Phase II Randomised Controlled Trial of 3MDR for Treatment Resistant Post Traumatic Stress Disorder (PTSD) in Military Veterans

Protocol – Version 6
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1. Background and Rationale

The majority of those who serve in the UK armed forces do well after they leave[1]. Military service, particularly combat experience, can, however, have adverse effects and these are of concern for the armed forces, other government departments, service personnel and veterans, and their families. Successive UK governments have been accused of neglecting veterans, with reports that homelessness[2], imprisonment[3], unemployment and alcoholism are the fate of many[4]. It is estimated that around 4% of British military veterans meet the criteria for PTSD[5]. The financial and social impact is considerable[6]. Many veterans with PTSD struggle in their transition to civilian and family life, are unable to work and in receipt of long-term incapacity benefits[7].

Only a limited proportion of people with mental health problems seek professional help. Among military populations this is true of veterans as well as serving personnel, though to a lesser extent[8]. Engaging veterans in mental health treatment programmes remains challenging due to stigma, perceived weakness in acknowledging emotional difficulties, and military macho cultures[9]. Most studies have found that informal sources of help such as family, friends and clergy are preferred[10, 11, 12].

In military and veteran populations, recent trials of the first-line trauma-focused interventions Cognitive Processing Therapy (CPT) and Prolonged Exposure (PE) have shown clinically meaningful improvements for many patients with PTSD[13, 14]. However, non-response rates have been high, many patients continue to have symptoms, and trauma-focused interventions only show marginally superior results compared with active control conditions[15]. There is a need for improvement in existing PTSD treatments and for the development and testing of novel treatments[16], including more intense interventions for those who have not responded to less intense interventions.

The Welsh Veterans' NHS service was founded in 2010 to assess and treat military veterans with mental health difficulties. It received over 542 referrals in 2014-2015, an increase of 152 on the previous year. Sixty four percent of those assessed were diagnosed with PTSD and, by the end of the year, 139 had begun out-patient psychological treatment

Veterans' NHS Wales uses evidence-based trauma focused psychological therapy to treat PTSD, including CPT, PE and Eye Movement Desensitisation Reprocessing therapy[17], as part of an integrated multiagency approach to improve general health and functioning[18]. Despite this, and consistent with the literature described above, outcomes following trauma-focused psychological therapy have been modest, with high levels of attrition and only limited improvements in PTSD symptoms. Those veterans with treatment resistant PTSD continue to report difficulties due to their symptoms, affecting their occupational, interpersonal and social functioning. Approximately 60% of veterans with PTSD engage in a course of out-patient treatment with Veterans' NHS Wales. Many, however, drop out of therapy early or report only a modest improvement on their overall symptoms (approximately a third describe significant improvements in their symptomatology, a third modest improvements and a third no improvement or drop out of therapy).

There is, therefore, an urgent need to identify effective treatments for military veterans who do not respond to, or are unable to engage with, current first line treatments. Modular motion-assisted memory desensitisation and reconsolidation (3MDR)[19] is a new treatment that aims to reduce cognitive avoidance and augment engagement with therapy. 3MDR is based on known therapeutic principles of virtual reality exposure therapy[20] and eye

movement desensitization and reprocessing (EMDR)[21], embedded in a novel context in which the patient walks on a treadmill whilst interacting with a series of self-selected images that are displayed on a large screen. Exposure by virtual reality, enhanced with walking, music and high affect pictures, eliminates cognitive avoidance during exposure and promotes presence. This is an important distinction between 3MDR and traditional trauma focused techniques which are sedentary; patients learn how to move through their avoidance by, literally, approaching their traumatic memories.

In 3MDR, a dual task is used to facilitate desensitisation and reconsolidation of the emotional content of the traumatic event that is captured on a deployment related photograph. This is congruent with working memory theory, which has been used to explain the therapeutic mechanism of EMDR[22]. According to this theory, working memory has limited resources; if a dual task (for example, following a specific object with your eyes) uses some of those resources, less memory will be available for other memory processes, which in turn will make the recollection of memories less vivid and less affect-laden. In 3MDR, the dual task is different from most EMDR treatments. Instead of making eye movements (or alternative bilateral stimulation) alone, numbers need to be called out whilst the patient is also walking, thereby optimally taxing working memory.

Preliminary results from research conducted by the originators of 3MDR in the Netherlands regarding the efficacy of 3MDR in veterans with treatment resistant, combat-related PTSD are promising. A pilot study[19] showed a decrease in PTSD symptoms and no dropout, with the two participants positive about the treatment. No adverse effects were reported and the time is now right to explore the potential efficacy of 3MDR further.

2. Aims and Objectives

The main aim of the proposed research is to determine whether 3MDR is able to reduce traumatic stress symptoms in British military veterans with treatment-resistant, combat-related PTSD, to a significantly greater degree than a waiting list.

The main objective is to answer the following research questions:

1. For British military veterans with treatment-resistant, operationally-related PTSD, does 3MDR reduce symptoms of PTSD as measured by the CAPS5 to a significantly greater degree than a waiting list? (Main research question)

2. For British military veterans with treatment-resistant, combat-related PTSD, what is the impact of 3MDR on quality of life, functioning, symptoms of depression, symptoms of anxiety, insomnia, alcohol and illicit substance use and perceived social support? (Secondary outcomes)

3. Is 3MDR acceptable to British military veterans with treatment-resistant, combat-related PTSD and those delivering the intervention as measured by qualitative semi-structured interviews?

4. What is the likely effect size of 3MDR?

5. What factors may impact efficacy and successful roll-out of 3MDR for treatment-resistant, combat-related PTSD, if 3MDR is shown to be efficacious? (Mechanism and process evaluation)

6. What is the behavioural response of the 3MDR sessions in terms of stress and cognitive processing during different dual task phases and how can this guide us in optimal design of the intervention and a Phase III definitive trial? (Mechanism evaluation)

7. Can examination of the integrity of the study protocol, trial recruitment rate, self-report outcome measures, clinician administered outcome measures, randomisation procedure, treatment integrity and acceptability enhance decision making in planning a Phase III definitive trial?

8. Is a Phase III definitive RCT indicated and feasible?

3. Methods

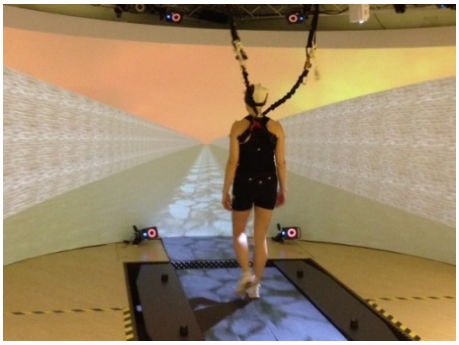
3.1 Study design

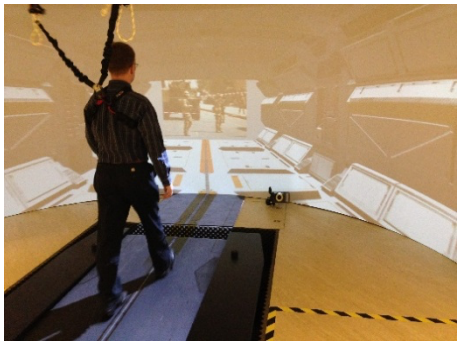
The study will be an exploratory single blind randomised parallel group controlled trial with nested mechanistic and process evaluation to assess fidelity, adherence and factors that influence outcome.

3.2 Setting

The School of Healthcare Sciences at Cardiff University has a Motek GRAIL system, which will be used for implementation of this study. The Motek Gait Real-time Analysis Interactive Lab (GRAIL) system uses an instrumented dual-belt treadmill, a motion-capture system and synchronized Virtual Reality (VR) environment, which comprises a 180° projection screen with 4 projectors and a surround sound system. The system is controlled by means of 6 computers in an integrated network using D-flow software. This is a control software suite that provides real-time data streams between many types of integrated hardware. The 3MDR module was designed to run in D-flow and therefore the intervention can be delivered comprehensively in the lab in Cardiff. The only extra equipment required is a Zephyr™ BioHarness™ 3 physiological monitor which measures multiple physiological parameters: Heart Rate (HR), Breathing Rate (BR), Temperature, Posture, and Activity Level and can be integrated with the GRAIL system through a Bluetooth-based data acquisition system. The sensor will be used for physiological status monitoring. The Motek company will install hardware and software required for this study and will provide the technical support as well as the training in the use of the system. For further reference please see:
http://www.motekmedical.com/products/grail-gait-real-time-analysis-interactive-lab/
http://www.zephyranywhere.com/products/bioharness-3

Figure 1: GRAIL system with a standard virtual environment displayed (left) and running the 3MDR protocol (right).





The GRAIL system will be able to record data continuously during each session at a high sampling rate (100 frames per second) and these data are stored as a digital file. Data recorded during a session will include information about 3MDR events such as phase transitions; repeated measurements of the score on the subjective units of disturbance (SUD) scale; physiological parameters from the sensor such as heart rate; and gait parameters from the instrumented treadmill such as walking speed and distance and ground reaction forces to calculate step width. Data will, therefore, be accessible for further analysis using Matlab software; a high-level programming environment to explore and visualise data. This is used to calculate gait parameters through the phases from the treadmill speed and ground reaction force data. Matlab will be used to create individual session profiles of the physiological (HR, BR, HR Variability)[23] and motor control (walking speed, cadence and step width variability)[24] response to the intervention through the phases and extract summary statistics to describe changes in these responses over time. Response over time through the phases of key parameters will be plotted and explored statistically using Pearson's correlation coefficients and cross-correlations[25]. Step width variability is suggested to provide insight into changes in cognitive demand and improvements in performance. Cognitive demand is expected to be greatest in the early stage of treatment when the emotional response is high (as demonstrated by HR variability) and during multi-task phases of the protocol.

3.3 Sample size

Although a standard power calculation is not appropriate for a Phase II exploratory trial we believe it appropriate to use a power calculation based on a previous study of TFCBT for PTSD[26] to inform our sample size and ensure it is adequate. The calculation suggests that for an 80% chance of detecting a mean 15 point difference on the Clinician Administered PTSD Scale between 3MDR and waiting list at a 0.05 confidence level assuming a standard deviation of 15.18, 17 subjects in each group will be needed. Allowing for a conservative estimate of a 20-25% drop out, an extra 4 subjects will be recruited to each arm representing a total proposed sample size of 42.

For the qualitative study, the sample size will be guided by preliminary analysis and constant comparison (comparing and contrasting themes from other interviews) during each data collection phase, until the research team is satisfied that there is data saturation and no new themes which are important to the research question arise[27]. However, it is helpful to have a guide to sample size for study planning. Based on previous research[28], we propose that interviews will be conducted with around 10 participants, purposively sampled, and all five therapists.

3.4 Inclusion/exclusion criteria

Wide eligibility criteria will be used to ensure good external validity. Given the high rate of co-morbidity of PTSD and other conditions such as depression and substance misuse, individuals with co-morbidity will be included if they satisfy the other inclusion/exclusion criteria and PTSD is considered the primary diagnosis. This is consistent with NICE guidance and will result in a pragmatic trial.

Inclusion criteria will be: Aged 18 or over; Informed consent; Meet DSM5[29] criteria for combat-related PTSD; treatment-resistance defined as prior receipt of a trauma focused psychological treatment without loss of PTSD diagnosis.

Exclusion criteria will be: Psychosis; DSM5 severe major depressive episode; Substance dependence; Change in psychotropic medication within one month; Suicidal intent; Inability to walk at a normal pace for 30-45 minutes on a treadmill.

3.5 Recruitment and consent

British military veterans and soliders that are currently serving in the armed forces who attend the Veterans' NHS Wales Service and/or Cardiff and Vale Traumatic Stress Service who are considered to be likely to fulfil the inclusion criteria for the study will be asked by a clinician involved in their care if they are willing for their details to be passed on to the research team. Veterans who have been discharged from the clinic will be sent a letter from the clinician inviting them to take part in the study and if the veteran is interested to contact the clinician. If clinicians don't hear back from the veteran within two weeks, they can follow up with a second letter but not a telephone call and if the veteran doesn't respond they will not be contacted again.
The clinical team will do all the necessary checks before sending out letters in order to avoid distress to the veteran and or their families.

The research team will contact potential participants and provide them with an information sheet about the study. They will be given at least 24 hours to consider this before being asked if they require further information or any questions answered. If potential participants wish to proceed, arrangements will be made to enter them into the study.

Informed consent will always be obtained before the initial assessment proceeds. The member of the research team who is conducting the assessment will check that the participant has read and understood the information sheet. They will check –

a. whether the participant has any questions arising from the information sheet and answer any that do arise.
b. that the participant understands their participation is voluntary and that they are free to withdraw at any time without giving any reason, without their medical care or legal rights being affected.
c. whether the participant agrees to their GP being informed of their participation in the study.
d. whether the participant agrees to take part in the study.

The member of the research team who is conducting the assessment will then request the participant to complete the consent form.

All work will be conducted in full compliance with the Data Protection Act.

3.6 Outcome measures

The primary outcome will be symptoms of PTSD measured by the Clinician Administered PTSD Scale for DSM5 (CAPS5)[30]. The CAPS5 is a 29 item structured interview for assessing PTSD diagnostic status and symptom severity. The CAPS is the gold standard in PTSD assessment and can be used to make a current (past month) or lifetime diagnosis of PTSD or to assess symptoms over the past week. Items correspond to the DSM5 criteria for PTSD. Previous versions of the CAPS have excellent reliability and excellent convergent and discriminant validity, diagnostic utility, and sensitivity to clinical change[31].

Secondary outcome measures will include self-report measures that are routinely collected by Increasing Access to Psychological Therapies (IAPT) services in England and veteran services at present (PTSD Checklist[32] for traumatic stress; Work and Social Adjustment Scale[33] for quality of life/functional impairment; Patient Health Questionnaire-9[34] (PHQ-9) for depression; General Anxiety Disorder-7[35] (GAD-7) for anxiety; AUDIT-O[36] for alcohol use) and changes in sleep will be measured by the insomnia severity index (ISI)[37]. In addition, the Multidimensional Scale for Perceived Social Support[38] will be used to assess perceived social support. Changes in health related quality of life will be measured by the EQ5D-5L[39].

PTSD Checklist (PCL-5) - The PCL-5 is a 20 item scale which aims to index self reported symptoms of PTSD as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The PCL -5 is based on an earlier version of the PCL, which is widely used and well validated[32].

The Work and Social Adjustment Scale (WSAS) is a self-report measure, which assesses the impact of a person's mental health difficulties on their ability to function in terms of work, home management, social leisure, private leisure and personal or family relationships. The WSAS is the outcome measure of choice for evaluating improvement in functioning in IAPT services. The WSAS has been demonstrated to show good reliability and validity and is sensitive to change[33].

The PHQ-9 is a widely used reliable and well-validated brief self-report measure of depression[34]. It is the outcome measure of choice for evaluating improvement in depressive symptoms in IAPT services[40].

The GAD-7 is a widely used reliable and well-validated brief self-report measure of anxiety[35]. It is the outcome measure of choice for evaluating improvement in anxiety symptoms in IAPT services[41].

The AUDIT-O[36] contains 10 multiple choice questions on quantity and frequency of alcohol consumption, drinking behaviour and alcohol-related problems or reactions over the preceding 3 months.

The Insomnia Severity Index (ISI) is a widely used 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. It has been shown to be reliable and valid in terms of detecting insomnia and in measuring treatment response in clinical patients[37].

The Multidimensional Scale for Perceived Social Support (MSPSS) is a widely used12-item Likert scale measuring the subjective assessment of adequacy of social support from family, friends, and partners[41]. The reliability, validity, and factor structure of the MSPSS have been demonstrated with a number of populations[38,42,43].

The EQ5D-5L[39] is a widely used instrument in health economic analysis and recognised by NICE as an appropriate measure for health related quality of life. The questionnaire provides a simple descriptive profile, which translates to a single utility score for health status. The first part of the instrument identifies the extent of perceived problems – across five levels - in each of five life dimensions: mobility; self-care; usual activities; pain and discomfort; and anxiety and depression. The responses to each of the five questions are used to generate a utility score for self-rated health status on a 0-1 scale, where 0 represents the worst possible health state and 1 the best possible health state. The second part is a visual analogue scale, which allows the responder to indicate their current health status on a 0-100 scale.

An experienced researcher blind to randomisation will conduct all assessments. The initial assessment will ensure that the inclusion criteria are satisfied. Demographic and other background data will be collected along with completion of all the outcome measures. Participants will then be asked to monitor their symptoms for two weeks. The baseline assessment of all the outcome measures will occur after this; those who continue to fulfil the inclusion criteria will be randomised to one of the two groups: 3MDR or wait list for 12 weeks followed by 3MDR. Follow up will occur 12 and 26 weeks after randomisation. This will involve re-administration of all the outcome measures. At 26 weeks participants will be asked to participate in semi-structured interviews to elicit their experience and views of the programme. Progress will be monitored with the PCL-5, PHQ-9 and GAD-7 at each treatment session.

3.7 Intervention

The 3MDR therapy will be delivered weekly over nine weeks (two weeks preparation, six weeks 3MDR and one concluding session) by experienced psychological therapists, trained in 3MDR and supervised by its originators, who work with Veterans' NHS Wales and Cardiff University. The waiting list group will receive no intervention for 12 weeks post-randomisation and then receive 3MDR over nine weeks.

Prior to the 3MDR sessions, participants will be asked to select and bring 12 pictures that evoke memories of the traumatic event. These may be from their deployment but may also be taken from the Internet. The therapist will guide the participant to limit avoidance during picture selection. Supported by the therapist, the pictures will be arranged according to psychological distress (SUD) score and theme. For each session, a maximum of 7 out of the 12 pictures can be used and will be selected based on the SUD score or a particular theme. Pictures may need to be repeated during a session, particularly if the associated SUD score is high, reducing the number of pictures used for some sessions. Participants will also choose two pieces of music. The first for the warm-up walk will aim to take the participant back to the time of deployment, e.g. music played a lot during this period. The second, for the warm-down, will aim to bring the participant back to the here and now. This is likely to be a recent piece of music.

Participants will be introduced to the intervention and research setup, and the general procedures that will be used will be explained. They will be asked to change into sport wear, or equivalent, and to wear a sensor on the chest, secured with a comfortable belt. A safety harness will be donned and this will be connected to the ceiling to guarantee safety during treadmill walking. After initial familiarisation with the GRAIL system, participants will be asked to walk on the treadmill using "self-paced mode" in a neutral environment. In this mode, preferred walking speed will be determined whereby participants familiarise themselves with the system which makes automatic adjustments. Once preferred walking

speed is established, participants will be asked to walk for 1 minute whilst their HR and step width variability is recorded as a baseline determination of their physiological and motor response. Participants will then be requested to walk for 1 minute whilst carrying out a standard dual-task: the Stroop test. The Stroop test involves naming the colour of a sequence of words; the words themselves represent a colour but do not match the colour the words are displayed in. This incompatibility results in increased demands for cognitive processing. HR and step width variability will be recorded during the test and, on completion, participants will give a score on the SUD scale.

In the 3MDR sessions an introduction phase, intervention phase, and final phase will be presented. The participant's preferred walking speed will be used to start the introduction phase. After each transition the operator, on request, can adjust the walking speed. During the introduction phase, the participant will see a pathway ahead and their deployment music will begin to play while verbal guidance prepares the participant for the intervention phase. The participant will then enter the first tunnel to approach the first picture whilst being guided by instructions on what to do at each stage. As soon as the participant sees their chosen picture, a literal description of this will be requested with a brief account of the related memories and feelings. The therapist will repeat every feeling so the operator can enter these on the screen. When the participant confirms there are no more new feelings to be identified, the dual task will be started: a red ball will move across the screen from left to right as a distracter stimulus. Whilst focussing on the feelings written on the screen, the participant will be asked to track the ball and call out the numbers displayed on the ball. After a while, the distracter stimulus is removed and a SUD score is requested and recorded. The next tunnel and picture will then appear. After the last picture, the final phase will begin with music, assisting the return to the here and now, and positive feedback about what has been achieved to conclude the session.

After the 3MDR session, the operator will remove the safety harness from the participant. A therapist-led discussion with the participant will then occur in a private room; open questions will be used to elicit how the session was for the participant and to discuss the meaning of the re-experiencing to the participant in this setting. The therapist will also ensure the participant is completely returned to the here and now and aim to enable the participant to attach a positive meaning to the 3MDR session. Participants will be asked to write their experiences and reflections down following each session in a diary format.

Every 3MDR session will be recorded and a report summarising the behavioural response to the intervention will be produced. HR and step width variability will permit exploration of the stress response and the cognitive demand during the different phases of each 3MDR session. This will also inform the process evaluation component of the study which is discussed below.

3.8 Study Timetable

Subsequent to ethical approval, it is intended that the proposed research will take place over 15 months, with the aim of completing data collection within 12 months. The remaining three months will be used for data analysis and the preparation of results for dissemination. The Gantt chart below shows the key tasks that will be undertaken and the approximate timescales.

Month:	3	6	12	18	24
	Recruitment, treatment and assessments of participants				
			Qualitative and Quantitative Analysis		

Gaining ethical and other approvals. Recruiting and training staff		Dissemination activities

4. Planned Analyses

Quantitative outcome data - Continuous intention to treat data will be analysed, to ensure all randomised participants are considered, by comparing means using ANCOVA with baseline scores as co-variates. Categorical data will be analysed using relative risk analyses. Regression analyses will also be performed to examine which factors are associated with a positive or negative outcome. All analyses will be performed at the end of the data collection period using SPSS or STATA software for statistical analysis.

3MDR session data - Results from the 3MDR quantitative analysis of how the experience affects the physiology and movement behaviour through the cycle of a 3MDR session will be compared with the subjective reports of disturbance (SUD scores) within sessions and with the qualitative data exploring the experience of the intervention. Review meetings involving the research team will be held to discuss the quantitative results from selected individuals after they have completed their intervention to inform topics to be explored in the qualitative interviews. The primary outcome measures along with individual diary notes made by participants during the intervention, to document their experience of it in real time, will also be used. The lab research assistant, therapists and statistical analyst will be kept blind to the details of these meetings to avoid introducing bias to the study. Post analysis of the overall results, further meetings will be held to compare the quantitative and qualitative results, achieve integration of the data and generate a deeper understanding of the experience of the intervention, its acceptability, and the ultimate effect it had on the subjects. These final meetings will be held with the complete research group to ensure that data are optimally compared.

Qualitative data - Semi-structured interviews will be audio-recorded and transcribed verbatim. Transcripts, data from the questionnaires and structured observations during the 3MDR sessions will be imported into QSR NVivo 10[44] software for Computer Aided Qualitative Data Analysis (CAQDA). Relevant themes will be identified using a process of Inductive Thematic Analysis, as described by Braun and Clarke[45]. Emerging themes will be tested for validity through a variety of recognised techniques, including discussion with the research team to ensure comprehensiveness, triangulation to compare results from different sources, and exploration of the participants' underlying reasoning and elements within the data that appeared to contradict the emerging themes (deviant case analysis). Data integration will be ensured by means of regular research team meetings.

5. Dissemination of Findings

If 3MDR is shown to be efficacious, the proposed research will benefit (1) *Military veterans with treatment resistant PTSD* by providing a new treatment option; (2) *clinical services* by providing a means of treating PTSD that has not responded to standard psychological treatment; and (3) *the families and friends of veterans, public and society* more generally by minimising the burden of PTSD. To achieve the goals of this study, adequate dissemination, exploitation and communication is a critical requirement.

Dissemination will start at the beginning of the project; early activities will include finalising a strategic dissemination plan, promotion and awareness raising. Findings will be disseminated widely using a variety of tailored methods targeting specific audiences. A summary report of trial results written in lay-language will be sent to study participants and other key stakeholders. The report will also be displayed and available at venues used for recruitment. We will hold informal participant-centred meetings to present the results orally and allow time for questions and clarification. We will also hold an open conference. We will send reports of trial results to NHS commissioners and disseminate the findings publicly through news items on the Veterans' NHS Wales and Forces in Mind Trust (FiMT) websites.

We will publicise the trial through social and local media not for recruitment but to inform the public that the trial is running. We have experience of successfully engaging local and national media and will work with the National Centre for Mental Health (NCMH) communications team to formulate strategies for press releases and the dissemination of findings through newspaper articles, television and radio features. Study outcomes will be presented to the academic community at national and international conferences by means of oral presentation, poster presentation, and interactive workshops. We will target conferences likely to be attended by large numbers of therapists and managers working in IAPT and other primary and secondary care NHS psychological treatment services across the UK. We will also disseminate to the third sector and other services likely to deal with individuals with PTSD who could potentially benefit from treatment (e.g. the UK veteran mental health charity Combat Stress). We aim to publish the results in high impact open-access, peer reviewed journals such as the British Journal of Psychiatry. We expect at least two high impact peer reviewed publications and three conference presentations.

All the dissemination activities will be supported by project specific web pages on the NCMH website. The web pages will include descriptions of the project, its progress and achievements in plain and scientific language, press releases and announcements of and registration for conferences.

The proposed research will increase our understanding of the potential benefits and advantages of 3MDR as a potential treatment option for treatment resistant PTSD in military veterans. It will assist NHS commissioners in determining whether or not rolling out 3MDR would result in service improvement.

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