AN OPEN TRIAL OF GROUP METACOGNITIVE THERAPY FOR ANXIETY AND DEPRESSION IN CANCER SURVIVORS (GMAC Study)

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Sponsor

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GLOSSARY OF ABBREVIATIONS

BCa	Breast Cancer
CBT	Cognitive Behaviour Therapy
CIC	Confidence in Concept Scheme
CRCa	Colorectal Cancer
MCT	Metacognitive Therapy
HADS	Hospital Anxiety and Depression Scale
NHS	National Health Service
CHPS	Clinical Health Psychology Service
MRC	Medical Research Council
PCa	Prostate Cancer
PTSD	Posttraumatic Stress Disorder
RLBUHT	Royal Liverpool and Broadgreen University Hospital NHS Trust

1. PROTOCOL APPROVAL/SIGNATURES

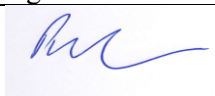
This protocol describes the GMAC study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the Study. Problems relating to this Study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

1.1 Chief Investigator

I, Dr Peter Fisher as Chief Investigator for the GMAC study confirm that I will be responsible to ensure that all members of the study team are appropriately trained on the study protocol and have the relevant qualifications and experience to carry out their role in accordance with the study protocol.

1.2 Protocol Authorised by:

Name	Site	Signature	Date
Dr Peter Fisher (Chief Investigator)	Psychological Sciences. University of Liverpool		10/05/17

2. STUDY SUMMARY

Survival rates in cancer continue to improve, with over 2 million adult cancer survivors in the UK, projected to increase to 4 million by 2030. Around 25% of these survivors require treatment for clinical levels of emotional distress. Current pharmacological treatments are not very effective and are not well tolerated by patients, who prefer psychological treatments. However, meta-analyses of well-controlled studies of psychological treatments indicate that these achieve only small effect sizes. Reflecting this limited efficacy in the face of the need for psychological treatment, the National Cancer Survivorship Research Initiative highlighted development and evaluation of practically feasible interventions for depression and anxiety in cancer survivors as an urgent research priority. It is recognised that current influential psychotherapeutic approaches need to be modified to meet the specific needs associated with cancer. However modifications have been pragmatic rather than theory-driven and have not improved efficacy.

Our study addresses the stages of 'development' and 'piloting and feasibility' in MRC guidance on intervention development, albeit with a relatively well-defined starting point given existing evidence for efficacy of MCT in other settings and promising preliminary evidence of applicability in cancer. We will conduct a phase I open trial to test the potential efficacy of group MCT in cancer survivors and the hypothesised causal metacognitive mechanisms underpinning treatment response. The evidence from this open trial will therefore allow us to progress to the next step in translating group MCT for cancer survivors: a randomised phase II controlled trial against the current gold standard approach, namely cognitive behaviour therapy.

KEYWORDS: Group Metacognitive Therapy; Cancer Survivors; Open Trial; Anxiety; Depression

Title:	An Open Trial of Group Metacognitive Therapy for Anxiety and Depression in Cancer Survivors (GMAC Study)
Design:	An open trial (single arm, single site) with follow-up at 3 and 6 months.
Aim:	To conduct an open trial of group MCT for cancer survivors experiencing clinically significant emotional distress.
Objectives:	1. To obtain evidence of potential efficacy of group MCT in alleviating emotional distress in cancer survivors. 2. To assess the acceptability of the intervention to patients. 3. To obtain data to inform sample size calculations for a subsequent Phase II trial 4. Determine whether group MCT for cancer survivors can be easily delivered in routine clinical practice
Measures:	*Primary endpoint:* Severity of depression and/or anxiety symptoms at post-treatment, and at 3 and 6 months follow-up, measured by the full scale score on the Hospital Anxiety and Depression Scale (HADS; [33]). *Secondary endpoints:* Cognitive Attentional Syndrome-1 [19]; Fear of Cancer Recurrence Inventory [35]; Impact of Events Scale-Revised (IES-R) [36]; Metacognitions Questionnaire-30 (MCQ-30) [37]; Functional Assessment of Cancer Therapy-General (FACT-G) [38].
Population:	Patients who are referred to the Clinical Health Psychology Service experiencing clinically significant distress, operationally defined as a score of ≥ 15 on the full scale score on the HADS [32].
Intervention:	The intervention will constitute 6 sessions of group MCT. Clinical psychologists trained in group MCT will deliver the therapy to groups of 4-8 patients referred to the Liverpool psycho-oncology service, who meet study criteria and consent to participate.
Study duration:	15 months maximum

3. BACKGROUND

There are over 2 million adult survivors of cancer in the UK, projected to increase to 4 million by 2030 [1]. Survivors are at increased risk of clinically significant distress. A population-based survey [2] reported 6% prevalence of psychiatric disorders in survivors; double that in the non-cancer comparison group, even when socio-demographic and clinical correlates were controlled. Furthermore, although not meeting specific diagnostic criteria, 25% of patients report clinically significant anxiety and depression [3]. Therefore, around 500,000 people have cancer-related distress warranting intervention. Our proposal addresses the need for effective help for this large population. We will study patients from tumour groups that provide the main populations of survivors including, but not limited to breast (BCa), prostate (PCa) and colorectal (CRCa). In each, distress is more prevalent than in the normal population. In PCa, incidence of anxiety and depression 3 years post-diagnosis is 23% and 26%, respectively [4]. In BCa, incidence of depression, anxiety or both, defined by meeting full or borderline diagnostic criteria, is 25% 4 years post-diagnosis [5]. Although neglected in other cancers, post-traumatic stress disorder (PTSD) affects 5% of BCa patients [6], with

troubling symptoms of PTSD affecting 34% of patients 5 years post-diagnosis [7]. Emotional distress has been less explored in CRCa, but evidence indicates clinical depression or anxiety in 22% 5 years post-surgery [7]. Emotional distress reduces quality of life and, in the context of cancer survivorship, causes wider damage, increasing pain and fatigue[8, 9], reducing treatment adherence and impairing treatment decision-making[10], and increasing demand for, and cost of, physical health care[11, 12]. Given the wide-reaching implications of emotional distress in cancer survivors, and patients' preference for psychological over pharmacological treatments, highly efficacious treatments are needed.

4. RATIONALE FOR CURRENT STUDY

Meta-analyses of well-controlled studies indicate that current "gold standard" psychological and pharmacological treatments achieve only modest effect sizes [14-17). Cancer survivors therefore need researchers to develop and evaluate psychological treatments that potentially have a better 'fit' with the cancer context, and are linked to theoretical models applicable to diverse forms of distress. Specifically, an intervention which identifies and modifies core psychological processes underpinning multiple forms of distress would offer the most promise to cancer survivors.

Our solution lies in recent developments of the area of 'metacognitive' theory and metacognitive therapy in mental health. Metacognitive therapy is derived from a trans-diagnostic model of metacognitive processes in psychopathology, the Self-Regulatory Executive Function (S-REF) model [18]. According to this model, emotional disorders are maintained by the cognitive-attentional syndrome (CAS) which comprises three processes: (i) perseverative thinking (worry and rumination); (ii) attentional strategies (monitoring for signs of potential threat); and (iii) counterproductive coping strategies (e.g. thought suppression and avoidance). Applying this to cancer survivors, multiple factors can temporarily activate the CAS, such as fears of recurrence or rumination about implications of cancer on work and family roles. For most patients, resulting worry and rumination are transient but, in those who will become depressed or anxious, sustained rumination (e.g. about current impact on family) or worry (e.g. about what will happen in future) occurs. The S-REF model specifies that such perseverative thinking is activated by metacognitive beliefs about the usefulness of worry and rumination: e.g. "worry will help me cope". Unfortunately, worry and rumination achieve the opposite, because they increase negative thoughts and broaden the sense of threat. The individual repeatedly acts as if the negative thought is valid and important, preventing the development of a more flexible relationship with thoughts that can reduce worry and rumination. Similarly, the S-REF model explains how threat monitoring (e.g. scanning for symptoms or for negative thoughts) is driven by metacognitive beliefs that this strategy will be helpful, whereas it has the opposite effect by maintaining the sense of threat and personal vulnerability so that emotional distress persists or escalates.

Metacognitive therapy (MCT) modifies the beliefs and cognitive processes that maintain distress using a range of well-specified strategies and techniques outlined in a treatment manual [19]. Clinical application of MCT differs in important ways from Cognitive Behaviour Therapy (CBT) – the current gold standard treatment for anxiety and depression in cancer patients. CBT focuses on reality-testing negative thoughts or core beliefs, whereas MCT targets cognitive processes (worry/rumination) rather than challenging cognitive content. For example, common concerns in cancer patients are fear of recurrence or functional limitations associated with the disease and treatment. By contrast with CBT, MCT would not challenge the content of these potentially accurate thoughts or explore their 'meaning'. Instead patients would be helped to understand the deleterious and counterproductive effects of worry and rumination, therefore enhancing motivation to suspend worry. Simultaneously, metacognitive beliefs about the uncontrollability of worry, which sustain worry, would be challenged using established MCT techniques, helping patients to suspend worry and rumination. Modifying negative metacognitive beliefs is centrally important in the S-REF model because, as long as patients believe that worry is uncontrollable, they will not attempt to control it. Therefore, in targeting cognitive processes rather than cognitive content, MCT offers a particularly close 'fit' with the needs of cancer survivors indicating potential for greater efficacy.

The evidence base for MCT is firmly established, with well over 150 empirical studies supporting the underpinning theory [19]. Metacognitive beliefs and processes have been implicated in emotional distress in diverse conditions including coronary heart disease, chronic obstructive pulmonary disease, chronic fatigue syndrome, Parkinson's disease, diabetes, and in cancer patients at all stages of the treatment trajectory [20-27]. Moreover, in terms of treatment outcomes, MCT is more effective than both wait-list control (Hedge's g=1.18) and CBT (Hedge's g=0.97) for anxiety and depression in mental health settings [28].

Translation of metacognitive theory and therapy to cancer is under way, with encouraging evidence for the explanatory and therapeutic utility of MCT in cancer. In patients with recently diagnosed breast cancer and prostate cancer, metacognitive beliefs predicted anxiety, after controlling for severity of worry and negative health beliefs [29]. In the first prospective study on the role of metacognition in breast and prostate cancer patients (n=206), metacognitive beliefs around the time of diagnosis predicted anxiety, depression and trauma symptoms 12 months later, after controlling for symptoms and cognitive beliefs at baseline [30]. We have conducted one open trial in young adult survivors of paediatric cancer (12 patients aged 18-24). MCT was highly acceptable and reduced anxiety, trauma symptoms and depression, with treatment gains maintained though to six months follow-up [31]. We are currently analysing data from a second open trial of MCT in a broader population of cancer survivors; preliminary data corroborate previous findings and indicate the effectiveness and acceptability of MCT to adult cancer survivors.

Given the growing evidence of its efficacy across a range of emotional disorders in mental health settings and potential efficacy in a range of cancer survivors, it is important now to further develop MCT for the broader cancer population, to evaluate its efficacy, and to determine the most effective form of delivery.

5. STUDY OBJECTIVES

The primary aim is to conduct an open trial of group MCT for cancer survivors experiencing clinically significant emotional distress.

Specific objectives are to:

1. Obtain evidence of potential efficacy of group MCT in alleviating emotional distress in cancer survivors.

2. Assess the acceptability of the intervention to patients.

3. Obtain data to inform sample size calculations for a subsequent Phase II trial

4. Determine whether group MCT for cancer survivors can be easily delivered in routine clinical practice

6. STUDY DESIGN

6.1. Design

An open trial (single arm, single site) with follow-up at 3 and 6 months.

6.2. Study Measures

All outcome measures will be administered pre-treatment, post treatment and at 3- and 6-months follow-up.

(i) *Primary outcome:*

Hospital Anxiety Depression Scale (HADS) [32] total was chosen because: 1) it has proven construct validity for measuring emotional distress in cancer patients [33], and 2) it is the optimal measure of general distress for evaluating treatment efficacy in heterogeneous cancer populations [34].

(ii) *Secondary outcomes*:

Cognitive Attentional Syndrome-1 [19] will assess rumination and worry. A single measure rather than separate measures of rumination and worry will reduce patient burden.

Fear of Cancer Recurrence Inventory [35] will assess fear of recurrence

Impact of Events Scale-Revised (IES-R) [36] will assess trauma related symptoms.

Metacognitions Questionnaire-30 (MCQ-30) [37] will assess metacognitive beliefs.

Functional Assessment of Cancer Therapy-General (FACT-G) [38], will assess cancer-specific quality of life.

(iii) Sample characteristics and potential covariates: We will record socio-demographic characteristics, time and nature of cancer diagnosis, psychiatric history, and previous and current treatment including any psychotropic medication.

6.3. Intervention

Group metacognitive therapy (MCT) is a brief psychological intervention designed to be delivered in small groups of 4-8 patients over a course of six, 90 minute sessions conducted on a weekly basis. Treatment is based on a manualised protocol [19] and is structured in the following way. In session 1, idiosyncratic case formulations based on the generic metacognitive model are developed for each participant. Socialization proceeds by Socratic Questioning to help the patients understand that worry/rumination and unhelpful coping strategies are maintaining emotional distress. Patients are then introduced to, and practice, the Spatial Attention Control Exercise (SPACE), which is designed to illustrate patients' control over their attention. The remaining sessions focus on modifying negative beliefs about uncontrollability of rumination/worry through training in detached mindfulness (DM) and in rumination/worry postponement. Patients will be helped to differentiate spontaneously occurring negative thoughts and images (e.g. "I'm useless", "What if my cancer returns?", or an image of the intensive care unit) from subsequent perseverative thinking (rumination and/or worry). They will be encouraged to regularly practice SPACE to demonstrate their control over their attention and thoughts. Rumination/worry postponement will be used as an experiment to challenge the metacognitive belief that perseverative thinking is uncontrollable. The final session addresses relapse prevention and involves modifying remaining use of the 'cognitive attentional syndrome', reviewing residual conviction in positive and negative beliefs and consolidating and strengthening alternative ways of responding to negative thoughts. All treatment sessions will be audio-recorded; individual supervision will be weekly by PF, who has internationally recognised expertise in developing and evaluating psychological therapies, particularly MCT and led the first evaluation of MCT for adolescent survivors of cancer [31]. MCT will be provided by MGC and AB, both of whom hold clinical contracts with RLBUHT and work clinically within the Clinical Health Psychology Service (CHPS).

6.4. Study Duration

Each participant will be involved in the study for 9 months and the total duration of the study will be 15 months.

7. PARTICPANT ENTRY

The participants will be consecutive consenting patients referred to the CHPS. At their initial assessment appointment with a psychologist, patients routinely complete the Hospital and Anxiety Depression Scale (HADS) [32]. Those patients scoring ≥15 on the HADS total scale and deemed potentially eligible[1] for the study will be given a GMAC invitation and Patient Information Sheet (PIS). The CHPS psychologist will explain the study and seek expression of interest. If the patient is interested, the psychologist will record their details on a form (name, address, gender, contact telephone number and HADS score). This form will be securely passed onto MGC and AB, who will enter these details into a secure database. MGC/AB will contact patients by telephone one week later to confirm that they have read and understood the PIS, answer any questions, and confirm interest and eligibility. Patients will be informed of the dates and times of the next available group MCT sessions. Prior to attendance at the first group session, MGC and AB will seek informed written consent for participation and will administer the baseline questionnaires. The original, signed copy of the consent form(s) will be retained by the University of Liverpool, a copy given to the patient and a copy placed in the patient's clinical notes.

7.1. Inclusion Criteria

(i) Cancer diagnosis at least 6 months previously
(ii) Scoring >15 on the full scale score of the Hospital Anxiety and Depression Scale (HADS) [32]
(iii) Sufficient understanding of English to consent and engage in therapy
(iv) Stable on, or free from, psychotropic medication
(v) Minimum of 18 years old

7.2. Exclusion Criteria

(i) History of psychotic disorder, learning disability, or organic mental disorder
(ii) Risk of self-harm or suicide warranting immediate intervention
(iii) In palliative phase of treatment
(iv) Being considered for risk-reducing or reconstructive surgery within 1 year
(v) Concurrent psychological intervention for emotional distress
(vi) Cognitive impairment precluding informed consent or participation
(vii) Undergoing acute medical treatment (e.g. chemotherapy, radiotherapy)
(viii) Current drug/alcohol abuse

7.3 Ineligible and non-recruited participants

Patients who are ineligible or decline to participate at any point will continue to be offered usual care by CHPS.

7.4 Discontinuation of participants

Participants may withdraw from the trial at their own request at any time, without any consequences to themselves, their healthcare or their ability to take part in future research.

[1] All psychologists within the Clinical Health Psychology Service will be fully briefed about the study and its eligibility criteria by members of the research team prior to study commencement. To aid determination of eligibility during assessment appointments, each psychologist within the service will also be provided with a checklist of inclusion and exclusion criteria, against which they can screen patients during their assessment appointment. Please see enclosure.

8. ADVERSE EVENTS

8.1. Definitions

Adverse Event (AE): An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or study-specific intervention and which does not necessarily have a causal relationship with this intervention. Note: An AE may therefore be any unfavourable and unintended sign (including abnormal findings), symptom or disease concurrently associated with the use of the study intervention, regardless of any relation to the intervention.

8.2. Reporting Procedures

The Clinical Psychologists delivering group MCT will monitor patient's mental and physical health in accordance with good clinical practice guidelines. Any adverse events identified as likely to be caused by the intervention during the period of recruitment or intervention on the GMAC study will be recorded at the study site using a AEs/SAE record form which will be completed by the health professionals. The study CI, Dr Peter Fisher will be informed and information inputted onto a secure database. The CI will also assess whether the nature of the event suggests that it is likely to have been induced as a result of the study intervention or processes.

One hypothesised adverse event which could occur due to the study intervention is as follows:

- Lowered mood and suicidality – a patient could become lower in mood or suicidal as a result of discussing their current health status.

Our proposed intervention does not withhold or significantly alter patient's usual medical care. The group MCT intervention is designed to improve patient's mood. However it is acknowledged that thinking or talking about distress can worsen mood or anxieties for some patients although this effect is rare and usually transient and is no more likely to occur with group MCT than with any other form of psychological treatment. However, in the event that patients feel more distressed following the intervention these patients will have access to continuing assessment and treatment by the CHPS.

The time period for detecting and recording AEs and SAEs in participants will be from the point of study inclusion until the end of the intervention.

9. STATISTICS AND DATA ANALYSIS

9.1. Sample size and feasibility

The study will require 40 patients to be recruited, allowing for attrition of 33% from baseline to 6-month follow-up to leave a sample of 27 (see power calculation). The CHPS receives approximately 400 new referrals annually. In a recently completed open trial of MCT hosted within the CHPS, approximately half of all referrals fulfilled eligibility criteria. Approximately 50% of eligible patients declined to participate. If we assume a more conservative 25% take-up, this will provide 50 patients, i.e. 25% more than needed.

To date, we have completed two MCT training groups. To determine the feasibility of the proposed study, we followed the methodology outlined above. Six out of nine patients (i.e. 66%) were considered treatment completers (i.e. they attended the first and last sessions, and at least two of the four interim sessions offered to them). Reasons for non-completion included disengagement (n = 1), work commitments (n = 1) and change in personal circumstances (n = 1). These preliminary data indicate that the proposed attrition rate outlined above is feasible for this patient group.

9.2 Power calculation

The primary indicator of efficacy will be change in HADS total between pre-treatment and 6-months follow up. In a recently completed open trial of MCT, the estimated between-patient standard deviation was approximately 7. As this is based on a small number of patients (n=20), a between-patient standard deviation of 12 will be used. No information on within-patient standard deviation is available so the between-patient standard deviation is used as a conservative measure. A trial with 95% power to detect a reduction in HADS score of 8 points, which is the minimum reliable difference we seek to obtain between baseline and 6 months follow up, requires 24 patients (one-sided alpha = 0.01). To account for clustering by group we will increase the sample size by a factor of 1.10 (1+ (average cluster size-1)) x intra-class correlation coefficient), therefore the required sample size will be 27.

9.3 Analysis Plan

Descriptive analysis will explore the acceptability of group MCT by examining the number of eligible participants who took up the offer of intervention and the retention rate. Analysis will test treatment effects across time (baseline, post-treatment, and 6-month follow-up) using repeated measure analysis of variance. Main effects will be followed by Bonferroni corrected pairwise comparisons for each outcome. Within-group effect size (Hedges' g) will be calculated for ITT and completer samples and will be used to estimate the required sample size for a full randomised trial. Clinical significance of treatment effects will be assessed using the Jacobson method [39] to establish whether participants could be considered recovered as a result of treatment. This method allocates each patient to one of four possible outcomes: (1) reliable deterioration; (2) no change; (3) reliable improvement; and (4) recovered. The first three outcomes are derived solely from a reliable change index (RCI) which compares treatment outcomes to normative data from non-clinical samples to determine whether the magnitude of change is statistically significant. To be classified as 'recovered', patients need to demonstrate both a reliable change and a score that falls below the established clinical cut-off. Therefore patients will classified as 'recovered' where post-treatment HADS total <13, RCI will be 8 based on normative data from a large non-clinical sample [40].

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1. Ethical Approval

This study will be subject to NHS Research Ethics Approval and Health Research Authority (HRA) approval. The study will be submitted to the Royal Liverpool and Broadgreen University Hospital for Confirmation of Capacity and Capability. This study will not be initiated before the protocol, informed consent forms and participant information sheets have received approval/ favourable Research Ethics Approval and HRA approval. Should a protocol amendment be made that requires Research Ethics Committee (REC) approval, the changes in the protocol will not be implemented until the amendment and revised informed consent forms and participant and (if appropriate) have been reviewed and received favourable REC and HRA opinion. The Chief Investigator will have a copy of the HRA approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

10.2. Sponsorship and Indemnity

The University of Liverpool will act as Sponsor for this study. Delegated responsibilities will be assigned to the Royal Liverpool and Broadgreen NHS Trust which is taking part in this study. The University of Liverpool holds indemnity and insurance cover with Marsh UK LTD, which apply to this study.

10.3. Participant Information and Informed Consent

The patient's consent to participate in the study will be obtained after a full explanation of the study has been given and the patient has been given sufficient time to discuss participation in the study with friends and family. A contact number will be given to the patient should they wish to discuss any aspect of the study.

The right of the patient to refuse to participate in the study without giving reasons must be respected. Similarly, the patient must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

10.4. Participant Confidentiality and Data Protection

All information collected during this study will be kept confidential in accordance with NHS Data Protection guidelines. Identifying information will be anonymised. Confidentiality will only be breached if a participant discloses information which may indicate harm to themselves or others. We will take every opportunity to discuss any possible breaches of confidentiality patients prior to informing any appropriate agencies e.g. oncology staff, GP or A&E services.

Participants will be allocated a study identity code number by the study team for use on all study documents and the electronic database. The study team will make a separate confidential database for the participants name, date of birth and study identity code to permit identification of participants enrolled in the study e.g. for follow-up. All other information will be anonymised. All study documents (including participant's written consent forms) which are to be held at the participating centre will be held in strictest confidence.

Data will only be available through restricted, shared areas on the secure University of Liverpool computer systems (password and username secured). Participants will be informed of this on the participant information sheet and will be asked to consent to this at the time of consent to the study. All paper forms shall be filled in using black or blue ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

All member of staff involved with the study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Statistical analysis will be directed and supervised by Dr Peter Fisher. No information which may allow identification of individual participants will be included in publications or dissemination activities.

NHS patient data collected within RLBUHT will follow the standard operating procedure which states all information involving NHS patients, interventional or observational should be retained for a minimum of 10 years after completion of the study in a secure storage area with limited access. The University of Liverpool will arrange appropriate storage and archiving of data.

10.5. Protocol Amendments

Any changes in research activity will be reviewed and approved by the Chief Investigator (CI) and submitted in writing to the appropriate REC and local research site for approval prior to being included in an amended protocol.

10.6. Audit

The study may be subject to inspection and audit by the University of Liverpool under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

10.7 *Funding*

This study is unfunded.

11. STUDY MANAGEMENT

The day to day management of the study will be coordinated through a study management team, which will be chaired by PF and will include the co-investigators (MGC; AB; AW). PF will supervise the clinical psychologists providing MCT (MGC; AB).

12. END OF STUDY

The study end date is deemed to be the date of the last data capture. The CI has the right at any time to terminate the study for clinical or administrative reasons. The end of the study will be reported to the REC within the required timeframe if the study is terminated prematurely. Investigators will inform patients of any premature termination of the study and ensure that the appropriate follow up is arranged for all involved. Following the end of the study a summary report of the study will be provided to the REC within the required timeframe

13. ARCHIVING

Documents will be stored by the University of Liverpool and at CHPS in a way that will facilitate the management of the study, audit and inspection. Study documentation will be securely stored and retained for a period of 10 years for possible audit or inspection. Access to these documents will be restricted to authorised persons.

14. PUBLICATION POLICY

The main findings will be published in open-access journals and secondary data will be reported in other peer reviewed journals.

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