**

Participants will be allocated with equal probability to each treatment arm with stratification by region. One participant was withdrawn from the trial after randomisation due to high suicide risk. They will still be included in the analysis.

Randomisation to the remote therapy or treatment as usual (TAU) arm was stratified by site with allocation conveyed to a trial administrator. Research assessors were masked to outcome.

One participant was randomized to the TAU arm but received the documentation and treatment in the therapy arm. As the study is adopting a ITT analysis this participant’s data will be analysed as if they were in TAU 23.

On participant was incorrectly allocated to Site 1 and subsequently moved the correct site 2. This resulted in a missing patient information number for site 1.

**5.2. Adherence**

Presence and meaningful participation during psychological therapy sessions will be recorded by the CBT practitioners. Adherence to psychological treatments is a measure of the acceptability of the intervention.

**5.3. Protocol deviations**

There was one randomization protocol violation. One participant who was allocated into TAU by the randomisation system was accidentally sent the incorrect treatment allocation letter resulting in them receiving the remote CBT therapy. This error was identified following the completion of treatment. The participant only completed the three month follow up questionnaire.

**5.4. Changes made to the planned statistical analyses**

No.

# 6. ANALYSIS OF EFFECTIVENESS/EFFICACY

## 6.1. Summary of primary and secondary outcomes

All outcome measures will be summarized by treatment arm across follow up times. The descriptive statistics will present mean standard deviation, median, minimum, maximum and number of observation for normally distributed data; the minimum, lower quantile, median, upper quantile and number of observation will be presented for skewed data; the categorical data will be summarized with frequency (percentage) for each observed level outcome variable. Continuous variables’ normality will be visually checked using histogram plot and normal PP plot, together with Shapiro-Wilk normality test.

## 6.2. Primary analysis

After exploratory analysis on outcomes variables, the treatment effects (95%CI and p-value) on HAI change from baseline will be quantified using multilevel modelling with time, treatment, and interaction between time and treatment as fixed effects, baseline HAI score as covariate, patient as level two unit21. The treatment differences at every follow-up time together with its 95% CI, will be derived from the multilevel modelling. STATA 15 will be used to perform all exploratory and multilevel modelling.

The basic two level MLM to be performed is:

Where is outcome change score from baseline for jth participant at ith follow-up time. Time was included as discrete time variable, group is binary variable, j is participant ID (level 2 unit) and i is follow-up time order (level 1 within patient unit). is the departure of jth participant change score from the overall average, is the patient level variance and is residual term with , is the group difference on outcome change from baseline measure. As a multicenter trial, the center effects will be adjusted using multilevel modelling with centered included as level three unit 24,25. Nevertheless, the center level variability will be examined at the beginning of multilevel modelling, center won’t be included in modelling if the variability is trivial. Non-significant group interaction will not be included in the modelling for model parsimony purpose 26,27.

6.3. Secondary/sensitivity analysis of primary outcome

To assess the robustness of result sensitivity to missing values, we also run multilevel modelling with only observed score.

**6.4. Secondary outcomes**

For all secondary outcome variables, same MLM will be performed to explore the arm difference on change score from baseline measures. See modelling details for primary outcomes analyzing.

## 6.5. Other analysis

# NO.

# 7. ANALYSIS OF SAFETY

## 7.1. Adverse events

### Definitions

An adverse event (AE) will include any clinically important exacerbation of a pre-existing illness, such as an increase in frequency or intensity of a pre-existing episodic event or condition and continuous persistent disease or symptoms present at baseline that worsen following the start of the study. This information will be recorded as adverse event data. All adverse events will be assessed for seriousness and causality, as in all other trials, as in all other trials and reported as required to comply with Good Clinical Practice.

Serious Adverse Events (SAEs) include catastrophic physical health events that are potentially life threatening or cause death such as myocardial infarction, pulmonary embolus or catastrophic mental health events such as suicide, self-harm with serious suicide intent or harm to others. The occurrence of serious adverse events that are causally related to participation in this study is expected to be rare as participants will only receive treatments that are available in routine NHS practice. Admission to hospital will not be regarded as a SAE or AE as these are common expected outcomes in people who frequently use urgent care.

### Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any AE. All AEs will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study treatment / intervention is not the cause. The Chief Investigator shall be responsible for all AE reporting and shall be informed immediately of any SAEs and shall determine seriousness and causality in conjunction with any treating medical practitioners.

All treatment related serious adverse events will be recorded and reported to the Research Ethics Committee (REC) as part of the annual reports. Unexpected serious adverse events will be reported within the timeframes to the REC as stated below. The Chief Investigator, Professor Richard Morriss will be responsible for all adverse event reporting.

## Trial Treatment / Intervention Related SAEs

A SAE that is unexpected in its severity and seriousness and deemed directly related to or suspected to be related to the trial treatment or intervention shall be reported to the ethics committee that gave a favourable opinion.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator. The Chief Investigator will assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention. They will then take appropriate medical action, which may include halting the trial and informing the Sponsor of such action. If the event is deemed related to the trial treatment or intervention they shall inform the REC using the reporting form found on the HRA web page within seven days of knowledge of the event. They shall, within a further eight days send any follow-up information and reports to the REC and make any amendments as required to the study protocol and inform the REC as required.

### Participant removal from the study due to adverse events

Any participant who experiences an AE may be withdrawn from the study at the discretion of the investigator. No adverse events are anticipated as a result of taking part in this study.

# 8. FINAL REPORT TABLES AND FIGURES

**Table template: treatment effects**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | TAU |  | treatment |  | Group comparison |  |
|  | Mean change  from baseline  (95%CI) |  | Mean change  from baseline  (95%CI) |  | Change difference  (95%CI) | P value |
| HAI |  |  |  |  |  |  |
| 3 month |  |  |  |  |  |  |
| 6 month |  |  |  |  |  |  |
| 9 month |  |  |  |  |  |  |
| 12 month |  |  |  |  |  |  |
| PHQ9 |  |  |  |  |  |  |
| 3 month |  |  |  |  |  |  |
| 6 month |  |  |  |  |  |  |
| 9 month |  |  |  |  |  |  |
| 12 month |  |  |  |  |  |  |
| GAD7 |  |  |  |  |  |  |
| 3 month |  |  |  |  |  |  |
| 6 month |  |  |  |  |  |  |
| 9 month |  |  |  |  |  |  |
| 12 month |  |  |  |  |  |  |
| PHQ15 |  |  |  |  |  |  |
| 3 month |  |  |  |  |  |  |
| 6 month |  |  |  |  |  |  |
| 9 month |  |  |  |  |  |  |
| 12 month |  |  |  |  |  |  |
|  | OTHERE |  |  |  |  |  |

# 9. REFERENCES

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