Identifying Factors Associated with 3MDR Treatment Outcome; A Phase II Randomised Controlled Trial of Virtual Reality and Exposure Therapy for Military Veterans with PTSD

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Summary

Trauma-focused (TF) psychological therapy has been shown to be the most effective treatment for Post Traumatic Stress Disorder (PTSD). However, a growing number of military veterans have been shown to either not respond or engage with existing treatment, which has resulted in a diagnosis of Treatment-Resistant (TR) PTSD. There is an urgent need to develop more effective and personalised treatments for military veterans with TR-PTSD. As with existing treatment, not all individuals will respond or engage with novel treatments, therefore identifying factors associated with treatment outcome is essential for improving its effectiveness.

The aim of this thesis is to explore factors associated with treatment outcome. A systematic review of factors associated with psychological treatment outcome for PTSD was conducted to identify the most commonly reported factors. The factors identified in the systematic review were applied to explore factors associated with outcome in a Randomised Controlled Trial (RCT) of Multi-Modular Motion assisted Memory Desensitization and Reconsolidation (3MDR). 3MDR is a novel intervention that combines virtual reality, movement, personalised music and photographs to expose the participant to their trauma. The RCT included 40 military veterans with TR-PTSD to identify whether 3MDR was more effective than waiting list control.

A quantitative analysis involved multiple regression analysis to examine whether any of the factors identified in the systematic review were associated with the 3MDR treatment outcome, as measured by a reduction in Clinician-Administered Post Traumatic Stress Disorder Scale for Diagnostic and Statistical Manual of Mental Disorders 5th edition scores. Qualitative thematic analysis was conducted on semi-structured interviews with 11 military veterans from the 3MDR sample to explore any novel factors associated with treatment outcome. No clear picture with respect to factors associated with outcome emerged and the results indicate that further research is required to examine factors associated with treatment outcome in a larger sample of routinely collected data before any clinical recommendation can be made.

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Publications

Papers resulting from work within the current thesis:

- **Barawi, K. S**.et al. 2020. A systematic review of factors associated with outcome of psychological treatments for post-traumatic stress disorder. European Journal of Psychotraumatology 11(1), article number: 1774240. (10.1080/20008198.2020.1774240)

Related papers to which I have contributed:

- Bisson, J. I., van Deursen, R., Hannigan, B., Kitchiner, N., **Barawi, K**.et al. 2020. Randomised controlled trial of multi-modular motion-assisted memory desensitisation and reconsolidation (3MDR) for male military veterans with treatment-resistant post-traumatic stress disorder. Acta Psychiatrica Scandinavica 142(2), pp. 141-151. (10.1111/acps.13200)

- Van Deursen, R., Hannigan, B., **Barawi, K**.et al. The psychophysiological response during post-traumatic stress disorder treatment with modular motion-assisted memory desensitisation and reconsolidation (3MDR)" (in prep)

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  Hannigan, B., Van Deursen, R., **Barawi, K**.et al. Factors associated with the outcomes of a novel virtual reality therapy for military veterans with PTSD: theory development and mixed methods analysis (in prep)

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List of Abbreviations

3MDR - Multi-Modular Motion-Assisted Memory Desensitisation and Reconsolidation
ACE - Adverse Childhood Experiences
ACT - Acceptance and Commitment Therapy
ANCOVA - Analysis of Covariance
APA - American Psychiatric Association
APD - Avoidance Personality Disorder
ASD - Acute Stress Disorder
ATM - Attentional Bias Modification
AUDIT - Alcohol Use Disorders Identification Test
BEP - Brief Eclectic Psychotherapy
BPD - Borderline Personality Disorder
BR - Breathing Rate
CAPS - Clinician-Administered Post Traumatic Stress Disorder Scale
CAREN - Computer Assisted Rehabilitation Environment
CBT - Cognitive Behavioural Therapy
CBT-TF - Cognitive Behavioural Therapy with a Trauma Focus
CDI - Composite International Diagnostic Interview
CET - Control Exposure Therapy
CONSORT - Consolidated Standards of Reporting Trials
COPE - Concurrent treatment of PTSD
COREQ - Consolidated criteria for reporting qualitative research
CPT - Cognitive Processing Therapy
CPTSD - Complex Post Traumatic Stress Disorder
CR - Cognitive Restructuring
CR - Conditioned Response
CRF - Case Report Form
CS - Conditioned Stimulus
CT - Cognitive Therapy
CT-TF - Cognitive Therapy with a Trauma Focus
DET - Dialogical Exposure Therapy
DoD - Department of Defense
DSM - Diagnostic and Statistical Manual
DSO - Disturbances in Self-Organization
DVLA - Driver and Vehicle Licensing Agency
E + CR - Imaginal Exposure + Cognitive Restructuring
EA - Experimental Avoidance
EFT - Emotional Freedom Technique
EFT - Emotional Freedom Therapy
EMDR - Eye Movement Desensitisation and Reprocessing
EQ-5D-5L - EuroQol five-dimensional descriptive system
ET - Exposure Therapy
FIMT - Forces In Mind Trust
GAD - Generalised Anxiety Disorder
GAF - Global Assessment of Functioning
GCSE - General Certificate of Secondary Education
GDPR - General Data Protection Regulation

GP - General Practitioner
HADS-A - Hospital Anxiety and Depression Scale – Anxiety
HADS-D - Hospital Anxiety and Depression Scale - Depression
HMD - Head Mounted Display
HR - Heart Rate
I-CBT - Internet-based Cognitive Behavioural Therapy
ICD - International Classification of Diseases
IED - Improvised Explosive Device
IET - Imaginal Exposure Therapy
IPD - Individual Participant Data
I-Psychoeducation - Internet-based Psychoeducation
IPT - Interpersonal Psychotherapy
IQ - Intelligence Quotient
I-SC - Internet-based Supportive Counselling
ISI - Insomnia Severity Index
ISTSS - International Society for Traumatic Stress Studies
LEC - Life Events Checklist
MBSR - Mindfulness-Based Stress Reduction
MC/RA - Medical Checks/Repeated Assessments
MDD - Major Depressive Disorder
MDMA - Methylenedioxymethamphetamine
MICE - Multiple Imputation by Chained Equations
MRC - Medical Research Council
MSPSS - Multidimensional Scale for Perceived Social Support
mTBI - mild Traumatic Brain Injury
NCMH - National Centre for Mental Health
NET - Narrative Exposure Therapy
NHMRC - National Health and Medical Research Council
NHS - National Health Service
NICE - National Institute for Health and Clinical Excellence
NTF - Non-Trauma Focussed
OCPD - Obsessive-Compulsive Personality Disorder
OEI - Observed and Experimental Integration
ONS - Office of National Service
PCBMT - Primary Care Brief Mindfulness Training
PCGT - Present Centred Group Therapy,
PCL-5 - Post Traumatic Stress Disorder Checklist for Diagnostic and Statistical Manual-5
PCL-C - Post Traumatic Stress Disorder Checklist for Civilians
PCL-M - Post Traumatic Stress Disorder Checklist for Military
PCT - Present Centred Therapy
PDD - Paranoid Personality Disorder
PE - Prolonged Exposure
PHQ - Patient Health Questionnaire
PI - Principal Investigator
PTSD - Post Traumatic Stress Disorder
QDA - Qualitative Data Analysis
RA - Research Assistant
RAF - Royal Air Force
RCT - Randomised Control Trial
REC - Research Ethics Committee

REM - Rapid Eye Movement
RT - Relaxation Therapy
RTM - Reconsolidation of Traumatic Memories
SAT - Structured Approach Therapy
SC - Supportive Counselling
SD - Standard Deviation
SEM - Structural Equation Modelling
SIT - Stress Inoculation Training
SPSS - Statistical Package for the Social Sciences
SSRI - Selective Serotonin Reuptake Inhibitors
STAIR + SupC - Skills Training in Affective and Interpersonal Regulation + Supportive Counselling
STAIR - Skills Training in Affective and Interpersonal Regulation
SUD – Substance Use Disorder
SUD - Subjective Units of Distress Scale
TARGET - Trauma Affect Regulation Guide for Education and Therapy
TAU - Treatment as Usual
TF - Trauma Focussed
TR - Treatment-Resistant
TSPD - Transient Situational Personality Disorders
TSRG - Traumatic Stress Research Group
UHW - University Hospital of Wales
UK - United Kingdom
USA - United States of America
VA - Veterans Health Administration
VNHSW - Veterans National Health Service Wales
VR - Virtual Reality
VRET - Virtual Reality Exposure Therapy
VSSP - Visuospatial Sketchpad
WET - Written Exposure Therapy
WHO - World Health Organisation
WL - Waiting List
WMM - Working Memory Model
WSAS - Work and Social Adjustment Scale

Chapter 1: Introduction

1.1 Background

Post Traumatic Stress Disorder (PTSD) is a psychological condition, with a lifetime prevalence of 8.3% and past-year prevalence of 4.7% within the general population [1], with rates of 6% to 17% in a systematic review of military samples [2]. PTSD can result from experiencing or witnessing traumatic events that involve actual or threatened death, serious injury, or sexual violence to the person or others [3]. Psychological therapy is considered the most effective form of treatment for PTSD; however, some people do not respond or engage with treatment, which causes further difficulties [4]. Among military populations, this is true of veterans and serving personnel to a lesser extent [5]. In this first chapter, I shall delve into the history of PTSD, including the evolution of its diagnosis and definition, with an emphasis on their contemporary epidemiology, before discussing treatments for PTSD and clinical guidelines for exploring treatment options with a focus on veterans' pathways to support.

1.2 A brief history of PTSD in the military

The history of PTSD is inextricably linked to the history and evolution of warfare. Pinel (1745-1826) first described psychological distress and somatic symptoms after exposure to war and conflict [6]. During the first European wars from the late 18th Century, soldiers were reported to sink into a stupor after exposure to combat, despite no physical harm. Mental health deterioration related to combat was later referred to as "vent du Boulet" syndrome, translated as 'wind of the ball,' that is, fear and anguish at the sight and sound of war [7]. A different perspective was acquired during the American civil war (1861-1865), which marked the beginning of the understanding that traumatic events during combat can lead to psychological problems. Jacob Mendez Da Costa (1833–1900), who researched the psychological consequences of war, coined the term 'Da Costa's Syndrome' to describe the difficulties experienced by exposure to combat. In 1871, Da Costa Syndrome included symptoms seen during a time of turmoil, similar to symptoms of PTSD today [8].

Further cases of soldiers experiencing war-related syndromes promoted speculation amongst

clinicians regarding the cause of patients' problems [9]. In 1917, medical officer Charles Myers invented the term "shell shock" to describe soldiers' distress following physical trauma. However, Myers emphasised the psychological burden of war by identifying symptoms such as fatigue, tremor, and utter exhaustion, which resulted in over 200,000 soldiers leaving the military due to 'shell shock' [10]. However, other clinicians suggested that psychological problems resulted from micro-structural lesions in the brain caused by carbon monoxide [11].

During World War II, cases of psychological trauma became more prevalent [12]. Nevertheless, the problems experienced by soldiers remained unrecognised by the government, who attributed distress to personal characteristics rather than distress related to war [12]. However, the lack of recognition could have been due to the screening which focused on innate susceptibilities to mental health problems rather than factors relating to the traumatic exposure. It was not until the 1960s that war-related psychiatric difficulties were thoroughly investigated [13]. The National Vietnam Veterans Readjustment Study [10] [14] used the clinician-administered Vietnam experience scale to investigate psychiatric conditions in veterans and found several symptoms related to psychological trauma [15].

In the 1890s, both Pierre Janet and Sigmund Freud independently considered that psychological trauma caused hysteria [16] and Jean-Martin Charcot, a 19th-century French Neurologist, considered the condition to be treatable via hypnosis [17]. As psychological research progressed, so did the role of mental health in combat-related cases [18], particularly in Britain and America [6]. Screening tests were developed to ensure that only psychologically stable individuals enter war [19]; however, high psychological traumatisation cases after conflict remained [6]. Changes in understanding the causes of the psychological consequences of trauma resulted in differential diagnosis and treatments [20].

1.3 The evolution of PTSD as a diagnosis

The early literature contained detailed descriptions of the development of PTSD. Early researchers in PTSD concluded that combat was the leading cause of the disorder. Further research identified that symptoms associated with PTSD were not restricted to combat. From the 3rd edition of the Diagnostic and Statistical Manual of psychiatry (DSM III) to the 5th

edition of the DSM [3], the diagnosis of PTSD has evolved, particularly in understanding the role of traumatic stressor characteristics from other stressful events.

1.3.1 DSM-I to the present day

The first edition of the DSM, published in 1952 [21], highlighted psychiatric problems that overlap and are related to extreme stress. However, symptoms have been added to the criteria over the years to reflect how individuals respond to traumatic events. DSM-I introduced 'Gross Stress Reaction' in a section on Transient Situational Personality Disorders (TSPD), which described the response to 'severe physical demands or extreme emotional stress', including exposure to combat. The diagnosis was considered a short-term solution, as it was agreed that it did not contain the symptoms of the 'normal' person who has experienced extreme distress. In 1968, DSM-II removed Gross Stress Reaction and added a diagnosis called 'Adjustment Reaction of Adult Life in a Transient Situational Disturbance' [22]. The disturbance was defined as an intense reaction to extreme stress, which results in psychological problems despite no history of mental health conditions. The examples of extreme stress listed were pregnancy or combat exposure. The diagnosis of PTSD was introduced in 1980 by the American Psychiatric Association (APA) in DSM III [22] and into the International Classification of Diseases 10th edition in 1992 (ICD-10: [23]) and then later revised in 2018 [24]. In previous editions, a diagnosis "Gross Stress Reaction" captured traumatic reactions; alternatively, such symptoms were assigned to "Situational Disturbances of Adult Life" [25]. Thus, once the DSM-III development neatly proposed PTSD, it summarised and conceptualised the symptoms into one category.

1.3.2 Definitions and diagnostic criteria of PTSD in DSM-5 & ICD-11

The descriptions of PTSD were continuously refined in subsequent classifications. There are currently two sets of diagnostic criteria for PTSD: DSM-5 [3] and ICD-11:[24] prepared by the World Health Organization (WHO). DSM-5 contained significant changes to the diagnosis of PTSD compared to the previous edition [3]. The diagnosis has retained most symptoms of feeling distressed by reminders of the traumatic event and avoiding people and places that trigger any thoughts or memories related to the trauma. The changes included moving PTSD from an anxiety-related disorder to a trauma- and stress-related disorder. The

new diagnosis includes four additional symptoms: 1) negative cognition, which includes negative beliefs about oneself and the world 2) negative emotions, which include guilt, shame, fear and horror for oneself and the world 3) risky behaviour that includes reckless behaviour, which has the potential to harm to oneself or others and 4) dissociative reactions to reminders of the traumatic event.

DSM-5 described PTSD as a psychological condition caused by extreme distress and actual or threat to life, serious injury or sexual violence [3]. DSM-5 criteria include twenty symptoms contained within four categories; 1) persistent re-experiencing of the traumatic event through flashbacks and nightmares, 2) avoidance of trauma or related reminders, 3) negative alterations in cognition mood, and 4) hyper-arousal and alertness. DSM-5 requires that symptoms continue for at least one month. The ICD-11 prepared by WHO proposes an alternative approach to diagnosing PTSD. ICD-11 includes three symptom clusters: 1) re-experiencing of the trauma in the here and now, 2) avoidance of traumatic reminders, and 3) a persistent sense of current threat presented through hypervigilance and arousal. Symptoms must be present for at least one month and cause clinically significant distress and functional impairment.

1.3.3 Complex Post Traumatic Stress Disorder (CPTSD)

Complex PTSD (CPTSD) is a diagnosis recognised in ICD-11 in 2018 [26]. This new diagnosis describes six clusters of symptoms that can arise from a single traumatic stressor but are often associated with sustained or multiple traumatic exposures [25, 27]. ICD-11 proposes three additional symptom clusters for CPTSD, defined as 'Disturbances of Self-Organisation' (DSO). These three additional clusters aim to describe the more pervasive symptoms seen in complex cases of PTSD. The symptoms are 1) affective dysregulation, 2) negative self-concept and 3) disturbed relationships.

1.3.4 PTSD vs CPTSD

It is crucial to differentiate between PTSD and CPTSD diagnoses, particularly as different diagnoses may lead to different treatment options and outcomes [28]. PTSD symptoms must first be present to consider a differential diagnosis of CPTSD [29]. According to ICD-11,

PTSD symptoms are limited to fear-based reactions, such as avoidance and hypervigilance, to the actual traumatic event or reminders of the experience [3] [24]. Additionally, CPTSD manifests in heightened emotional reactivity accompanied by deep and pervasive feelings across various contexts, regardless of the proximity of traumatic reminders. Difficulties in regulating emotion may increase sensitivity or a lack of emotions and lapses into dissociative states. Individuals can engage in self-destructive or reckless behaviour with frequent violent outbursts. The self-concept cluster in CPTSD refers to negative thoughts that focus on feelings of low self-worth, guilt and shame, e.g., not working and providing for loved ones or overcoming the problems and preventing others' suffering. Problems in relationships can manifest differently but often relate to difficulties feeling close to others or developing trusting relationships.

Exposure to a traumatic event is considered an essential diagnostic criterion for PTSD and CPTSD [3, 24]. Exposure to multiple forms of trauma, particularly childhood trauma, has been associated with the increased risk of CPTSD [25]. In contrast, single-incident traumatic exposure, mainly occurring later in development, has been shown to elevate the risk of PTSD [25]. Trauma history is essential to highlight, potentially leading to different treatment and contributing to treatment outcome [26]. The main differences between the two PTSD classification systems (DSM-5 and ICD-11) and CPTSD (ICD-11) and the additional symptoms of DSO are highlighted in bold below (Table 1-1).

Table 1-1 Symptom profile for DSM-5 and ICD-11 PTSD and ICD-11 CPTSD criteria according to DSM-5 and ICD-11. Differences are highlighted in bold.

DSM-5 PTSD	ICD-11 PTSD	ICD-11 CPTSD
Re-experiencing: Flashbacks, Nightmares	Re-experiencing: Flashbacks, Nightmares	Re-experiencing: Flashbacks, Nightmares
Avoidance: Thoughts, people, place activities	Avoidance: Thoughts, people, place activities	Avoidance: Thoughts, people, place activities

Sense of threat: Hypervigilance, startle	Sense of threat; Hypervigilance, startle	Sense of threat; Hypervigilance, startle
Negative cognition: negative thoughts about oneself and the world.	Duration of at least one month	Duration of more than one month.
Duration of at least one month	Clinically significant distress/impairment	Clinically significant distress/impairment
Clinically significant distress/impairment		Emotion dysregulation: deep and pervasive feelings of anger and shame.
Duration of at least one month		Negative self-concept: worthless, guilt
Clinically significant distress/impairment		Interpersonal problems: feel disconnected and unable to sustain close relationships.

DSM-5 (The 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5: American Psychiatric Association [12], ICD-11 (11th revision to the International Classification of Diseases (ICD-11: [13]), PTSD (Post Traumatic Stress Disorder), CPTSD (Complex Post Traumatic Stress Disorder).

1.3.5 CPTSD vs Borderline Personality Disorder (BPD)

It is essential to highlight the validity of CPTSD as empirically distinct from Borderline Personality Disorder (BPD), which leads to different treatment implications. BPD is defined in DSM-5 (2013) by a pervasive pattern of emotional dysregulation, instability in personal relationships and self-image from a young age, precipitating traumatic victimisation in various contexts [25]. The critical difference between BPD and CPTSD is that BPD symptoms come from an inconsistent self-concept, whilst external triggers provoke CPTSD symptoms. CPTSD requires the presence of a stressor and the core symptoms of PTSD to be diagnosed. Therefore, treatment guidance suggests focusing on the enhancement of trauma memories [26]. BPD does not require a traumatic stressor or PTSD symptoms. The key features are fear of abandonment, unstable identity, and the inability to form close and sustained relationships [30]. Furthermore, research has also demonstrated that an estimated 50% of people with a diagnosis of BPD engage in frequent attempt to self-harm, compared to

significantly fewer people with PTSD and CPTSD [25]. However, adverse experiences, such as childhood physical and sexual abuse, are commonly present in the life histories of individuals diagnosed with BPD [31]. Similarly, for BPD and CPTSD, the symptoms related to attachment or insecurity are distinct; for a CPTSD diagnosis, trauma is required, but this is common but not essential for BPD diagnosis [25]. Therefore, according to the research BPD and CPTSD symptoms are distinctly different with regards to their expression from one another. The only symptoms that overlap are feelings of emptiness, suggesting that the symptom is not specific to either condition [25]. Therefore, in line with ICD-11 guidelines, it is possible for CPTSD to be comorbid with BPD, and in DSM-5, for PTSD to be comorbid with BPD [25]. Therefore, despite the early debates, CPTSD is consistently considered a separate clinical diagnosis to BPD [25, 32].

1.4 Epidemiology

1.4.1 General population

The prevalence of PTSD within the general population according to DSM-IV [1] has been estimated to be between 6.4% to 6.8% across the lifetime [1]. For those within the general population who have experienced prolonged trauma or Adverse Childhood Experiences (ACE's), the prevalence of PTSD can reach up to 30% [33]. Comorbid conditions and maladaptive coping strategies such as drug and alcohol problems can also develop alongside PTSD symptoms, increasing the burden of illness for the individual [34].

1.4.2 Military veterans

The prevalence of PTSD among military veterans is often drawn from retrospective samples. A meta-analysis of 49 studies found the prevalence of PTSD to vary across different eras and combat zones due to differences in deployments, populations, countries and sample sizes [35]. Epidemiological studies of veterans have also reported a wide range of current and lifetime prevalence estimates which could be due to a longer timeframe between the traumatic event and time of recall, impacting the recall reliability of reported symptoms [35]. The variation in prevalence rates has led to debates around the true PTSD prevalence amongst military personnel. Researchers from King's College London have conducted the

most comprehensive study in the UK, examining PTSD in 8093 military veterans [36]. In 2018 the reported prevalence of probable PTSD was 6.2% (including serving personnel and veterans) and 7.4% when restricted to veterans. The prevalence of PTSD increased to 17.1% when examining veterans deployed within a combat role [2]. PTSD was found to be higher in those deployed to Iraq (12.9%) compared with those deployed to Afghanistan (7.1%) [2].

Another UK based study found the prevalence of PTSD amongst veterans was highest for deployment in Iraq (19.1%) and then Afghanistan (11.3%) and lower for other deployments (8.5%) [37, 38]. It has been suggested that veterans exposed to more extended deployments, such as those during the Afghanistan and Iraq war, are likely to experience more complex mental health problems [39]. Different studies that have examined PTSD prevalence according to DSM-IV within the military across countries, are summarised below.

Comparing prevalence rates across different periods raises questions about whether PTSD is a static construct over time. This may be a result of the different measures that were used to collect information regarding PTSD symptoms. For example, studies which used self-report measures compared to those which used clinician administered measures could result in different prevalence rates due to over or under reporting. Furthermore, as clinician administered measures are based on static constructs, self-report measures, such as PCL-5 may measure different aspects of symptoms which could also account for the differences in prevalence rates. These studies show that PTSD is a continuing mental health problem among military veterans who present with complicated psychopathology and often comorbid diagnoses that can make adequate treatment response more difficult. Table 1-2 provides a summary of studies examining the prevalence of PTSD within the military population.

Table 1-2 A summary of studies focusing on PTSD in military population – differences between studies and countries

Study	Country	Measure	% Of PTSD
Litz, Orsillo, Friedman, Ehlich, & Batres (1997) [40]	USA	PCL-M	8%

Hoge et al. (2004) [41]	USA	PCL-C	12.6%
Rona, Jones, French, Hooper, & Wessely (2004) [42]	UK	PCL-M	2.5%
Hotopf et al. (2006) [43]	UK	PCL-C	6% presented with combat PTSD and 3% presented with non-combat PTSD
Sareen et al. (2007) [44]	Canadian	CDI	2.3%.
Greenberg, Iversen, Hull, Bland & Wessely, (2008) [45]	UK	PCL-M	3.6%
Mental Health in the Australian Defence Force, (2010) [46]	Australian	CDI	8.3%
Mulligan et al. (2010) [47]	UK	PCL-C	3.4%.

Post Traumatic Stress Disorder (PTSD) PTSD Checklist-Military (PCL-M), National Centre for PTSD Checklist (PCL-C), Composite International Diagnostic Interview (CDI) – Version 3.

1.5 Comorbidity

Comorbidity can be defined as the co-occurrence of two disorders [48]. Research indicates that it is common for individuals with PTSD to have a comorbid diagnosis [49]. Comorbidity

with PTSD is associated with an increased risk of functional impairment and disability across various disorders [50], such as depression [51].

Systematic reviews have suggested that military veterans in the UK diagnosed with PTSD are more likely to experience comorbidity with depression and anxiety [51] and alcohol and drug misuse than non-veterans [50]. Comorbidity with substance misuse can worsen PTSD symptoms and can lessen treatment effectiveness [23]. Similarly, independent exposure to trauma or a previous diagnosis of depression or anxiety disorder increases the risk for PTSD once exposed to a traumatic event [52]. The self-medication hypothesis suggests high comorbidity rates with PTSD due to managing symptom experience [44]. Research by Lowe suggests that substance misuse may create short-term relief from PTSD symptoms, such as hypervigilance and arousal [53].

A meta-analysis identified Paranoid Personality Disorder (PPD), Avoidant Personality Disorder (APD), and BPD to be highly comorbid in individuals with PTSD amongst the general population [54]. Dunn et al. (2004) [51] examined Personality Disorders (PDs) in 115 male combat veterans with PTSD and depression, and 52 were diagnosed with at least one PD, with 20 diagnosed with PPD, 19 with Obsessive-Compulsive Personality Disorder (OCPD), 14 with APD and 10 with BPDs. However, as causality could not be determined, the nature of the comorbidity is yet to be understood. Some researchers have suggested that a diagnosis of PD may also impair social relationships, leading to social isolation, contributing to PTSD [55]. It is crucial to consider comorbidity in the context of treatment for PTSD, as additional difficulties could influence treatment choice and treatment outcome.

1.6 Treatment

Psychological therapies for PTSD fall into two broad categories. Trauma-Focused (TF) therapy, which concentrates on thoughts and memories related to the trauma and non-trauma focused therapy, which also aims to reduce symptoms of PTSD but not by targeting trauma-related thoughts and feelings. Cognitive Behavioural Therapy with a Trauma Focus (CBT-TF) and Eye Movement Desensitisation and Reprocessing (EMDR) are currently recommended as the treatments of choice for PTSD within the general population in the UK

[28].

1.6.1 Eye Movement Desensitisation and Reprocessing (EMDR)

Eye Movement Desensitisation and Reprocessing (EMDR) is a psychotherapy developed by Francine Shapiro and used primarily to treat PTSD [56]. The theoretical model suggests that trauma survivors experience intrusive thoughts and emotions because of the incorrect storage of the traumatic event in implicit memory [56]. EMDR therapy identifies the stored memory and processes it to form an adaptive and less intrusive memory [57]. The individual focuses on a traumatic memory while taking part in bilateral stimulation. Each aspect of the memory is targeted individually and attempts to evoke all the emotions, cognitions, and sensory stimuli associated with the traumatic memory. Following this, individuals are guided through the traumatic memory and any associated memories that cause them distress whilst receiving bilateral stimulation. This is said to facilitate the association between adaptive memory, providing an opportunity for the memory to change [57].

Although the therapy very quickly became an established technique, there was considerable criticism around the lack of sufficient theoretical evidence [58]. Critics suggested there was little research to explain the 'Eye movement' element of the treatment [59]. Researchers attempted to retrospectively explain that completing EM and recalling the traumatic memory limited the resources of the working memory capacity, as both competed for attention [60]. This, in turn, made the traumatic memories less vivid and intrusive. As the current systematic reviews of EMDR have identified that there are only a few large RCTs that show a significant decrease in PTSD symptoms after EMDR, therefore, the quality of the research remains an issue. In order to further understand the theoretical underpinning of EMDR therapy, further research is required. EMDR is recommended for treating adults with PTSD as meta-analysis data provides substantial evidence to support its effectiveness [61]. Although according to NICE guidelines, there is insufficient evidence to recommend EMDR for combat-related PTSD [28].

1.6.2 Cognitive Behavioural Therapy- Trauma Focused - (CBT-TF)

CBT was developed by psychiatrist Aaron Beck [62]. The treatment works by targeting negative thoughts and emotions that lead to distress. In PTSD, the negative thoughts stem from before, during, and after the traumatic events. For example, veterans may feel that they were responsible for their comrades death, and if they were to have done things differently, they would have survived. Other misinterpretations may be that the individual may experience perceived threats in everyday life, such as a veteran who packs an emergency bag every time they go outside in case of an explosion. In CBT-TF, the individual is encouraged to reduce behaviours and cognitive strategies that promote negative distortions, e.g., extreme precautions to prevent further trauma [63]. A systematic review of 1,923 individuals with PTSD has shown that CBT-TF had better remission rates than non-trauma focused or supportive therapies [61]. A meta-analysis found a strong evidence base for the effectiveness of CBT-TF for the treatment of PTSD [61].

1.6.2.1   Cognitive Processing Therapy (CPT)

Cognitive Processing Therapy (CPT; [64]) is a type of CBT-TF that uses elements from CBT to change an individuals' thoughts and feelings around their trauma. CPT was initially developed to treat individuals with sexual assault-related PTSD but is now used to treat PTSD to various trauma types. Information processing theory refers to how information is encoded, stored in memory, and recalled [65]. CPT suggests that faulty thinking patterns are formed after a traumatic event due to fear [66]. The therapy suggests that avoidance and intrusion symptoms result from conflict between prior negative thinking patterns and new information. The theoretical model encourages individuals to feel and not suppress the emotions associated with the trauma as a form of exposure. The model also suggests education around the cognitive components of memory retrieval to help process information related to the traumatic event [66]. Evidence from meta-analysis indicates that CPT is highly effective and has a robust clinical evidence base for treating PTSD [61].

1.6.2.2   Cognitive Therapy with a Trauma Focus (CT-TF)

Cognitive Therapy (CT) is based on a specific cognitive theory of PTSD developed by Ehlers and Clark [67]. The theory suggests that individuals with PTSD form a negative interpretation of the traumatic memory, leading to a strong negative response to traumatic

reminders. Kubany et al. (2004) [68] suggested that traumatic memories may trigger negative thoughts (e.g., guilt and shame) that can lead to distress and attempts to avoid any reminders of the traumatic event. Therefore, the goal of CT is to alter negative thoughts and feelings by identifying triggers and changing the internal narrative associated with the memory by removing the problematic behavioural and cognitive strategies. Cognitive restructuring involves developing awareness of negative internal dialogue and replacing it with rational and functioning thoughts about themselves, the world and the trauma [69-71]. A meta-analysis indicated that CT had one of the strongest evidence bases for effective psychological treatment in adults with PTSD [61].

1.6.2.3   Prolonged Exposure (PE)

Prolonged Exposure (PE) is a specific form of behavioural therapy that gradually exposes individuals to feelings and emotions related to their trauma. Keane [72] and Foa [73] were the first to develop an exposure-based treatment for individuals with PTSD. The first guide to using an exposure-based treatment for PTSD was developed by Foa & Roathbaum (1998) [74]. Exposure therapy aims for the individual to confront their traumatic memory and evoke an emotionally sensitive response. PE treatment for PTSD can be done in two ways: imaginal exposure or in vivo exposure [75]. Imaginal exposure or narrative writing involves recalling the traumatic memory by writing about it or imagining the traumatic event and describing their thoughts and feelings. The process is repeated until the traumatic memory is less distressing. In vivo exposure physically confronts the feared stimuli, which causes distress but no danger, e.g., walking in the park after being physically attacked in the same area. Repeated exposure to the traumatic stimuli will make the individual less fearful and realise that there is no longer a threat [75]. PE is among the most empirically supported treatments for PTSD [61].

1.6.3 Virtual Reality Exposure Therapy (VRET)

Virtual Reality Exposure Therapy (VRET) combines multi-sensory input into an interactive and immersive environment [77]. VRET has been used for several mental health conditions and recently for military veterans with Treatment-Resistant (TR) PTSD [78]. VRET can be used as an alternative to traditional exposure therapy and has the added benefits of promoting

the emotional processing of traumatic memory through exposure to reminders. Active engagement with personalised sensory input, reducing avoidance and facilitating engagement with traumatic stimuli [78]. The process of habituation and extinction, where the individual experiences a reduction in anxiety and fear response, results from repeated exposure to the feared stimuli. The process makes the traumatic memory less intrusive and less meaningful, which in turn reduces PTSD symptoms. Meta-analysis results suggest emerging evidence to support a single session of VRET to treat PTSD [61].

1.6.4 Other CBT-TF

Several other CBT-TF aims to address symptoms of PTSD [61]. Written Exposure Therapy (WET; [79]) is an exposure-based intervention which is a modification of Pennebaker and Bealls' [80] written disclosure procedure which Sloan and colleagues [79] [81] found to reduce PTSD symptom severity significantly, but not significantly more than a control writing condition [82]. Results from a meta-analysis suggest emerging evidence to support WET for the treatment of adults with PTSD. Narrative Exposure Therapy (NET) was first developed to target the needs of refugees who had experienced repeated traumatisation. NET is a systematic short-term approach that lasts from 4 to 10 sessions to treat several trauma types in different settings [83]. During each session, the individual is encouraged to speak about their trauma and relive the emotions attached to the traumatic event while staying in the 'here and now.' Some emerging evidence supports single session NET to treat PTSD [61]. In addition, Brief Eclectic Psychotherapy (BEP) is an eclectic therapy that adopts a cognitive and psychodynamic approach, including cognitive restructuring, and psychoeducation, in a phase-oriented approach [84, 85]. Meta-analysis results suggest there is inadequate evidence to recommend BEP for the treatment of PTSD [61]. Lastly, Emotional Freedom Technique (EFT (Church, Hawk et al., 2013)) was pioneered in 1995 and has since been manualised for clinical treatment [86]. EFT involves identifying the critical traumatic event impacting the individuals' symptoms, thoughts, beliefs, and bodily sensations. The therapy involves a combination of cognitive and exposure therapy and somatic stimulation. Meta-analysis of psychological therapy for PTSD suggests insufficient evidence to recommend EFT to treat PTSD [61].

1.6.5 Non-Trauma-Focused therapies for PTSD

1.6.5.1 Cognitive Behavioural Therapy (CBT) – non-trauma focused

CBT without a trauma focus is based on the cognitive model of mental health, initially developed by Beck [62]. The theory underlying CBT suggests an individuals' emotions are the results of perception and are maintained by cognition [87]. Beck suggested that it is not the event that causes cognitive and behavioural problems but how they perceive it [62]. The therapy, therefore, aims to change these internal thoughts, which can lead to maladaptive behaviour. Meta-analysis results indicate support for CBT without a trauma focus and emerging evidence to support group and individual CBT without a trauma focus, although not as strong as CBT-TF for adults with PTSD [61].

1.6.5.2 Present Centred Therapy (PCT)

Present-Centred Therapy (PCT) was initially developed as a treatment comparator for CBT-TF and has been adapted to treat PTSD [88]. Components of PCT include (1) psychoeducation on PTSD to help patients understand how symptoms are disrupting their day-to-day functioning, (2) effective strategies for approaching day-to-day challenges, and (3) homework outside the session by which individuals can monitor stressors and practice new problem-solving skills. Meta-analysis results suggest PCT showed a positive effect compared to waiting list treatment as usual and some evidence to support PCT in a group. However, the evidence for PCT was not considered as strong compared to EMDR or CBT-TF to treat PTSD [61].

1.6.5.3 Interpersonal Psychotherapy

Interpersonal Psychotherapy is a treatment developed by Gerald Klerman and Myrna Weissman that concentrates on improving the individuals' social and interpersonal functioning [89]. The therapy is based on Harry Stark Sullivan and John Bowlby's research on the psychosocial effects of depression [90]. IPT for PTSD helps the individual understand rather than avoid feelings and build skills to manage social interaction and build trust. Developing methods to help reconnect an individual to their surrounding may help facilitate

social interactions and reduce PTSD. One of the main advantages of IPT for people with PTSD is that, unlike other therapies, it does not depend on exposure to the traumatic event. Instead, it focuses on increasing interpersonal functioning and social networks [89, 91], commonly negatively affected by PTSD (APA, 2000), and essential targets for change. There is insufficient evidence to support Interpersonal Psychotherapy to treat PTSD [61].

1.6.5.4 Relaxation Training

Relaxation training involves the use of relaxation exercises to help reduce anxiety and distress. Marks et al. (1998) [69] found that relaxation therapy was less effective than exposure therapy at reducing PTSD symptoms. Relaxation training may reduce hyperarousal symptoms, which makes the individual less distressed [92, 93]. Relaxation training may create the right environment to expose individuals to trauma-related stimuli. There is insufficient evidence to support relaxation training to treat PTSD [61].

1.6.6 Pharmacotherapy

Pharmacotherapy and psychological therapy help treat PTSD [94], although pharmacotherapy to a lesser extent than psychological therapy [95]. Effective medications include selective serotonin reuptake inhibitors (SSRI) and venlafaxine [28]. Antidepressants such as paroxetine, sertraline, and mirtazapine are used to treat depression and anxiety symptoms and help sleep and concentration in individuals with PTSD [95]. Although psychotherapeutic interventions are the first advised form of treatment, the patients' preference and stability are considered for pharmacotherapies provided in most clinical settings and require less therapeutic input. An emerging new approach to treating PTSD is a combination of psychological and pharmacological treatment [95]. Treatment such as MDMA assisted therapy is receiving emerging evidence and is likely to be one of many new treatments that combine the two disciplines.

1.6.7 Treatment of PTSD with comorbidity

The evidence suggests that individuals with PTSD and a comorbid condition, such as depression or anxiety, can present with additional impairments, making treatment for PTSD

less effective [96, 97]. A recent systematic review and meta-analysis on the effects of psychological and pharmacotherapy on CPTSD and comorbidity show that CBT-TF is the most effective at reducing PTSD and comorbid depression [98]. The review also highlighted that a phased approach that included stabilisation, skills training and psychoeducation, was more successful at reducing CPTSD [98]. However, it may be that unless comorbid conditions are tackled first or integrated treatment for the comorbidity is provided, that individuals with comorbidity are likely to face poorer outcomes than individuals with PTSD alone [96]. A recent systematic review examined early psychological interventions following recent trauma within samples of participants with comorbid diagnosis. The review found that from the 14 studies of participants with Acute Stress Disorder (ASD) or PTSD, 6 of the studies had comorbidities with PTSD, which included ASD, depression and anxiety. The 6 studies reported to have responded better to CBT-TF than waiting list control group and supportive counselling [99]. A significant difference was also found favouring CT compared to waiting list control [99]. Continued research is required to identify factors associated with treatment outcomes in individuals with CPTSD and PTSD with comorbidities to better match individuals with the most effective form of therapy.

1.6.8 Treatment for military veterans

According to the NICE guidelines, TF psychotherapy such as CBT-TF and EMDR is recommended to treat PTSD in civilians. However, only CBT-TF is recommended to treat military veterans but not EMDR due to the lack of evidence to support effective treatment outcomes [28]. Kitchiner et al. [100] conducted a systematic review of psychological therapies for PTSD in serving and ex-serving military personal. They found individual CBT-TF to be the most effective treatment for PTSD compared to usual care, and individual CBT-TF was shown to be more effective than group CBT-TF [100]. The results support the NICE guidelines as EMDR was ineffective compared to the waiting list/usual care [28], suggesting that EMDR should not be a recommended first-line treatment for PTSD in military veterans. Further research is required to examine its efficacy. Despite these results, EMDR is still being used worldwide to treat veterans with PTSD [100]. One of the review's main disadvantages was the small sample sizes and lack of power of the included studies, which may have resulted in a lack of significant difference between therapies [100]. However, the review followed rigorous Cochrane guidelines and methodology.

1.6.9 Veterans Support and Care

The National Health Service (NHS) in the UK is responsible for providing military veterans with health care [28]. Research suggests that TF psychological therapy is likely to benefit a significant group of these veterans if they seek the help available [100]. However, the research suggests several barriers to seeking support, resulting in underutilisation of these services [41], with only 50% of veterans seeking help for mental health difficulties [41, 101]. Access to treatment often entails long waiting lists [41], and those with a long-term diagnosis of PTSD are likely to experience low quality of life [101] and difficulties developing and maintaining close relationships [137]. Stigma is a recognised factor that prevents veterans from seeking PTSD and negative attitudes about mental health services [101, 102]. Research suggests potential recovery may jeopardise veterans' secondary gains, such as housing and income, which may discourage engagement in treatment [101]. Therefore, it is essential to build on existing research and identify further barriers that prevent veterans from seeking help for PTSD to improve care pathways. Knowledge of barriers to accessing support can help develop interventions aimed at specific difficulties found in the veteran with a diagnosis of PTSD.

1.7 Clinical guidelines

Clinical practice guidelines are developed to guide clinicians on the most suitable treatment method for their patients [103]. Guidelines are used across the world by clinicians, academics, and governmental bodies. Table 1-3 summarises the key clinical guidelines.

Table 1-3 Clinical Practice Guidelines for Posttraumatic Stress Disorder

Name of Guidelines	Abbreviation	Reference
1. National Institute for Health and Care Excellence [28].	NICE	(http://www.nice.org.uk/Guidance/CG26)

2. The International Society for Traumatic Stress Studies [104].	ISTSS	(https://istss.org/home)
3. Veteran Affairs, in collaboration with the Department of Defense (2004)	V.A./DoD	(http://www.healthquality.va.gov/Post Traumatic Stress Disorder PTSD.asp)
4. American Psychiatric Association (2004)	APA	(http://www.psychiatryonline.com/pracGuide/pracGuideTopic 11.aspx)
5. The Australian National Health and Medical Research Council (2020).	NHMRC	(https://www.phoenixaustralia.org/australian-guidelines-for-ptsd/)

National Institute for Health and Clinical Excellence (NICE), The International Society for Traumatic Stress Studies (ISTSS), V.A./DoD = Veterans Affairs/Department of Defence (V.A./DoD), American Psychiatric Association (APA), National Health and Medical Research Council. Guidelines Australian Centre (NHMRC).

As stated above, the NICE guidelines recommend CBT-TF and EMDR as a first-line treatment for PTSD for non-combat related trauma. Similar to the NICE guidelines, the International Society of Traumatic Stress Studies (ISTSS) guidelines published in 2018 [105] and updated in 2010 [75] recommend TF psychological therapies for the treatment of PTSD and present supporting evidence from systematic reviews. The NICE guidelines suggest insufficient evidence to recommend EMDR for military veterans, while ISTSS does not make any specific recommendation for military or combat-related trauma [28]. APA also suggest that EMDR and CBT-TF are effective therapies for the treatment of PTSD. The fact that mostly psychologists are used to establish the APA guidelines may explain discrepancies between these guidelines and others which rely more heavily on the input of a multidisciplinary team [21]. Unlike the other guidelines, the NHMRC guidelines recommend EMDR and CBT but not with a trauma focus as the most effective therapy for PTSD [106]. The NHMRC suggests providing psychological first aid immediately after the traumatic event. The VA/DoD [107] guidelines suggest TF psychological therapies for PTSD. However, they differ from the other guidelines, namely NICE, due to the recommendation of

EMDR as a first-line treatment for veterans with PTSD. All guidelines suggest that if the individual does not engage or respond to psychological therapies, pharmacotherapy is recommended to stabilise PTSD symptoms.

The main differences in the recommendations across the guidelines include a) the use of medication, b) the choice of psychotherapy for individuals with PTSD, namely whether EMDR is appropriate for veterans, and c) the level of research evidence obtained before a recommendation is provided. It is essential to recognise a significant overlap between recommendations despite distinct differences between the different guidelines. These include a) all guidelines recommend psychological therapy as the first-line treatment for PTSD and b) recognise that medication benefits from providing relief and stabilising symptoms. CBT-TF is the recommended first-line treatment for PTSD in the UK, with insufficient evidence to support non-trauma focused psychological therapies or medication in isolation.

1.8 Summary

PTSD is a debilitating psychological condition [108]. The recognition and treatment of PTSD have changed over time [6]. Serving military personnel and veterans represent a population at risk of experiencing multiple traumatic events during exposure to combat [108]. According to NICE guidelines, psychological interventions are regarded as a first-line treatment for PTSD [28]. Of the wide variety of psychotherapies available, CBT-TF and EMDR are considered to have the strongest evidence for reducing the symptoms of PTSD but not for military veterans. Research suggests that approximately two-thirds of veterans retain symptoms or PTSD diagnosis after treatment [94]. However, there is little information regarding the factors associated with veterans doing better or worse in psychological treatment for PTSD. Therefore, more effective treatment is needed for veterans who do not respond or engage with first-line psychological treatment, and it is essential to know what factors are associated with treatment outcomes to inform future research and clinical practice. In order to gain a better understanding of how and why current treatments are not affective for military veterans, further research is required to examine the variables that may influence outcome. Below is a conceptual framework to explain the current treatments, possible factors to consider in treatment and desired outcomes.

Figure 1-1 Conceptual Framework

PTSD treatment
characteristics
Trauma Focussed Cognitive
Behavioural treatment
Exposure based interventions

Demographic characteristics
Age
Gender
Education level
Employment status
Homework adherence

Clinical characteristics
PTSD symptom severity
Time since trauma
Comorbidities with other
conditions

**Desired PTSD treatment
characteristics**
Significant reduction in
symptoms
Responsiveness
Personalised healthcare
Engagement
Sense of wellbeing

Chapter 2: Aims and objectives

2.1 Aim

To examine factors associated with the outcome of Multi-Motion Assisted Memory Desensitisation and Reconsolidation Therapy (3MDR) for Military Veterans TR-PTSD.

2.2 Objectives

To conduct a systematic review of factors associated with the outcome of psychological treatments for PTSD.

To explore factors associated with military veterans doing better or worse in a Randomised Controlled Trial (RCT) of 3MDR treatment, as measured by a loss of diagnosis or a significant change in Clinician-Administered Post Traumatic Stress Scale for Diagnostic Statistical Manual 5th Edition (CAPS-5) scores. Multiple linear regression analysis will be used to test factors associated with treatment outcomes.

To explore factors associated with military veterans doing better or worse in an RCT of 3MDR treatment, as derived from qualitative semi-structured interviews. An Inductive Thematic analysis will be used to explore participants' experiences and perspectives within and between cases.

Chapter 3: A systematic review of factors associated with the outcome of psychological treatments for Post-Traumatic Stress Disorder (PTSD)

3.1 Background

It is essential to understand the factors associated with better and worse treatment outcomes to improve the effectiveness of psychological therapies for PTSD [109, 110]. While psychological therapies perform reasonably well for many patients, recent estimates suggest that up to 50% of people with PTSD who engage in treatment fail to respond sufficiently [111]. Furthermore, 10%–20% of individuals from the general population and 20-40% of military veterans exposed to trauma experience PTSD symptoms that persist and are associated with impairment despite treatment [112, 113]. It is unclear why treatments work more or less well for different people with PTSD, and there is an urgent need to accurately identify factors that moderate treatment outcome in PTSD.

Enhancing understanding of factors associated with treatment outcome is important for several reasons. First, this knowledge can help determine treatment choice, mainly because not all patients respond to first-line psychological interventions [114]. Second, increased knowledge may lead to insight into the fundamental processes underlying treatment and facilitate adaptations or the development of new approaches that improve outcomes. Third, clinicians will be enabled to adjust current treatment delivery and planning to reduce inadequate response. Understanding factors associated with treatment outcome will help researchers and clinicians better match people to effective treatment while reducing the risk of side effects [114].

3.1.1 Treatment response

A wealth of clinical research suggests that military veterans do not respond to first-line psychological intervention for PTSD [94]. Several studies have suggested factors associated with poor treatment outcomes in psychological therapies for PTSD, such as symptom severity and comorbidity with other disorders [115]. Furthermore, research suggests that those with a comorbid diagnosis have a higher risk of inadequate treatment response than those without

comorbidity [116, 117]. It has been suggested that veterans take a long time to seek help, and therefore symptoms can worsen and increase the risk of developing maladaptive coping strategies, which can make engagement in therapy difficult and increase the likelihood of poor treatment outcome [118].

A longitudinal study examined the trajectory of PTSD of 1885 UK military veterans at four-time points over 14 years. It used the PTSD checklist – Civilian version (PCL-C) to examine treatment outcomes [119]. The research found that 90.2% of the sample did not develop mental health problems throughout the follow-up period. However, 9.8% of the sample had PTSD; 4.1% had initially shown a high PCL score but improved after treatment, while 5.7% had the opposite, initially having low scores but deteriorating throughout follow-up. The youngest participants and those within combat roles were more likely to be associated with the deteriorating group [15]. Both groups were associated with childhood adversity, antisocial behaviour, substance misuse, and a long time since leaving service, compared to those in the resilient group [120][15]. Therefore, the results suggest that further research is necessary to understand what factors are associated with treatment outcome. This review aimed to a) undertake the first comprehensive systematic review of factors associated with poor treatment outcomes in RCTs of psychological treatments for individuals with PTSD, and b) use a narrative synthesis to develop a description of common factors associated with outcome.

3.2 Method

The protocol for this systematic review was published via PROSPERO [121]. This was a systematic review of RCTs. The standards for the conduct of Cochrane Intervention Reviews (MECIR) [122] were implemented. A narrative synthesis was conducted following the 'Guidance on the Conduct of Narrative Synthesis in Systematic Reviews' [123]. The work described in this chapter has been published in the European Journal of Psychotraumatology [124].

3.2.1 Selection criteria

The review included RCTs of psychological therapies aimed at the reduction of PTSD symptoms in comparison with a control group or other psychological therapies. To be included in the narrative synthesis, data needed to be available regarding factors associated

with treatment outcome. There was no restriction on the type of analysis used to consider this association. Published studies in English of adults aged 18 or over were considered. Participants were required to be diagnosed with PTSD for at least three months. Diagnosis of PTSD was determined by clinical diagnosis or a clinician-administered PTSD measure. Comorbidity was allowed as long as PTSD was the primary diagnosis; this led to the exclusion of studies that solely focused on comorbid PTSD and Substance Use Disorder (SUD) populations.

3.2.2 Search method for identification of studies

This systematic review and narrative synthesis were undertaken alongside reviewing the efficacy of psychological therapies for PTSD to update The International Society for Traumatic Stress Studies (ISTSS) treatment guidelines [104]. The Cochrane Collaboration searched to update a previously published Cochrane review with the same inclusion criteria [125]. This search generated a group of RCTs related to the psychological treatment of PTSD in adults. Data on factors associated with treatment outcome were extracted from these papers.

3.2.3 Data extraction and management

Data based on study characteristics and treatment outcome were extracted by one reviewer using a pre-designed data extraction spreadsheet. The review's outcome measures were both diagnostic status and magnitude of change over time, measured by reducing the severity of PTSD symptoms at the end of treatment using a standardised measure. When possible, clinician-rated measures were included in the narrative review (e.g., CAPS) [126]. If a clinical administered measure was not used or reported, self-report measured were included (e.g., PTSD Checklist for DSM-5 (PCL-5)) [127]. Study authors were contacted to obtain missing data and if any clarification was required.

Information on the following variables that had previously been identified within the literature to be associated with treatment outcome in PTSD, anxiety, and depression were extracted:1) age; 2) gender; 3) ethnicity; 4) marital status; 5) employment status; 6) university education; 7) history of psychological intervention; 8) current use of psychotropic medication; 9) type of trauma; 10) time since trauma; 11) time of onset of symptoms after

trauma; 12) duration of trauma, and 13) the number of traumatic events. This list was not intended to be exhaustive, and information on other factors considered was extracted if present.

3.2.4 Data synthesis

The a priori intention was to undertake a meta-analysis. However, there was limited data reported in the studies identified by this review, and, when collected, the data was inconsistent in terms of measures used and time points. Therefore, it was decided to undertake a narrative synthesis as opposed to a meta-analysis to synthesise the data in as meaningful a manner as possible. Information on factors associated with treatment outcome was tabulated. Factors were coded as either a) not reported (the factor was not reported in the paper); b) no association (the factor was reported to have no bearing on treatment outcome); c) significant increase (the factor was associated with a significant increase in PTSD symptom severity or diagnostic change); or d) significant decrease (the factor was associated with a significant reduction in PTSD symptom severity or diagnostic change). Factors were studied at the end of treatment follow up.

3.3 Results

3.3.1 Systematic search results

The update search for the ISTSS treatment guideline in March 2018 included 114 RCTs. Twelve additional RCTs were identified in an updated search in November 2019 and included in this review, which resulted in 126 eligible RCTs. Fifteen of these RCTs reported on factors associated with treatment outcome. One hundred and eleven authors were contacted for additional information, 87 responded, 19 supplementary analyses of RCTs were received and reviewed for eligibility. Nine did not meet inclusion criteria as they did not report any factors associated with treatment outcome. This resulted in a total of 126 eligible studies, and 25 (20 %) RCTs reported on factors associated with treatment outcome. Figure 3-1 presents a flow diagram for study selection, and Table 3-1 summarises the factors associated with treatment outcome).

Figure 3-1 Study Flow Diagram

```
┌─────────────────────┐
│   5554 potentially  │
│   eligible studies  │
└─────────────────────┘
          │
          │
┌─────────────────────┐        ┌─────────────────────┐
│   5554 Studies      │ ─────► │   5428 studies      │
│   screened          │        │   excluded          │
└─────────────────────┘        └─────────────────────┘

                               ┌─────────────────────┐
                               │ 12 new studies were │
                               │   identified that   │
                      ───────► │ provided additional │
                               │     analyses        │
                               └─────────────────────┘

┌─────────────────────┐        ┌─────────────────────┐
│ 126 full text studies│       │ 110 full text studies│
│   were assessed for │ ─────► │     excluded        │
│     eligibility     │        │                     │
└─────────────────────┘        └─────────────────────┘
          │
          ▼
┌─────────────────────┐
│  25 studies included│
│     in narrative    │
│      synthesis      │
└─────────────────────┘
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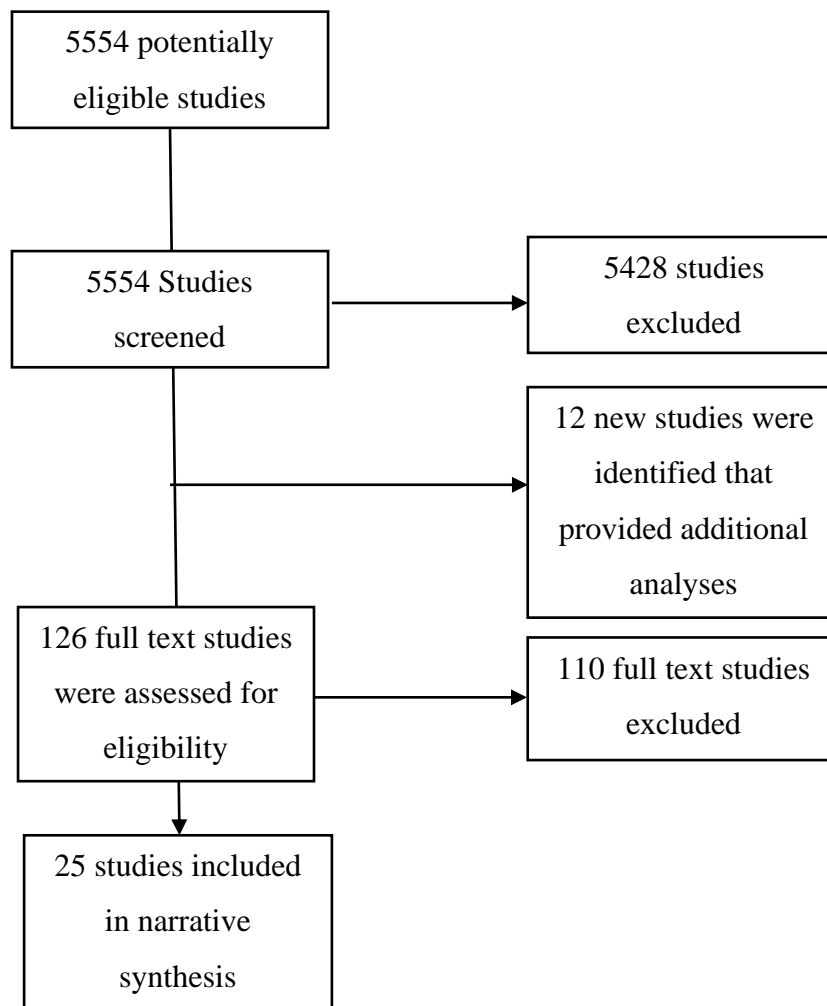
Table 3-1 A Summary of the factors affecting PTSD treatment outcome

Factors associated with Treatment Outcome	Number of studies with a negative association with treatment outcome	Number of studies with a positive association with treatment outcome	Number of studies with no association with treatment outcome
Factors considered in two or more studies			
Adherence to homework		2	1
Age (younger)			3
Concurrent psychotropic medication			2
Diagnosis of Anxiety			1
Diagnosis of Depression	2		
Gender of participant			6

Higher education		1	5
Higher Severity of PTSD at baseline	1		7
Less time since trauma		2	3
Low income			2
Lower severity of PTSD at baseline		1	
Married		1	3
Number of psychotherapy sessions/modules			3
Unemployment			2
Factors considered in one study only			
Ability to describe internal experiences		1	
Ethnicity (non-Hispanic white or other)			1
Greater dorsal lateral activation		1	
Greater startle response during virtual reality		1	
High emotional regulation (anger management and general emotion regulation capacity)		1	
History of psychiatric illness			1
Improvement in negative regulation		1	
Interpreter presence during therapy			1
Received higher no of psychotherapy treatment previously			1
Reduction in depression and anxiety throughout therapy			1
Refugee status			1
Stressors outside of therapy (not specified)			1
Therapeutic alliance		1	
Therapist gender			1
Therapy type EMDR versus E+CR			1
Type of trauma			1

Eye Movement Desensitisation and Reprocessing (EMDR), Imaginal Exposure (IE) and Cognitive Restructuring (CR)

3.3.2 Characteristics of included studies

The number of randomised participants ranged from 10 to 837. Studies were conducted in Australia (9), Canada (2), China (2), Denmark (1), Germany (5), Iran (2), Israel (1), Italy (2), Japan (1), the Netherlands (8), Norway (1), Portugal (1), Romania (1), Rwanda (1), Spain (1), Sweden (3), Syria (1), Thailand (1), Turkey (3), Uganda (2), UK (11), and USA (77). Participants were traumatised by military combat (28 studies), sexual assault or rape (9 studies), war/persecution (9 studies), road traffic accidents (6 studies), earthquakes (4 studies), childhood sexual abuse (9 studies), political detainment (1 study), physical assault (2 studies), domestic violence/intimate partner violence (4 studies), trauma from a medical diagnosis/emergency (3 studies) and crime/organised violence (4 studies), and interpersonal violence (1 study). The remainder (56 studies) included individuals traumatised by a variety of different traumatic events. There were 27 studies of females only and 9 of only males; females in the remaining studies ranged from 2% to 96%. Participant populations were mainly from the general public (89 studies), followed by military personal/veterans (37 studies), asylum seekers and refugees (8 studies), genocide survivors (1 study), and incarcerated women (1 study). (Table 3-2 presents the characteristics of all the studies).

Table 3-2 Characteristics of all the studies reviewed.

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Population	% Unemployed	% of University Educated
(Acarturk et al., 2016) [128]	EMDR	WL			Refugees	Unknown	4
(Adenauer et al., 2011) [83]	NET (CBT-T)	WL			Refugees	Unknown	Unknown
(Ahmadi et al., 2015) [129]	EMDR	REM Desensitisation	WL		Military Personnel/Veterans	Unknown	33.3
(Akbarian et al., 2015) [130]	Group CBT-T	MC/RA			General Population	Unknown	Unknown
(Asukai et al., 2010) [131]	PE (CBT-T)	TAU			General Population	Unknown	Unknown
(Basoglu et al., 2005) [132]	Single-session CBT-T	WL			General Population	Unknown	5.1
(Basoglu et al., 2007) [133]	Single-session CBT-T	MC/RA			General Population	Unknown	10
(Beck et al., 2009) [134]	Group CBT-T	MC/RA			General Population	54	Unknown
(Bichescu et al., 2007) [135]	NET (CBT-T)	Psychoeducation			General Population	0%	72
(Blanchard et al., 2003) [136]	CBT-T	SC	WL		General Population	Unknown	Unknown
(Bradshaw, et al., 2014) [137]	OEI	WL			General Population	0	Unknown
(Brom et al., 1989) [138]	CBT-T	Psychodynamic Therapy	WL		General Population	49	Unknown
(Bryant et al., 2003) [139]	CBT-T	SC			General Population	Unknown	Unknown
(Bryant et al., 2011) [140]	CBT-T	SC			General Population	84%	Unknown

(Buhmann, et al., 2016) [141]	CBT-T	WL			Refugees	Unknown	Unknown
(Butollo et al., 2016) [142]	CPT (CBT-T)	DET			General Population	Unknown	Unknown
(Capezzani et al., 2013) [143]	EMDR	CBT-T			General Population	Unknown	Unknown
(Carletto et al., 2016) [144]	EMDR	RT			General Population	Unknown	Unknown
(Carlson, et al., 1998) [145]	EMDR	RT	TAU		Military Personnel/Veterans	62	Unknown
(Castillo et al., 2016) [146]	Group PE/CT	WL			Military Personnel/Veterans	44%	Unknown
(Chard, 2005) [147]	Group + Individual CPT	WL			General Population	Unknown	Unknown
(Cloitre et al., 2002) [148]	CBT-T	WL			General Population	24%	52
(Cloitre et al., 2010) [149]	STAIR (CBT-NTF)	CBT without a trauma focus			General Population	31%	Unknown
(Cloitre et al., 2016) [150]	STAIR/EXP	STAIR/SupC	SupC/ EXP		General Population		
(Cooper & Clum, 1989) [151]	Imaginal Flooding	Standard Group Treatment			Veterans		
(Cooper et al., 2017) [152]	PE	Sertraline			General Population		
(Devilly et al., 1998) [153]	EMDR	TAU			Military Personnel/Veterans	Unknown	Unknown
(Devilly GJ, 1999) [154]	EMDR	CBT-T			General Population	Unknown	Unknown
(Dorrepaal et al., 2012) [155]	Group Stabilising Treatment	TAU			General Population	83%	Unknown
(Duffy et al., 2007) [156]	CT (CBT-T)	WL			General Population	Unknown	Unknown

(Dunne et al., 2012) [157]	CBT-T	WL			General Population	31%	73
(Echeburua et al., 1997) [158]	CBT-T	RT			General Population	Unknown	20
(Ehlers et al., 2005) [71]	CT (CBT-T)	WL			General Population	25%	35
(Ehlers et al., 2003) [159]	CT (CBT-T)	MC/RA			General Population	Unknown	Unknown
(Ehlers et al., 2014) [160]	CT (CBT-T)	SC	WL		General Population	23	26
(Falsetti et al., 2008) [161]	Group CBT-T	WL			General Population	Unknown	Unknown
(Fecteau & Nicki, 1999) [162]	CBT-T	WL			General Population	Unknown	Unknown
(Feske, 2008) [163]	PE (CBT-T)	TAU			General Population	29%	90%
(Foa et al., 1991) [164]	PE (CBT-T)	CBT without a trauma focus	Supportive counselling	WL	General Population	Unknown	Unknown
(Foa et al., 1999) [165]	PE (CBT-T)	CBT without a trauma focus	WL		General Population	38%	41%
(Foa et al., 2005) [166]	PE (CBT-T)	WL			General Population	17%	34%
(Foa et al., 2018) [167]	Spaced PE (CBT-T)	PCT	MC/RA		Military Personnel/Veterans	100%	66%
(Fonzo et al., 2017) [168]	PE (CBT-T)	WL			General Population	Unknown	Unknown
(Forbes et al., 2012) [10]	CPT (CBT-T)	TAU			Military Personnel/Veterans	36%	Unknown
(Ford et al, 2011) [169]	CBT without a trauma focus	PCT	WL		General Population	Unknown	22%
(Ford et al., 2013) [170]	TARGET (CBT-T) Trauma Affect	Group Supportive Counselling			Incarcerated Women	Unknown	Unknown

	Regulation: Guide for Education and Therapy						
(Galovski et al., 2012) [171]	TARGET-Group (CBT-T)	MC/RA			General Population	Unknown	Unknown
(Gamito et al., 2010) [172]	VRE (CBT-T)	Control Exposure	WL		Military Personnel/Veterans	Unknown	Unknown
(Gersons, 2000) [173]	BEP (CBT-T)	WL			General Population	Unknown	Unknown
(Gray et al., 2017) [174]	RTM (CBT-T)	WL			Military Personnel/Veterans	Unknown	Unknown
(Haagen et al., 2017) [175]	EMDR + Stabilization	Stabilisation			Refugees and Asylum Seekers		
(Hensel-Dittmann et al., 2011) [176]	NET (CBT-T)	CBT without a trauma focus			Asylum Seekers	Unknown	Unknown
(Hien et al., 2017) [177]	COPE + PE	Relapse Prevention Therapy	The active monitoring control group		General Population		
(Hinton, et al., 2005) [178]	CBT-T	WL			Refugees	Unknown	Unknown
(Hinton, et al., 2011) [179]	Group CBT-T	WL			General Population	Unknown	Unknown
(Hogberg, 2007) [180]	EMDR	WL			General Population	Unknown	Unknown
(Hollifield, 2007) [181]	Group trauma-focused CBT	WL			General Population	Unknown	40%
(Ironson, 2002) [182]	EMDR	PE (CBT-T)			General Population	Unknown	Unknown
(Ivarsson et al., 2014) [183]	I-CBT	WL			General Population	8%	65%
(Jacob et al., 2014) [184]	NET (CBT-T)	WL			Genocide Survivors	Unknown	Unknown

(Jensen, 1994) [185]	EMDR	WL			Military Personnel/Veterans	68	Unknown
(Johnson et al., 2011) [186]	CBT without a trauma focus	TAU			General Population	73	7%
(Johnson, et al., 2016) [187]	CBT without a trauma focus	TAU			General Population	77	5%
(Karatzias et al., 2007) [188]	EMDR	E+CR			General Population		
(Karatzias et al., 2011) [189]	EMDR	EFT			General Population	37	47%
(Keane, 1989) [72]	CBT-T	WL			Military Personnel/Veterans	Unknown	Unknown
(Krupnick et al., 2008) [190]	Group IPT	WL			General Population	80	13%
(Kearney 2013) [191]	MBSR	TAU			Veterans		
(Krakow et al., 2000) [192]	Imagery rehearsal	WL					
(Kubany et al., 2003) [193]	CBT-T	WL			General Population	Unknown	Unknown
(Kubany et al., 2004) [70]	CBT-T	WL			General Population	Unknown	Unknown
(Laugharne et al., 2016) [194]	EMDR	PE (CBT-T)			General Population	Unknown	Unknown
(Lee, 2002) [195]	CBT-T	EMDR			General Population	Unknown	Unknown
(Lewis et al., 2017) [196]	I-CBT	WL			General Population	19	62%
(Littleton et al., 2016) [197]	I-CBT	I-Psychoeducation			General Population	Unknown	Unknown
(Litz et al., 2007) [198]	I-CBT	I-SC			Military Personnel/Veterans	Unknown	Unknown
(Lindauer et al., 2005) [199]	BEP	WL			Police officers		

(Marcus, 1997) [200]	EMDR	TAU			General Population	Unknown	Unknown
(Markowitz et al., 2015) [201]	IPT	PE (CBT-T)	Relaxation Therapy		General Population	21	Unknown
(Marks et al., 1998) [69]	PE (CBT-T)	Cognitive Restructuring	PE (CBT-T) (CBT-T)(CBT-T)and Cognitive Restructuring	Relaxation without PE (CBT-T) (CBT-T)(CBT-T)or CR	General Population	54	Unknown
(McDonagh et al., 2005) [202]	PE (CBT-T)	PCT	WL		General Population	17	Unknown
(McLay et al., 2011) [203]	VRE (CBT-T)	TAU			Military Personnel/Veterans	Unknown	Unknown
(McLay et al., 2017) [204]	VRE (CBT-T)	CET			Military Personnel/Veterans	Unclear	Unclear
(Monson et al., 2012) [205]	Couples CBT-T	CET			General Population	40	Unknown
(Monson, et al., 2006) [206]	CPT (CBT-T)	WL			Military Personnel/Veterans	Unknown	Unknown
(Miyahira et al., 2012) [207]	VR	Minimal attention			Active military		
(Morath et al., 2014) [208]	NET (CBT-T)	WL			Refugees	Unknown	Unknown
(Mueser, 2008) [209]	CBT-T	WL			General Population	Unknown	Unknown
(Nacasch et al., 2011) [210]	PE (CBT-T)	TAU			Military Personnel/Veterans	63	Unknown
(Neuner, et al., 2010) [211]	NET (CBT-T)	TAU			Refugees	Unknown	Unknown
(Neuner et al., 2008) [212]	NET (CBT-T)	TAU	Monitoring		Refugees	49	Unknown
(Neuner et al., 2004) [213]	NET (CBT-T)	SC	Psychoeducation		Refugees	28	Unknown

(Nijdam et al., 2012) [214]	BEP (CBT-T)	SC			General Population	Unknown	30
(Pacella et al., 2012) [215]	PE (CBT-T) (CBT-T)	EMDR			General Population	Unknown	Unknown
(Paunovic et al., 2011) [216]	CBT-T	MC/RA			General Population	74	11
(Peniston & Kulkosky, 1991) [217]	CBT-T	WL			Military Personnel/Veterans	Unknown	Unknown
(Polusny et al., 2015) [218]	MBST	PC-GT			Veterans		
(Pigeon et al., 2015) [219]	PCBMT	Primary Care			Veterans		
(Power, 2002) [220]	EMDR	TAU	WL		General Population	Unknown	Unknown
(Rauch et al., 2015) [221]	PE (CBT-T) (CBT-T)	CBT-T			Military Personnel/Veterans	Unknown	Unknown
(Ready, 2010) [222]	VRE (CBT-T)	PCT			Military Personnel/Veterans	Unknown	Unknown
(Reger et al., 2016) [223]	VRE (CBT-T)	PCT	WL		Military Personnel/Veterans	Active duty	7
(Resick et al., 2015) [224]	CPT-Group	PE (CBT-T)			Military Personnel/Veterans	0	8
(Resick et al., 2002) [225]	CPT (CBT-T) (CBT-T)	Group PCT	Minimal Attention		General Population	Unknown	Unknown
(Resick et al., 2017) [111]	CPT (CBT-T) (CBT-T)	PE (CBT-T)			Military Personnel/Veterans	100	19
(Rothbaum et al., 1997) [226]	EMDR	Group CBT-T			General Population	19	43
(Rothbaum et al., 2005) [227]	PE (CBT-T)	WL	WL		General Population	Unknown	Unknown
(Sautter et al., 2015) [228]	Couples CBT without a trauma focus	EMDR			Military Personnel/Veterans		

(Sautter et al., 2016) [229]	SAT	PTSD family education intervention			Veterans	12	75
(Scheck, 1998) [230]	EMDR	Couples Psychoeducation			General Population	Unknown	Unknown
(Schnurr et al., 2003) [231]	Group CBT-T	SC			Military Personnel/Veterans	51	Unknown
(Schnurr et al., 2007) [87]	PE (CBT-T) (CBT-T)	Group PCT			Military Personnel/Veterans	38	Unknown
(Schnyder et al., 2011) [232]	BEP (CBT-T)	Group PCT			General Population	Unknown	Unknown
(Schoorl et al., 2014) [233]	ABM	AC			General Population		
(Shemesh et al., 2011) [234]	IET	Control education condition			General Population		
(Sloan et al., 2012) [82]	WET	MC/RA			General Population	78	41
(Sloan et al., 2018) [81]	WET	WL			General Population	Unknown	13
(Smyth et al., 2008) [235]	Expressive Writing; writing about their traumatic experience	Control Group (writing about time management)			Veterans		
(Spence et al., 2011) [236]	I-CBT	CPT (CBT-T)				41	Not Clear
(Stenmark, et al., 2013) [237]	NET (CBT-T)	WL			Refugees	Unknown	25
(Suris, et al., 2013) [238]	CPT (CBT-T)	TAU			Military Personnel/Veterans	43	16
(Stirman et al., 2018) [239]	Cognitive processing therapy with trauma account	Cognitive Processing Therapy without trauma account			General Population		

(Taylor, 2003) [240]	PE (CBT-T)	PCT	EMDR		General Population	13	Unknown
(Stapleton et al., 2006) [241]	PE	EMDR	Relaxation Therapy		General Population	Unknown	Unknown
(Ter Heide, et al., 2011) [242]	EMDR	Stabilisation			Asylum Seekers and Refugees		
(Tylee et al., 2017) [243]	RTM (CBT-T)	Relaxation Therapy			General Population		
(Vaughan, 1994) [244]	CBT-T	WL	EMDR		General Population	Unknown	Unknown
(Wells et al., 2015) [245]	PE (CBT-T)	RT	WL		General Population	6	Unknown
(Wells & Sembi, 2012) [246]	CBT without a trauma focus	CBT without a trauma focus			General Population	Unknown	Unknown
(Wittmann et al., 2012) [247]	BEP	Minimal attention Control Condition			General Population		
(Wilson et al., 1995) [248]	EMDR	WL			General Population		
(Yehuda et al., 2014) [249]	PE (CBT-T)	WL			Military Personnel/Veterans	Unknown	Unknown
(Zang et al., 2014) [250]	NET (CBT-T)	MC/RA			General Population	Unknown	Unknown
(Zang et al., 2013) [251]	NET (CBT-T)	WL			General Population	Unknown	Unknown
(Zlotnick et al., 1997) [252]	Group CBT-T	WL			General Population	Unknown	33

ATM = Attentional bias modification, BEP = Brief Eclectic Psychotherapy, CBT = Cognitive Behavioural Therapy, CBT-T = Cognitive Behavioural Therapy with a Trauma focus, CET = Control Exposure Therapy, COPE = Cocurrent treatment of PTSD, CPT = Cognitive Processing Therapy, CR = Cognitive Restructuring, CT = Cognitive Therapy, RTM = Reconsolidation of Traumatic Memories, DET = Dialogical Exposure Therapy, E + CR = Imaginal Exposure + Cognitive Restructuring, EFT = Emotional Freedom Technique, EMDR = Eye Movement Desensitisation and Reprocessing, I-CBT = Internet-based Cognitive Behavioural Therapy, IET = Imaginal Exposure Therapy, I-Psychoeducation = Internet based Psychoeducation, IPT = Interpersonal Psychotherapy, I-SC = Internet based Supportive Counselling, MBSR = Mindfulness Based Stress Reduction, MC/RA = Medical Checks/Repeated Assessments, NET = Narrative Exposure Therapy, NTF = Non

Trauma Focussed, OEI = Observed and Experimental Integration, PCBMT = Primary Care Brief Mindfulness Training, PCGT = Present Centred Group Therapy, PCT = Present Centred Therapy, PE = Prolonged Exposure, REM Desensitisation = Rapid Eye Movement Desensitisation, RT = Relaxation Therapy, SAT = Structured Approach Therapy, SC = Supportive Counselling, STAIR + SupC = Skills Training in Affective and Interpersonal Regulation + Supportive Counselling, STAIR = Skills Training in Affective and Interpersonal Regulation, TAU = Treatment as Usual, TARGET = Trauma Affect Regulation: Guide for Education and Therapy, VR = Virtual Reality, VRE = Virtual Reality Exposure, WET = Written Emotion Therapy, WL = Waiting List

3.3.3 Factors associated with treatment outcome

3.3.3.1 Clinical characteristics

Symptom Severity: The severity of PTSD symptoms at baseline was one of the most commonly reported factors examined concerning treatment outcome. The majority of studies that examined this association (n = 7 studies) found that PTSD symptom severity scores at baseline had no association with treatment outcome [121, 133, 159, 175, 188, 232, 247]. However, findings were inconsistent: one study reported that the most severe PTSD symptoms at baseline were associated with benefiting less from treatment [150].

Comorbid symptomatology: Comorbid diagnosis of depression was associated with a significant increase in PTSD symptom severity in two studies [175], [150], which found that those diagnosed with depression did less well in treatment than those without the diagnosis.

Aspects of treatment: Three studies found that the number of sessions or modules completed was not associated with treatment outcome [175, 188], [121]. Concurrent use of psychotropic medication was not associated with treatment outcome [183, 188].

Time since trauma: One study found that more recent trauma was associated with a slightly improved effect [196]. However, three papers found that time since trauma had no association with treatment outcome [133], [159], [188].

Type of trauma: One study found no association between the type of trauma and treatment outcome [188].

3.3.3.2 Patient characteristics

Younger age was found to have no association with treatment outcome in three studies [133]; [188], and [196].

Education was considered in six studies; one found that those who had completed higher education had more significant treatment effect [196]; and five studies found no association between years of education and treatment outcome [132, 133, 183, 192, 248]

Employment status had no association with treatment outcome in two studies [183, 188].

Adherence to homework was found to be positively associated with treatment outcome in two studies [69] [253]. However, one study found no association with the amount of time spent on completing homework and treatment outcome [236]. Completing homework was associated with better outcomes for patients with fewer years of formal education than those who reported more years of education [239].

Marital status was associated with more significant gain from treatment in one study [248] yet had no association with treatment outcome in three other studies ([183], [192], [188]).

Lower household income was reported not to have any association with treatment outcome in two studies [192, 248].

Participants' gender was reported in seven studies to have no association with treatment outcome [133, 136, 175, 183, 188, 196, 248].

3.3.3.3   Other factors identified

Better emotional regulation was positively associated with treatment outcome in two studies; one found an association with better functioning [150] and a more significant reduction in PTSD [177]. Furthermore, low emotional dysregulation was associated with reducing substance abuse [177] and improvements in negative mood regulation [148]. Three other studies found that the number of previous traumas had no association with treatment outcome [132, 133, 175].

One study found that participants who could describe their internal experiences, thoughts, emotions, and sensations in a non-judgmental manner were associated with a significant reduction in CAPS score [254].

Ethnicity was not found to be associated with treatment outcome in one study [192]. Refugee status [175] and the presence of stressors during the treatment [241] had no association with treatment outcome. (Table 3-1 presents a summary of the factors associated with treatment

outcome, and Table 3-3 presents the characteristics of the papers that reported any factors associated with treatment outcome).

Table 3-3 Characteristics of the studies: The following are studies that reported factors associated or not associated with treatment outcome of psychological therapies of PTSD.

Study	Country	Intervention	Participants	Type of trauma	Factors associated (or not) with treatment outcome
(Basoglu et al., 2005) [132]	Turkey	Single-session CBT	59	Earthquake	Greater PTSD severity, higher education and past trauma had no significant association with treatment outcome as measured by the CAPS-IV. However, it was associated with less improvement in the Patients Global Impression (a self-measure that reflect a patient's belief about the efficacy of treatment).
(Basoglu et al., 2007) [133]	Turkey	Single-session CBT	31	Earthquake	Age, gender, education, past psychiatric illness, history of past trauma, time since the earthquake, and the pre-treatment clinical ratings were not significantly associated with treatment outcome.
(Blanchard et al., 2003) [136]	USA	Trauma-focused CBT	98	Road Traffic accidents	There was no main effect or interaction with therapist gender or no main effect of gender of the patient to treatment outcome.
(Cloitre et al., 2002) [148]	USA	CBT-T	58	Various	Predictors of improvement were therapeutic alliance and improvement in negative mood regulation as measured by the NMR as measured by the CAPS. Significant reduction post-treatment in depression and anxiety were not associated with PTSD symptom severity reduction.
(Cloitre et al., 2016) [150]	USA	Skills training in affective and interpersonal regulation (STAIR) after Prolonged Exposure (EXP)	104	Childhood sexual and physical trauma/abuse	Higher emotional regulation predicted better functioning compared to those with lower emotional regulation. Those with high 'Symptom burden' (PTSD, depression, dissociation and interpersonal problems) were associated with worse treatment outcome and did least well in exposure, moderately well in skills and best in the combination as measured by the PTSD symptom severity assessed via the CAPS.
(Dorrepaal et al., 2012) [155]	Netherlands	Stabilising Group Treatment	71	Child Abuse	Diagnosis of Borderline Personality Disorder (BPD) was associated with greater compliance, defined by completed

					treatment, as opposed to those without the personality diagnosis.
(Ehlers et al., 2003) [159]	UK	Cognitive Therapy (CT)	85	Road Traffic accident	Time since trauma and the degree of change in PTSD severity (PDS) score using self-monitoring measures were not associated with outcome.
(Fonzo et al., 2017) [168]	USA	Prolonged Exposure (PE)	66	Not specified	Less Blood Oxygen Level Dependent activation (signal) in the brain at baseline was associated with more significant reductions in symptom scores in the waiting list group in two right and two left dorsolateral prefrontal clusters. Finally, greater dorsal anterior cingulate activation at baseline was associated with more significant reductions in symptom scores in the treatment group but not in the waiting list group
(Galovski et al., 2012) [171]	USA	Modified Cognitive Processing Therapy (M-CPT)	100	Various	Treatment dropouts were younger, had fewer years of education and had lower annual household income and significantly higher pre-treatment CAPS severity at baseline assessment. Participant age, time since index trauma and pre-treatment CAPS and Beck Depression Inventory-II scores were identified as potential predictors of length of therapy.
(Haagen et al., 2017) [175]	Netherlands	Eye Movement Desensitisation and Reconsolidation and Stabilization (EMDR-S).	72	Various	Individuals with depression, measured by The Hopkins Symptom Checklist (HSC), had less reduction in PTSD. Other factors, pre-treatment PTSD severity, refugee status, interpreter presence during therapy, the number and nature of traumatic events, gender, number of psychotherapy sessions, and treatment dropout, were not associated with treatment outcome.
(Hien et al., 2017) [177]	USA	Concurrent Treatment of PTSD and SUD using Prolonged Exposure (COPE).	110	Various	Baseline emotional dysregulation (ED) severity moderated treatment outcomes such that high ED was associated with a more significant reduction in PTSD severity among those who received COPE relative to RPT and AMCG. In contrast, low ED is associated with a more significant reduction in substance use among those in RPT relative to COPE and AMCG.

(Ivarsson et al., 2014) [183]	Sweden	Guided Internet Delivered Cognitive Behaviour Therapy for PTSD.	62	Various	Participants lost to follow up were, on average, younger compared to those who completed the study. Gender, age, marital status, highest educational level, unemployment status, psychopharmacological medication and history of psychotherapy were not associated with treatment outcome.
(Karatzias et al., 2007) [188]	UK	Eye Movement Desensitisation and Reprocessing (EMDR) Vs Imaginal Exposure and Cognitive Restructuring (E+CR)	48	Various	Lower baseline CAPS-5 scores were associated with fewer required sessions and better improvement post-treatment. Age, gender, marital status, occupation, type of trauma, time since trauma, therapy type, number of sessions, psychotropic medication, CAPS total (baseline), HADS-A, HADS-D were not associated with treatment outcome, as measured by pre and post CAPS severity scores.
(Krakow et al., 2000) [192]	USA	Imagery Rehearsal Therapy (IRT)	169	Sexual assault	Demographic covariates; ethnicity, marital status, annual income, or education were not significant in any of the analyses.
(Kubany et al., 2004) [255]	USA	Cognitive Trauma Therapy for Battered Women (CTT-BW)	125	Domestic Abuse	Comorbidity with depression, low self-esteem, younger age, less educated, and more shame prone at the initial assessment were associated with non-completers of treatment.
(Lewis et al., 2017) [196]	UK	Internet-based guided self-help	42	Various	There was no significant effect modification by age, gender, baseline CAPS score, number of modules completed, or number of therapist minutes. However, more recent trauma experienced a slightly improved effect. Higher education was associated with the most significant treatment effect, and those with a higher degree experiencing a more significant improvement in CAPS scores.
(Marks et al., 1998) [69]	UK	Prolonged Exposure (PE) Vs Cognitive restructuring	87	Various	Adherence to homework was associated with more improvement on the Global Improvement scale.

(McDonagh et al., 2005) [202, 254]	USA	Primary Care Brief Mindfulness Training (PCBMT) Cognitive Behavioural Therapy (CBT)	6274	Military Trauma Child Sexual Abuse	The ability to describe internal experiences, thoughts, emotions and sensations, in a non-judgemental way was associated with a decrease in PTSD symptoms. Participants who dropped out of CBT endorsed more depression and more significant anxiety reported lower quality of life and endorsed more distorted schemas on The Traumatic Stress Institute Beliefs Scale (TSI; Pearlman, 2001) than those who stayed in treatment.
(Schnurr, et al. , 2003) [231, 254]	USA	Trauma-focused Group Psychotherapy Primary Care Brief Mindfulness Training (PCBMT)	36062	Military Trauma	Individuals lost to follow-up, scored lower on Global Assessment of Functioning (GAF), more likely unemployed and have a history of substance misuse. The ability to describe internal experiences, thoughts, emotions and sensations, in a non-judgmental way was associated with a decrease in PTSD symptoms.
(Schnurr, et al. , 2003) [87, 231]	USA	Prolonged Exposure (PE) vs Present-centred therapy (PCT).Trauma-focused Group Psychotherapy	277360	Female Veterans Military Trauma	Participants in Present Centred Therapy (PCT) received an increase in or new medication during the study compared to those in the prolonged exposure group. Sub-group analysis yielded no significant association between medication change and treatment outcome. Those lost to follow up were associated with lower Global Assessment of Functioning (GAF), unemployment and a history of substance misuse.
(Schnurr, et al. , 2007) [87, 236]	USA	Internet-delivered Cognitive Behavioural Therapy (I-CBT) for PTSD. Prolonged Exposure (PE) vs Present-centred therapy (PCT).	125277	Various Female Veterans	There was no significant relationship between post-treatment outcome, the amount of time spent on the homework or the amount of time spent on thought challenging. Participants in PCT received an increase or new medication during the study compared to those in the prolonged exposure group. Sub-group analysis found no association between medication change and treatment outcome.
(Spence et al., 2011) [236, 239]	USA	Cognitive Processing Therapy (CPT). Internet-delivered Cognitive Behavioural	140125	Sexual or physical violence Various	Completing homework was associated with a more significant decrease in PTSD symptom severity score, as measured by the PTSD symptom scale (PSS). There was no significant relationship between post-treatment

		Therapy (I-CBT) for PTSD.			outcome, the amount of time spent on the homework or the amount of time spent on thought challenging.
(Stirman et al., 2018) [239, 241]	USA	Prolonged Exposure (PE) Cognitive Processing Therapy (CPT).	60140	Various Sexual or physical violence	No evidence that treatment outcome varied as a function of the pre-treatment severity of anger or guilt. The additional presence of stressors had no association with treatment outcome. Completing homework was associated with a more significant decrease in PTSD symptom severity score, as measured by the PTSD symptom scale (PSS).
(Stapleton et al., 2006) [241, 248]	USA	Eye Movement Desensitisation and Reprocessing (EMDR)Prolonged Exposure (PE)	8060	Various	PTSD-I scale symptom severity at baseline, years of education, income, gender, the gender of the therapist were not associated with treatment outcome. Participants who were married were associated with more significant gain. No evidence that treatment outcome varied as a function of the pre-treatment severity of anger or guilt. The additional presence of stressors had no association with treatment outcome.
(Wilson et al., 1995) [248]	USA	Eye Movement Desensitisation and Reprocessing (EMDR)	80	Various	PTSD-I scale symptom severity at baseline, years of education, income, gender, the gender of the therapist were not associated with treatment outcome. Participants who were married were associated with more significant gain.

3.4 Strengths and limitations

The systematic review and narrative synthesis were completed alongside a review of the efficacy of psychological therapies for PTSD for the ISTSS treatment guidelines [104]). The systematic review followed rigorous methodology and examined 126 RCTs, which increases the validity and the generalisability of the results. The data was extracted and discussed between two research staff, who independently examined the data and identified the appropriate RCTs which met the inclusion criteria. The systematic review extracted data from RCTs, which used clinician-administered measures to examine PTSD severity administered by clinicians or trained research staff, reducing the subjectivity and increasing the results' reliability. On occasions where this was not available, self-report measures such as the PCL-5 collected data on PTSD symptom severity. Limiting the review to RCTs may have excluded studies with other research designs that reported associations with treatment outcomes. A meta-analysis was not considered appropriate due to the heterogeneity between studies and the lack of consistent reporting. An alternative method is a meta-analysis of Individual Participant Data (IPD), which is a type of systematic review that collects and analysis data from each individual study [256]. However, the resources and time required for such analysis was not available to me and therefore it was agreed that a narrative synthesis of the data was sufficient.

3.5 Summary

This was the first systematic review to consider factors associated with treatment outcome of psychological treatments for PTSD. A comorbid diagnosis of depression and higher PTSD symptom severity at baseline was associated with poor treatment outcome [257]. Some evidence was also found that higher education, adherence to homework, and experience of more recent trauma were associated with better treatment outcome. While some factors were associated with treatment outcome, the evidence is limited and inconsistent. The review has highlighted a current lack of knowledge about factors associated with the treatment outcome of PTSD. This is further complicated by the inconsistency of reported factors and the variance in treatment outcome among patients with PTSD [258]. Hopefully, they will stimulate the generation of a more rigorous and clinically relevant framework that can inform treatment selection in the future. Future studies must explore factors associated with treatment outcome.

Chapter 4: Multi-Modular Motion Assisted Memory Desensitisation and Reconsolidation (3MDR)

4.1 A brief history of the components

A novel intervention called 3MDR was developed by psychiatrist Eric Vermetten and colleagues in the Netherlands to treat military veterans with TR-PTSD [259]. 3MDR was first described in a pilot case study [259] and has been further developed over the last six years. 3MDR aims to expose people with PTSD to images of their trauma to promote engagement with the distressing memory and overcome avoidance [78]. The therapy requires people with PTSD to walk on a treadmill towards self-selected images of their trauma displayed on a 180° Virtual Reality (VR) screen. At the same time, personalised music evokes emotions related to the trauma [259]. After presenting each image on the VR screen, a swinging red ball is shown with different numbers presented during every swing, activating bilateral stimulation [260]. The critical components of 3MDR, as first described by Van Gelderen [78], are VR, dual attention task, movement, and multi-sensory input to create an immersive environment. The multi-sensory input and movement aspects are novel, yet some treatment elements have been used to treat mental health for many years [28]. The different components of 3MDR are discussed below.

4.1.1 Virtual Reality (VR)

Basic VR was first used in 1968; Ivan Sutherland and Bob Sproull developed a Head-Mounted Display (HMD) system for a VR environment [261]. VR technology combines interactive computer images and other sensory inputs to immerse the individual into a virtual environment [261]. An immersive interactive environment can provide a safe place where individuals can experience a difficult situation and, combined with psychological treatment, overcome associated problems [77].

VR technology has developed significantly in the last 50 years; through its application to entertainment, education, and mental health [262, 263]. As a result, advanced versions of VR technology are now available, promoting exposure to chosen stimuli, referred to as VRET

within a controlled environment [264]. Several VR applications have been developed for use in mental health, including for specific phobias [265], sexual dysfunction [266], anxiety disorders [267], and treatment for schizophrenia [268]. VR has also been used to assist people with Traumatic Brain Injury (TBI) [269]. According to Foa and Kozak [73], the mechanism of VRET therapy can be explained through emotional processing theory. The theory suggests that the stored memory must first be activated through VR to change the memory structure, so new, more adapted information can be stored in the latest memory structure [73]. The mechanism suggests that VR therapy reduces fear towards the selected stimuli through repeated exposure to the traumatic images. The immersive environment in 3MDR therapy is personalised as self-selected images of the participant's trauma are projected onto the 180º screen, covering the individuals' peripheries (Figure 4-1). Unlike imaginal exposure, where individuals may find it difficult to imagine their feared stimuli, VRET in 3MDR therapy forces the individual to confront their traumatic memory face on, which is thought encourages active engagement [2] and facilitates emotional release [77]. Both methods achieve the same outcome, although it could be argued that VRET creates a more engaging and controlled setting.

Figure 4-1 shows the Cardiff university 3MDR VR environment for the Phase II RCT.

4.1.2 Dual-attention task: bilateral stimulation

The dual-attention task paradigm requires the individual to perform two tasks simultaneously [270-272]. The primary task requires visual attention, while the second task requires auditory attention. The primary task is often projected into a central gaze, while the second task is presented in the peripheries. The increase in cognitive demand during the dual-attention task causes either a delay or unsuccessful execution of both tasks [273]. Changes in levels of performance are a result of performing both a visual and auditory task together.

There are two explanations for the dual-task effects: first, the bottleneck effect, and second, the central capacity sharing model [274]. The bottleneck effects suggest that two tasks that require similar attention cannot be performed successfully together [275]. The central capacity model suggests that there is limited capacity to perform two tasks simultaneously [276]. Therefore, tasks can be performed together if it does not reach capacity. The theory suggests that tasks that exceed capacity will experience a decline in performance on one or both tasks.

The dual-attention task used in EMDR: the participant is asked to follow tapping or a moving finger from side to side) is similar to the task applied 3MDR. The VR exposes the most emotionally charged aspect of the memory through images on a screen. Subsequently, the individual is presented with a dual-task in the form of a swinging ball with different numbers presented with every swing. The dual-task creates a competition between retaining the new memory and concentrating on the swinging visual and auditory stimuli. The dual-task reduces the vividness of associated memories and intensity of associated emotions [276]. The dual-task facilitates reconsolidating the old memory to a new adaptive, lower intensity memory that replaces the fear-conditioned response to the traumatic event [277, 278]. The reconsolidation process and the underlying mechanism of action are described in detail below.

Figure 4-2 shows a diagram of the 3MDR machine and the dual-attention task.

4.1.3 Movement

One of the unique aspects of 3MDR is its use of movement. Movement refers to the action of the individual walking on the treadmill towards self-selected images of their trauma (Figure 4-3). The movement could be considered a dual-attention task, which allows the individual to explore a new perspective [279]. It has been demonstrated that a repetitive motion facilitates the consolidation of fear extinction (4.2.4.2), as evidenced by its use as a reinforcement tool in exposure therapy [280]. The participant receives positive body feedback, which results in a positive evaluation of the trauma-related stimuli and accompanying traumatic memories [281, 282].

The movement aspect of 3MDR is suggested to have several benefits. According to Van Gelderen [8], walking is a dual-attention task that taxes the working memory capacity and suggests that a steady walking rhythm may create a steady thinking space that promotes creative thinking [283], which encourages creativity [279]. Second, behaviour theories suggest that walking may reduce trauma-related avoidance and increase self-efficacy and control [78]. From a more therapeutic standpoint, walking towards a feared stimulus could

provoke a feeling similar to marching towards war, encouraging catharsis. Finally, cardiovascular exercise promotes dopamine levels that increase low latent inhibition, which helps absorb more information [284]. The 3MDR pioneers encouraged the walking to be quick yet steady to encourage active engagement of the feared stimuli (Figure 4-3). As walking challenges individuals both physically and mentally, the movement aspect of 3MDR could be critical to the therapy's effectiveness.

Figure 4-3 shows the movement component of 3MDR in the Netherlands.

4.1.4 Multi-sensory input

3MDR is a novel approach to treatment for PTSD, as it focuses on personalised multi-sensory input to help avoid specific emotions and memories that the individual finds distressing. The multi-sensory input refers to the personalised images presented on the virtual reality screen, and the music played at the start and end of each treatment session (Figure 4-4). Gradual exposure to traumatic memory within a safe environment can reduce avoidance and trauma-related anxiety through desensitisation [285].

In 3MDR, individuals must select 20 images of their trauma and two pieces of music that evoke a strong emotional response. These photographs and music are discussed with the treating therapist, and the individual decides the selection and ordering of photographs in each treatment session. Vermetten and colleagues specified how using multi-sensory input

can improve memory retrieval [78]. Research suggests that a visually engaging environment enhances the 'learning environment' described in psychotherapy to understand better the information exchanged between participants and therapists [286]. Suppose visual reality in 3MDR facilitates communication and processing; it is a valuable addition to the traditional conversational methods employed in psychological therapies and promotes engagement through exposure.

Figure 4-4 shows the latest version of the multi-component computer software program linked with the new 3MDR machine.

4.1.5 Summary

3MDR comprises several components, some of which are based on existing psychological treatments for PTSD. The novel components include movement, which involves walking on a treadmill and multi-sensory input that involves selecting personal images and music that evokes an emotional response. These features place the individual at the centre of treatment and pave the way towards a more personalised approach to psychological treatment for PTSD. The VR environment provides an immersive alternative to exposure therapy that encourages engagement and reduces the avoidance of feared stimuli.

4.2 Theories that informed the development of 3MDR

This section will focus on Conditioning theory, The Working Memory Model (WMM), and ET to explain the possible development of 3MDR.

4.2.1 Conditioning theory

3MDR is based on Conditioning theory, which suggests that a response to a stimulus, in this case, photographs related to the trauma, can be altered through learning or conditioning [287]. Conditioning theory suggests that a conditioned response occurs when a neutral stimulus such as a plane and an unconditioned stimulus (US) such as a plane crash results in a previously neutral but now conditioned stimulus (CS) and creates a conditioned response (CR) such as re-experiencing the plane crash and avoidance of reminders, as doing so causes fear and distress [74]. The conditioned learning describes how the memories have been formed and sustained – unconditioned stimuli – conditioned stimuli – conditioned response (fear and distress) – avoidance.

4.2.2 The Working Memory Model (WMM)

The model that informed the development of 3MDR is the WMM [288]. WMM proposed by Baddeley includes a central executive system responsible for higher-order cognitive functions such as planning; and two slave systems - the phonological loop stores verbal and auditory data; and the visuospatial sketchpad (VSSP), which stores visuospatial data [289, 290]. Both systems have limited capacity; therefore, simultaneous visual or spatial processing will selectively interfere with short-term memory for visual information by competing for VSSP resources. A secondary visuospatial task also disrupts verbal memory depending on VSSP cues [291-295]. Andrade & Baddeley [296] found that counting made auditory images less vivid while tapping made visual images less vivid. Therefore, the WWM functioning becomes less efficient when there is an increase in cognitive tasks, such as simultaneously performing two tasks [296]. Research indicates that when the task becomes more complicated, the focus and performance on the primary task decreases, i.e. walking or following the oscillating ball in 3MDR while focussing on the memory reduces the vividness of the memory and associative emotions [297]. Tasks such as visual or auditory stimuli are

passive and may require fewer resources that may have little or no impact on memory's vividness.

The effect is present when the individual is forced to split their focus between the traumatic memory and the competing stimuli. Andrade suggested that eye movements may be more efficient than other dual attention tasks as they utilise visual and spatial components [297]. The WMM predicts that tapping is less effective at reducing the vividness due to less demand on the working memory, consistent with the literature [297, 298]. Gunter found that eye movement reduces the vividness and emotionality of traumatic memories when the central executive functioning is taxed during a distractor task [60]. EMDR has been shown to produce effects faster than exposure therapies [220]. Gunter suggests that this may be because the distraction task in EMDR makes focusing on the traumatic memories less unpleasant [60]. A similar theory can be applied to 3MDR as focusing on the oscillating ball and the walking element may make the traumatic memories less vivid and, in turn, less intrusive.

4.2.3 Exposure Therapy (ET)

Exposure Therapy (ET) was pioneered by Foa [299] and is now a commonly used therapy for mental health conditions. Several RCTs demonstrate their efficacy and feasibility as an effective treatment for PTSD [110]. ET is based on Lang's informational theory of fear [300]. The theory suggests that the memory structure is altered after exposure to a fearful stimulus, resulting in an excessive response to reminders. Foa applied the emotional processing theory to PTSD. She proposed that the memory structure is altered to avoid or escape fearful stimuli and develops pathological meaning elements, which result in two negative cognitions. First, the world is a dangerous place and no one can be trusted, and second, the individual feels worthless. Foa proposed that an effective psychological intervention can help alter the pathological memory structure and challenge the negative cognitions [301]. ET exposes the individual to fearful stimuli to reduce the fearful response.

ET can aim to do this in two ways: Flooding, which aims to expose the individual to the fearful stimuli abruptly, and systematic desensitisation, which aims to progressively expose the individual to the fearful stimuli (4.2.3.1). ET often requires individuals to either talk,

imagine or write about their experiences and focus on core cognitive beliefs about the traumatic event. ET aims to revisit the traumatic memory to 1) prove that the memory of the incident is no longer dangerous, 2) challenge negative thoughts and feelings about the event, and 3) and challenge any inaccurate thoughts and feelings surrounding the traumatic incident. The repeated activation of the emotionally charged memory allows recontextualizing new information and altering the memory structure [76]. Exposure to the emotionally charged memory encourages a reduction in negative cognition associated with the memory [63].

4.2.3.1 Systematic desensitisation

3MDR therapy can be described as systematic desensitisation as the treatment combines cognitive and behavioural methods to improve functioning and tolerance towards traumatic memories [302]. In 3MDR, participants are first asked to rate their traumatic photographs from least to most feared. The exposure to the fearful stimuli is measured by the individual who assigns each personal image with a Subjective Units of Discomfort (SUD) score. The SUD scale measures levels of anxiety ranging from 0 'not at all' to 10, 'the highest level of anxiety you could imagine'. After assigning each photograph with a SUD score, they decide how they will be presented on the VR screen. Systematic desensitisation to the feared photographs encourages engagement with, rather than avoidance of trauma-related triggers. Each time the photograph is presented on the VR screen, the therapist helps the participant assess the exposure and its consequences and then addresses negative cognitions associated with the feared stimuli. Once there is a reduction in a negative association with the memory, the therapist moves on to more feared stimuli in a stepwise manner and repeats the same process.

3MDR differs from the traditional application of systematic desensitisation to PTSD. 3MDR combines graded VRET with physiological monitoring to increase levels of exposure. 3MDR is designed to allow individuals to confront their most feared traumatic experiences within a safe yet fully immersive VR environment. As with other exposure therapy approaches for PTSD, 3MDR encourages engagement rather than avoidance of trauma-related triggers. The individuals are trained to recognise their responses to the stimuli and adapt their reactivity over time. One of the main advantages of the systematic desensitisation using a VR technique is that it allows individuals who struggle to identify, imagine, or talk about their trauma, learn

to confront their memories, and develop skills applied to several other stressful situations.

4.2.4 Experiential Avoidance (EA)

Experiential Avoidance (EA) is a state of unwillingness to experience a negative feeling, emotion, or memory and, as a result, develop mechanisms to stop them from occurring [303, 304]. The avoidance of reminders may reduce distress in the short term. However, as there is no new information or learning, the individual is stuck in a perpetuating loop of negative patterns [305, 306], which causes disruption to the integration of long term memory and can prevent remission [307, 308] [309-311]. This can establish avoidance, a key symptom cluster of PTSD [312, 313]. There are three primary forms of EA; 1) cognitive avoidance refers to the inability to think about and rationalize events, 2) behavioral avoidance refers to avoiding people and places that remind the individual of the traumatic event, and 3) emotional avoidance involves efforts to avoid feelings associated with the traumatic event, e.g., guilt or shame.

3MDR targets the various aspects of EA using personalised, self-selected images of trauma that have been previously avoided or suppressed by the individual. Personalised music and images actively encourage the engagement and processing of the trauma to achieve recovery. Active engagement with the feared stimuli reduces the chance of EA by increasing their cognition towards a goal-directed activity which increases positive reinforcement with the memory. 3MDR promotes acceptance of private events in conjunction with behavioural change strategies, such as cognitive and memory restructuring [4] to help reduce PTSD symptoms [303, 309].

4.2.4.1   Habituation

Habituation is defined as reducing reactivity or arousal through repeated exposure to a stressor, described as 'unlearning' or 'adaption' [314]. Despite researchers' assumptions that habituation is the simplest form of learning, little is known about the underlying mechanism of change [315]. Researchers who have examined habituation in animals suggest that it is a way to focus on essential stimuli and ignore irrelevant stimuli, facilitating learning. Focusing on central stimuli and ignoring other unrelated or useful stimuli may also require other

learning forms. Therefore, habituation has a critical role to play in forming a conditioned response [315].

In 3MDR, habituation refers to a decrease in response to repeatedly presented self-selected images of the participant's trauma. However, habituation to one stimulus does not prevent or result in habituation to an additional stimulus, as the feared response occurs when the feared stimuli are paired with novel stimuli [316]. In 3MDR, participants initially select twenty images and rotate them in sets of 6 to be presented onto the VR screen. This encourages habituation to various stimuli, all associated with similar traumatic memories. Therefore, prolonged exposure during 3MDR treatment sessions helps people with PTSD habituate their response to the trauma, allowing more energy and concentration to be placed on more adaptive memories.

4.2.4.2   Extinction

Extinction refers to unlearning a conditioned response to a feared stimulus and withstanding reminders without experiencing extreme distress [227, 301]. Extinction works when the individual is exposed to just the conditioned stimuli, without the unconditioned stimuli, for a prolonged period, reducing the potency of the conditioned stimuli and thus a reduction or elimination of the conditioned response [317]. If the extinction of the feared stimuli is not maintained, it can contribute to symptoms of hyperarousal and hypervigilance in PTSD [316] [37, 318]. For example, a military veteran who heard a loud noise from an Improvised Explosion Device (IED) explosion is likely to feel fear when they hear any loud noise. If a veteran survives the IED explosion, this forms a strong association between loud noises and the explosion's aftermath. Fear extinction of these stimuli occurs when a veteran can experience loud noise without any negative consequences. Therefore, the goal of 3MDR treatment is the unlearning or the extinction of the conditioned response associated with the personalised images and memories.

4.2.5   Summary

Conditioning theory has been applied to 3MDR to explain alteration in the emotional memory structure, which causes individuals to develop a conditioned response consistent with symptoms of PTSD. The WMM described the underlying mechanism of change, which

suggests that exposure to traumatic memories and, subsequently, bilateral stimulation reduces the vividness of the traumatic memories and, in turn, the emotional sensitivity. The reduction in vividness may be due to competing for the working memory resources. The same area of the brain associated with bilateral stimulation is also associated with negative memory recall. The personal photographs projected onto the virtual reality screen have been described as a form of exposure therapy, as repeated exposure to the feared stimuli reduces feared response (habituation) and, over time, eliminate the fear associated with the memory (extinction). Figure 4-5 demonstrates the application of theory and model to 3MDR interventions. The current theories may prove inadequately broad once we move towards a better understanding of the context of change in 3MDR.

Figure 4-5 The application of Conditioning theory and Exposure therapy to the 3MDR intervention.
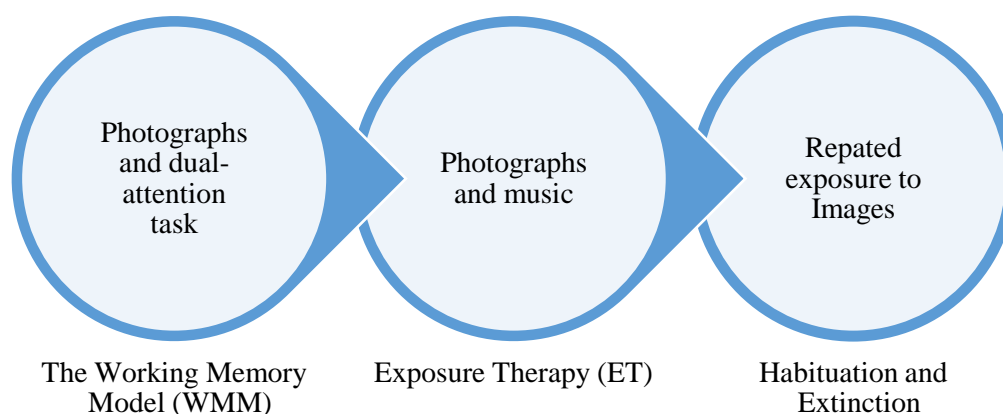
4.3 The Evidence

3MDR is a relatively new therapy with emerging evidence [302]. There have been two pilot studies [256], two RCTs, and several ongoing pieces of work [78, 302]. The research so far demonstrates that 3MDR can be effective in Dutch uniformed and military personal, Canadian military veterans and British military veterans compared to a waiting list control. The published evidence and ongoing work in 3MDR are described below.

4.3.1 Pilot study: Netherlands

In the pilot study, two veterans with chronic PTSD attended four weekly sessions of 3MDR [259]. The treatment sessions were created in a Computer Assisted Rehabilitation Environment (CAREN) facility. 3MDR was shown to be effective at reducing PTSD symptoms in both individuals. The pilot study provided the starting point for research into the effectiveness of 3MDR as a treatment for PTSD. However, the study had several limitations, including a small sample size of two participants, limiting the reliability and generalisability of the findings. The study reported a reduction of PTSD symptoms in both participants, although no standardised measures were used. Instead, each participant's qualitative response indicated positive treatment effectiveness, limiting the findings' internal and external validity. It would have been helpful if more extensive qualitative semi-structured interviews were conducted in addition to the collection of quantitative data. The study also failed to report any adversity or ethical considerations, such as any discomfort or distress experienced due to 3MDR, to help instruct future research. The pilot study provided the first clear instructions on how to conduct 3MDR in a controlled setting. An RCT aims to replicate the study using a rigorous method to examine the efficacy and feasibility of 3MDR in a larger sample of participants with PTSD.

4.3.2 Pilot study: Canada

Researchers in Edmonton, Canada, has conducted a pilot study examining the effect of 3MDR on PTSD in Canadian armed forces with combat-related trauma [319]. The study recruited eight participants with chronic combat-related PTSD who completed six 3MDR treatment sessions. The outcome measures included PCL-5, Generalised Anxiety Disorder (GAD-7) and SUD scores administered before and after 3MDR treatment. The results indicated a 10 point reduction in PTSD symptoms as measured by the PCL-5 post-treatment. The study reported positive participant feedback, although no standardized question or semi-structured interview was analysed. Three participants did not complete the study, which meant the sample size was relatively small. The participant scores were all based on self-report measures, which reduced the generalisability and reliability of the results.

4.3.3 Phase II trial: Netherlands

The phase II RCT in the Netherlands was designed for veterans diagnosed with TR-PTSD, defined by an inadequate response to first-line psychological therapy [78]. The study included forty military veterans with combat-related PTSD [78]. Before the treatment sessions, participants received guidance on photograph selection and the music played before and after the sessions. Everyone was also offered psychoeducation about possible reactions before, during, and after each session. The therapy consisted of nine sessions, with two introductory sessions and six treatment sessions. The purpose of the introductory sessions was for the therapist and participant to build rapport, discuss the trauma and select the images that were to be projected onto the screen.

The RCT benefited from adherence to strict inclusion and exclusion criteria, and PTSD diagnosis was confirmed using the CAPS-5 [3], a gold standard PTSD measure. However, after the sixth 3MDR treatment sessions, participants still experiencing symptoms received one to three additional integrative and supportive sessions (45 minutes), which may have biased the results. The integrative sessions were to address any ongoing difficulties and provided techniques to prevent relapse. The effects of the 3MDR treatment sessions were evaluated and assessed after these additional sessions. The results were positive as participants reported a significant reduction in PTSD symptoms after treatment and the additional sessions.

4.3.4 Phase II trial: Cardiff

The phase II RCT of 3MDR aimed to explore the efficacy and feasibility of 3MDR within British military veterans with TR-PTSD. Of the fifty-two military veterans referred to the study, forty-two participants were randomised. The retention rate was 83% at 12 weeks post-randomization and 86% at 26 weeks post-randomization (Figure 4-6). Outcome data were collected at baseline, 12 weeks, and 26 weeks post-randomisation. The results demonstrated more significant improvement for participants in the immediate arm versus the delayed arm at the primary endpoint of 12 weeks [320]. Figure 4-7 illustrates the relative reductions in CAPS-5 scores over time between those randomised to the immediate arm and those to the delayed arm.

The research study followed CONSORT guidelines for reporting the methodology [321]. The randomisation process reduced allocation bias as participants were randomly allocated into

two groups by an independent researcher. Researchers assessed for PTSD used the gold standard CAPS-5, which increased the results' generalisability and statistical reliability. The participants completed eight self-report questionnaires measuring comorbidities, such as sleep disturbance, depression, and social support. The measures were all standardised and well used, although the self-report measures are subject to reporting bias. Researchers conducting the assessments remained blind to what group participants were allocated throughout the trial, which minimised assessment bias. The inclusion criteria increased the internal and external validity as it ensured a homogeneous sample. The eligibility criteria excluded anyone with a suicidal intention or alcohol dependency, which reduced any ethical concerns. However, the strict inclusion criteria limited the sample population, and thus the results are less reflective of a real-life setting.

Figure 4-6 CONSORT Flow Diagram
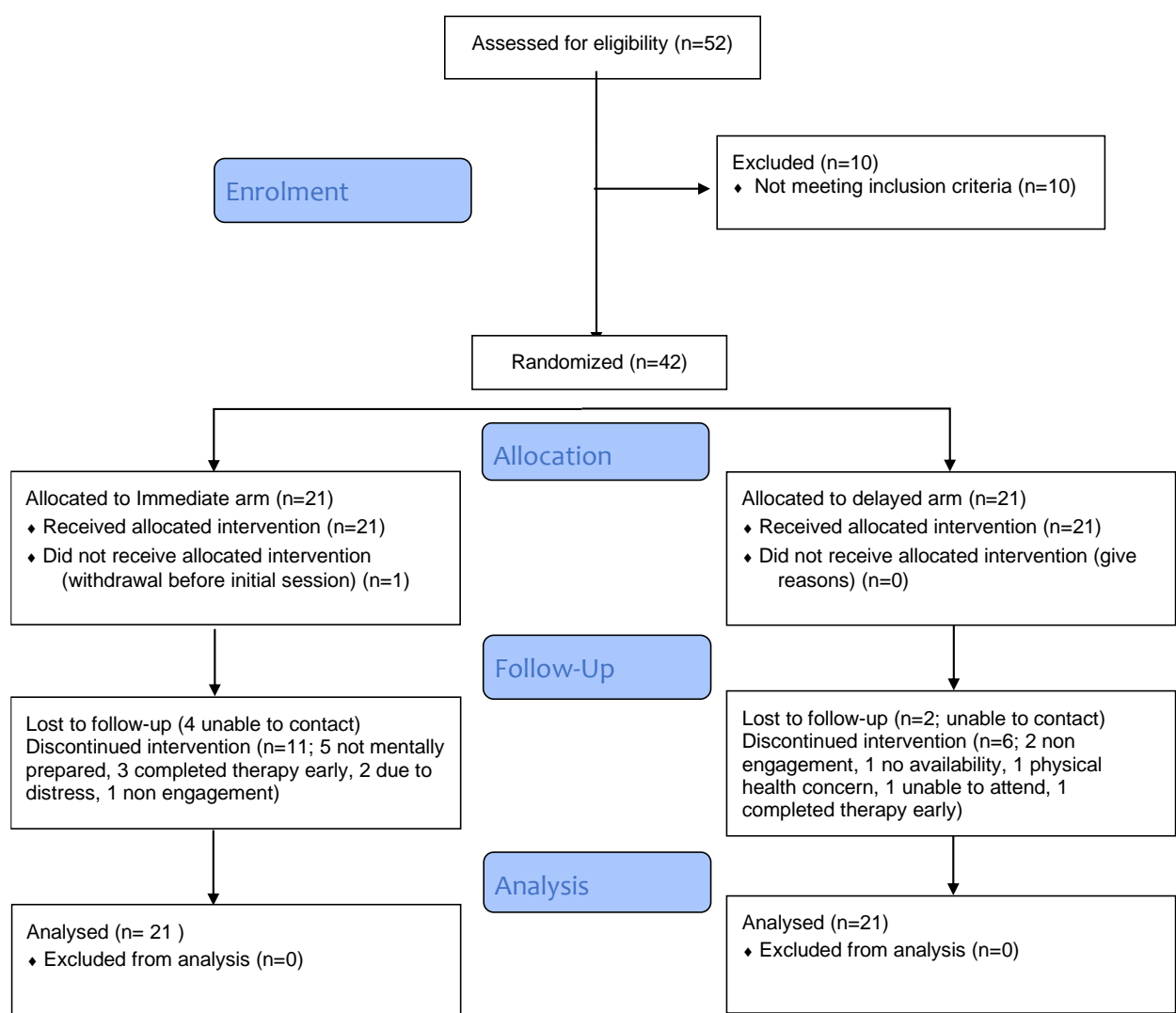
Figure 4-7 Mean CAPS-5 over time by randomisation arm
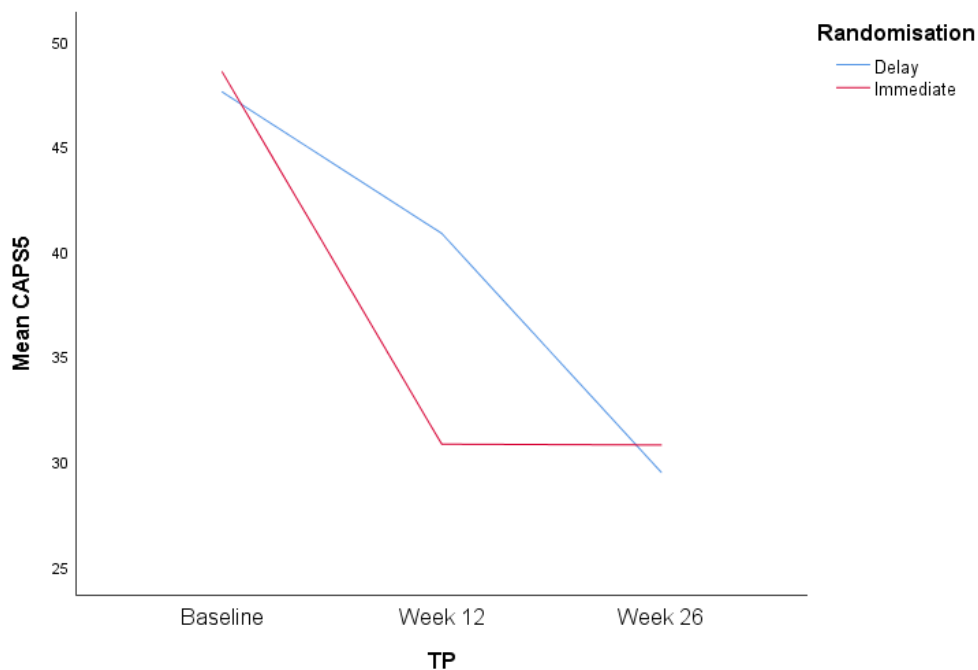
Note: Clinician-Administered Post Traumatic Stress Scale (CAPS5), Time Point (TP)

4.4 Ongoing work

4.4.1 Netherlands: University of Leiden and ARQ Centrum' 45

Researchers in the Netherlands are currently conducting a Walk and Talk study; An RCT of 3MDR vs Treatment As Usual (TAU), for patients with PTSD as registered via Netherlands trial register NL6837 (NTR7074). The study comprises two conditions: the experimental 3MDR intervention and the usual care condition is conventional TF psychological therapy. Participants are being randomised to receive 3MDR treatment (10 weekly sessions) or TAU (16 weekly TF psychological therapy sessions). The protocol states that differences in PTSD will be measured before, during and after treatment. The study aims to recruit 134 military veterans with combat-related PTSD, which will provide a large sample for analysis. However, the protocol does not specify what analysis will be conducted nor whether a quantitative, qualitative or mixed-method approach will be used to measure PTSD and other related symptoms.

The second RCT in the Netherlands aims to determine whether 3MDR delivered using an

HMD is non-inferior to traditional 3MDR using the CAREN system. The aim is to recruit 60 participants and randomise them into two conditions: 3MDR with CAREN (N = 30) and 3MDR with HMD (N = 30). Further therapy will not be provided to participants who respond to treatment at 6 or 8 weeks. However, for those that do require further therapy, this will continue through to 10 weeks. The primary outcome measure will be a CAPS-5 to assess PTSD symptom severity. A limitation of the methodology is that participants who respond less well to treatment receive additional sessions, which may bias the results and make it more challenging to assess the actual effect and difference between the two groups.

4.4.2 Canada: The University of Alberta in Edmonton

Researchers at Edmonton are currently conducting a mixed-method RCT for Canadian Armed Forces service members with combat-related TR-PTSD as registered via ISRCTN Registry (11264368). The study is comprised of two conditions: an experimental group (N = 20) who will receive six sessions of 3MDR once a week followed by TAU and a waiting-list control group (N = 20) who will receive TAU for nine weeks and then offered 3MDR therapy for six sessions before resuming TAU. Both quantitative and qualitative data will be collected at one, three, and six months post-therapy. A strength of this study is that biomarkers and self-report measures include information on PTSD, moral injury and resilience. However, a disadvantage is that no CAPS measure will be collected. A further strength is using qualitative semi-structured interviews to further identify the participant experience of 3MDR and factors associated with treatment outcome, which will be analysed using thematic analysis.

4.4.3 USA: Walter Reed medical centre

The Walter Reed Medical Centre in Washington is conducting a pilot prospective RCT to test the effectiveness of 3MDR for people with PTSD compared to those with a mild (TBI). The protocol is published via Clinicaltrials.gov (NCT03796936). The study aims to recruit 24 active duty or retired military personnel diagnosed with PTSD and have experienced at least one mTBI with continued persistent symptoms. The study aims to randomise participants in one of two conditions: 3MDR with Eye Movement Component and the other condition received 3MDR without Eye Movement Component. The main limitation is that the primary outcome measure will be PCL-5 to assess self-reported PTSD symptom severity compared to

a clinician-administered interview. Secondary measures will also consist of several self-report measures that measure conditions commonly comorbid with PTSD.

4.4.4 Israel: The University of Haifa in Mount Carmel

An RCT is also being conducted at the University of Haifa in Mount Carmel, Israel. The study follows rigorous RCT guidelines and uses gold standard clinician-administered measures to collect PTSD symptom severity. The study is limited due to the homogeneous populations, as the study aims to focus on uniformed personnel, limiting the external validity of the results. However, the studies will provide further information regarding the efficacy of 3MDR in different populations. To our knowledge, no protocol is currently published or readily available.

4.5 Summary

Due to a need for more effective and tailored treatment for people with TR-PTSD, a novel intervention called 3MDR has been developed. This intervention draws on several therapies and techniques, including VRET and dual-attention tasks. The therapy pioneers propose that 3MDR works by taxing the WM as traumatic memories are desensitised, and a dual-attention task promotes new learning through reconsolidation. Alternatively, conditioning theory could explain 3MDR as a form of exposure therapy and the reduction and eventual elimination of PTSD symptoms result from habituation and extinction. Research into 3MDR for the treatment of PTSD is in its early stages. A major strength of 3MDR is that it continues to evolve and future refinements include reducing the size and creating a more accessible, less assisted version to reduce the cost and maximise the accessibility as a treatment for PTSD. However, a limitation is that it is still likely that individuals with TR- PTSD will require additional knowledge and support from a therapist, which may still prove a complicated and costly treatment to implement. Therefore, as it currently stands the cost of the equipment and training makes the intervention inaccessible and expensive to roll out within the NHS. Furthermore, due to the intensity of the exposure in 3MDR, it is likely that it may not be suitable for all trauma types, as it may lead to re-traumatisation. The next step is to examine what factors were associated with participants doing better or worse in treatment to improve the effectiveness of 3MDR and, in turn, inform other psychological treatment outcomes.

Chapter 5: Methodology

5.1 My role

The sample and data utilised throughout this thesis were from a Phase II RCT of 3MDR therapy for military veterans with TR-PTSD [302]. I joined Cardiff University's Traumatic Stress Research Group (TSRG) in January 2017. I was responsible for obtaining ethical approval, participant identification, recruitment, quantitative assessments, and day-to-day trial data management. I conducted a secondary analysis of both quantitative and qualitative data for my thesis.

5.2 Ethical approval

The trial had UK NHS Research Ethics Committee (REC) approval (MREC/97/7/01) and Research and Development approval in all contributing NHS Wales health boards. Recruiting sites were a military veterans' mental health services in four health boards: Cardiff and Vale University, Aneurin Bevan University, Swansea Bay, and Cwm Taf Morgannwg University Health Boards. All participants provided written informed consent. The study was conducted in line with the ethical guidelines proposed by the World Medical Association Declaration of Helsinki (1964) and later revisions [322]. On the 14[th] of February 2017, confirmation of the NHS REC's favourable ethical approval was secured. Subsequently, there were five substantial amendments. The trial was sponsored by Cardiff University and funded by the Forces in Mind Trust (FIMT) with revenue from the National Lottery. The Principal Investigator for this trial was Professor Jonathan Bisson (Cardiff University).

5.3 Study design

The work was embedded within a Phase II RCT of 3MDR therapy for military veterans with TR-PTSD. A mixed-methods research approach was chosen for this thesis. Both quantitative and qualitative data were collected and analysed [323, 324]. Quantitative analysis was chosen to explore factors associated with military veterans doing better or worse in 3MDR treatment, as measured by a loss of diagnosis or significant change in CAPS-5. Qualitative analysis was chosen to explore factors associated with treatment outcome, as derived from qualitative

semi-structured interviews. A 'mixed' method approach involves combining data collection methods, analysis, and interpretation of the data to incorporate diverse perspectives and identify connections between the various methodologies to answer the research question [325, 326].

5.3.1 Sample size calculation

Although a standard power calculation was not expected for a Phase II exploratory trial, it was considered wise to use a power calculation based on the results of a previous trial of CBT-TF for PTSD [327] to inform the sample size and ensure it was likely to be adequate. The calculation suggested that for an 80% chance of detecting a mean 15-point difference on the CAPS-5 [328] at the 5% significance level, with a standard deviation of 15.2, 17 subjects per arm would be needed. An extra four subjects were added to each arm to provide a conservative estimate of a 20–25% dropout, representing a total proposed sample size of 42.

5.3.2 The identification of the qualitative sample

Qualitative interviews were conducted with both trial participants and therapists. However, for my analysis, I focused just on participants. The decision was made to use purposive sampling based on who had completed the treatment and those who had dropped out to participate in an interview after completing the 3MDR intervention. The qualitative research lead (Professor Ben Hannigan) ensured that a participant from each therapist was interviewed to overview the participants' experience. The qualitative lead conducted in-depth semi-structured interviews with 11 trial participants after treatment was completed, from 14 who had received an invitation from four health boards. The 11 participants were a sub-sample of the 42 participants in the study. To learn from a wide range of participants, veterans with a diverse range of demographic and clinical characteristics were selected. This included:

- Who adjusted to the 3MDR therapy sessions.
- Who did not adjust to the 3MDR therapy sessions.
- Participants were selected from both treatment arms.
- Participants from the treatment list of all 3MDR-providing therapists.
- Across a wide range of length of time since trauma, and previous therapy experience.

- Participants who had dropped out of treatment.

5.3.3 Inclusion and exclusion criteria

Participants recruited to the 3MDR trial were 18 years of age and over and provided informed written consent. They met the DSM-5 criteria for combat-related PTSD, TR defined as persistent PTSD despite prior receipt of a trauma-focused psychological treatment. Individuals were excluded from the trial if they were unable to walk at an average pace for up to 45 minutes on a treadmill, had a change in their psychotropic medication within one month, were substance dependent, had any suicidal intent or had a primary diagnosis of psychosis, or a diagnosis of a major depressive episode.

5.4 Sample recruitment

The primary recruitment method was a referral from one of six veterans NHS therapists (Trauma-Focused Post Traumatic Stress Specialists) in outpatient primary care clinics within local primary mental health services. Five of the therapists were employed by Veterans' NHS Wales (VNHSW), and one was employed by Cardiff University. VNHSW is a service that aims to improve the mental health and wellbeing of veterans with combat-related mental health problems. VNHSW received self-referrals, referrals by family members, or other services. The therapists were responsible for identifying participants who had not responded to trauma-focused psychological treatment and fulfilled the trial's eligibility criteria. Once an expression of interest was made, the therapist completed a Case Report Form (CRF) with the participant's contact details and sent it to the research team via email in a password-protected document.

The second method of recruitment was to contact discharged patients from one of the four VNHSW clinics. These participants had either failed to engage with psychological treatment or responded inadequately and continued to experience PTSD symptoms. Letters were sent out that explained why they were being contacted, gave details of the trial, and listed the inclusion criteria. Participants were instructed to send back the reply slip if they were interested in participating in the trial, providing consent to be contacted via email, phone, or post.

The third method was to identify potential participants from the National Centre for Mental Health (NCMH) database and the PTSD registry. The NCMH is a Welsh Government-funded research centre that investigates psychiatric disorders across the lifespan. The PTSD registry is a cohort of individuals' information for research into trauma and mental health. Once all potential participants were identified, the same process of contacting participants, as mentioned above, was followed.

5.5 Randomisation

Blocked randomisation was used to allocate participants to the two comparison arms (3MDR and waiting list). A statistician (Tim Pickles) used a computer programme to create randomisation codes for each participant on a 1:1 basis with a block size of 6 and no stratification. The allocations were enclosed in sequentially numbered, opaque, sealed envelopes numbered from 1 to 42. An impartial research assistant allocated consecutive participants by opening the envelopes sequentially and only after the individual envelope had been irreversibly assigned to the participant.

5.6 Blinding

The research nurse and I were blinded from which arm each participant was randomly assigned. Throughout the process, the research nurse and I did not attend any meetings that discussed treatment arms, nor were we able to access the database or any information revealing the allocation. All other members of staff were aware of the allocation of each participant.

5.7 Assessment procedure

5.7.1 The quantitative assessment procedure

Following participant identification, the research nurse and I contacted participants and used the PCL-5 [119] to screen for PTSD. The PCL-5 is a self-report measure that examines the 20 DSM-5 symptoms of PTSD. The PCL-5 was used to evaluate symptom change during and after treatment. Participants who were considered eligible were also asked to complete a two-

week diary after their telephone screening and before the baseline appointment. The purpose of the diary was to monitor symptom severity across two weeks, as this had previously been associated with a reduction in symptoms [329]. Participants were also asked to attend a baseline assessment after these two weeks. The research nurse and I interviewed participants at baseline and after randomisation at 12 and 26 weeks follow up. All assessments were held in rooms in the Hadyn Ellis Building, Division of Psychological Medicine and Clinical Neuroscience, School of Medicine at Cardiff University. Participants who were not available to attend the clinic in person were given the option to complete the assessment via telephone. Following a complete description of the trial, voluntary consent was obtained. Participants then underwent a structured clinical assessment lasting approximately an hour and a half. Participants were asked to complete the Life Events Checklist for DSM-5 (LEC-5) [330], followed by the CAPS-5 and then a series of demographic and mental health history questions.

Participants were interviewed using the CAPS-5; [328] a semi-structured interview to assess PTSD symptoms and establish a clinical diagnosis. The CAPS-5 is considered the gold standard in PTSD assessment [320]. The CAPS-5 is an assessment tool that is based on the DSM-5 criteria for PTSD. The CAPS-5 comprises a 30-item semi-structured interview that assesses PTSD symptoms across a lifetime, one month or one week and covers PTSD severity and dissociative symptoms. The CAPS-5 provides a severity measure by assessing frequency and intensity of symptoms, interpersonal and social functioning and overall validity and reliability of answers. Researchers completed the one-month CAPS-5 assessment at baseline and 26 weeks and the one-week CAPS-5 version at 12 weeks. The CAPS-5 assessment took between 45-60 minutes. After baseline assessment was completed, a CRF containing the participant's contact information was passed onto an impartial research colleague (statistician: TP) who randomly allocated them to receive the 3MDR intervention (the active arm) or waiting list (the control arm).

5.7.1.1 Questionnaire outcome measures

After the interview, participants were asked to complete a set of seven self-report questionnaires. The questionnaires are described below and aimed to evaluate distressing life events, depression, anxiety, alcohol consumption, nature of sleep, perceived social support, and quality of life.

- The LEC-5 is a self-report tool designed to be used before administering the CAPS-5 assessment. The LEC-5 explored 16 traumatic events and includes one additional item assessing any other distressing event not captured in the 16 items [330].

- The Patient Health Questionnaire (PHQ-9) is a well-validated and reliable brief self-report measure of depression [331].

- The Generalised Anxiety Disorder (GAD-7) is a widely used, reliable, and a well-validated brief self-report measure of anxiety [332].

- The Alcohol Use Disorders Identification Test (AUDIT-O) comprises ten self-report questions that measure the quantity and frequency of alcohol intake. Ten questions, 8 used to measure drinking behaviour across three months and two across the lifetime [333].

- The Insomnia Severity Index (ISI) is a self-report measure that contains seven questions assessing problems with insomnia. It is widely used and is considered reliable at detecting the presence and impact of insomnia [334].

- The Multidimensional Scale for Perceived Social Support (MSPSS) comprises 12 questions that measure family, friends, and partner support. The reliability and validity of the MSPSS have been shown with several populations [335].

- The Work and Social Adjustment Scale (WSAS) is a self-report measure that assesses the individuals' mental health difficulties with work, social activities, and personal or family relationships [335].

- The EuroQol five-dimensional descriptive system (EQ-5D-5L measures health-related quality of life) [336]. The first part of the questionnaires identifies problems in five areas of physical health; mobility, self-care; usual activities; pain and discomfort; and anxiety and depression. Each response is rated on a 1-5 scale, where 1 represents no problems and 5 represents the worst health problem. The second part is a visual scale, which measures current health status on a 0-100 scale.

5.7.1.2   Quantitative data capture

All information and data obtained from participants were kept confidential by the research team following the General Data Protection Regulation (GDPR, 2018). All data will be stored for 15 years after the end of the study following Cardiff University's Research Governance Framework Regulations for clinical research.

The CAPS-5 interview and questionnaire measures described below were designed as (CRFs. All assessment data were recorded manually on CRFs and recorded electronically on a password-protected excel spreadsheet. Personal identification data were held on a separate spreadsheet to maintain data protection. All paper CRFs were securely stored in the Hadyn Ellis Building. All electronic records were kept in a password-protected folder on a confidential and secure Cardiff University server. Each participant was identified by a unique participant number to ensure anonymity and confidentiality of records was maintained.

5.7.2 The qualitative procedure

Interviews were active and meaningful communication to understand the participant's perspective. The semi-structured interview consisted of a small number of questions with a loose structure that could act as a starting point for data collection while guiding the interviewer and participant. The use of prompts or probes aimed to help the participant explain their answers. Questions were open-ended, which is a way of allowing the participant to provide in-depth and meaningful answers. In more structured interviewing, answers might be relatively limited, leading to short answers and less information.

5.7.2.1 Qualitative data capture

All interviews were digitally audio-recorded and varied in length, from 25 to 76 minutes. The data collected from all the interviews were transcribed by the qualitative lead or by a professional transcriber. The transcripts amounted to 9 hours and 13 minutes or 548 minutes of interviewing. All transcripts were anonymised, with the names of participants removed. All anonymised transcripts were then uploaded onto NVivo 10, a Qualitative Data Analysis (QDA) package created by QSR International [337].

5.7.2.2 The qualitative interviews

The interview structure and content of the questions are detailed below. Veterans were invited to talk about:

- The integration of 3MDR into everyday life;

- Initial thoughts and expectations at the start of therapy, including discussions with family and friends and the selection of images and music;

- First impressions of the clinic and experiences of 3MDR being explained;

- Selections of images and music within and across sessions, and experiences and views of therapy sessions over time;

- Factors helping continuation with therapy;

- Discussions (if any) with family or friends about 3MDR experiences;

- The extent to which expectations have or have not been fulfilled;

- Helpful and unhelpful aspects of 3MDR and views on continuation if available;

- Views on recommending 3MDR to others with similar experiences;

- For a participant who had dropped out, factors hindering continuation;

- How 3MDR might be organised or delivered differently.

5.7.3 The intervention

The 3MDR treatment centre was in the Ty Dewi Sant building in the University Hospital of Wales (UHW), Heath Park campus. UHW is a general hospital linked with Cardiff University. The referring Veterans' Therapist usually performed 3MDR. However, where this was not possible, participants were allocated to the next available therapist. All Veterans' therapists received training and were considered competent by the Netherlands trainers in 3MDR therapy.

5.7.3.1 The intervention procedure

3MDR was implemented once a week for six weeks with two introductory sessions before starting treatment and one concluding session. Participants allocated to receive 3MDR were scheduled to attend the introduction session as soon as possible. Participants allocated to a waiting list control received 3MDR treatment 12 weeks after randomisation. The therapists received monthly supervision from the lead therapist and supervision every three months from the Netherlands team. Supervision aimed to discuss the delivery of treatment.

5.7.3.2 Strategy and procedure for improving and monitoring adherence

Participant adherence to treatment sessions was measured by the therapist log of attended, rescheduled, and delayed 3MDR sessions. If participants were scheduled to be away, then treatment was postponed for up to three weeks. Similarly, adherence to assessment sessions was measured by the researcher log of scheduled, rescheduled, and delayed appointments. Participants were reminded of appointments a week before and the day before to confirm attendance and improve adherence. Also, participants received follow up phone calls or letters following any missed appointments to rearrange their session, maximising therapy completion.

5.7.3.3 Assessment of harm and invasiveness

During the 3MDR intervention, participants were exposed to self-selected images of their trauma, altering their mood and psychological state. Participants were advised to contact the PI if they felt they were experiencing any harm because of taking part in the trial. If any adverse events requiring additional support occurred, each health board's PI and therapist arranged appropriate medical or psychological support.

5.8 Data analysis

5.8.1 Quantitative analysis

The analyses undertaken for the RCT were conducted according to the intention-to-treat principle, where participants are analysed based on the initial randomised treatment group, regardless of adherence or the eventual treatment received. This exploratory analysis employed multiple linear regression that tested whether comorbidity with depression, age,

time since trauma, adherence to homework, level of education, and employment status was associated with treatment outcome. Continuous intention to treat data were analysed to ensure all randomised participants were considered by comparing the means using ANCOVA with baseline scores as covariates. Regression analyses were performed to examine which factors were associated with a positive or negative outcome. All data analyses were performed at the end of data collection using SPSS version 25 (International Business Machines: IBM Corp. Released 2017 [338]) for statistical analysis. All linear regression requires that the residuals should be normally distributed. Normality was checked with a residual-versus-fitted plot. A multiple linear regression analysis was conducted to test the interaction between the arm and multiple independent factors.

The method of investigating interaction and non-interaction by the regression analysis introduced by Yates [339] was applied to the 3MDR data. The possible interactions between factors associated with treatment outcome and treatment arm could be recognised as specific competitive factors. The regression technique forms a valuable approach to the discovery and classification of these effects among the sample. Regression analysis was applied to all 6 factors to identify any significant associations with treatment outcome, with and without interaction.

Sensitivity Analysis (SA), also referred to as 'what-if' analysis, examines the robustness of the results and whether altering the variables, model, or assumption changes the conclusion [340]. SA was conducted to determine the reliability of the assumptions and which assumption or model is the most significant to the outcome [341]. The standard SA for clinical trials to determine if a factor is associated with the outcome is to interact with the arm variable in the regression analysis to determine the primary outcome. The factors considered were identified before conducting the analysis to avoid any influence from the knowledge of the data. According to guidelines, the arm variable should be included in a clinical trial analysis, regardless of the type or relevance of the analysis [342].

Table 5-1 Factors selected as associated with treatment outcome

Factor	Measures	Definition	Variable Type	Categories
PTSD symptom severity	CAPS-5	PTSD symptoms as measured by the CAPS-5 scores at Baseline assessment.	Continuous	

Depression	PHQ-9	Depressive symptoms as measured by the PHQ-9.	Continuous	
Age	NCMH	The age of the participant at baseline assessment.	Continuous	
Time Since Trauma	LEC-5	The time in months or years since their trauma.	Continuous	
Adherence to pre-treatment homework	Diaries	Whether or not participants completed and handed in their diaries at baseline assessment	Categorical	• Yes • No
Employment	NCMH	1. Employed (full time) 2. Employed (part-time) 3. Self-employed or freelance 4. Homemaker 5. Student 6. Retired 7. Volunteering 8. Unable to work (including Driver and Vehicle Licensing Agency: DLA) 9. Out of work and looking for work 10. Out of work but not currently looking for work	Nominal	• Employed (Full) • Self-employed • Retired • Volunteering • Unable to work

Education	NCMH	1. 'No academic or professional qualifications 1-4 GCSEs or equivalent.' '5+ GCSEs or equivalent' 'Apprenticeship': Apprenticeship. '2+ A Levels or equivalent' (Level 3 qualifications): 2+ A level 2. 'Degree level or above' (Level 4 qualifications and above): Degree (for example BA, BSc), 3. 'Other qualifications': Vocational/Work-related Qualifications, Foreign Qualifications/ Qualifications gained outside the UK (NI) (Not stated/level unknown)	Nominal	• 1-4 GCSE or equivalent • 5+ GCSE or equivalent • 2+ A level or equivalent • Degree or above

National Centre for Mental Health (NCMH), Clinician-Administered Post Traumatic Stress Scale for Diagnostic Statistical Manual 5th Edition (CAPS-5), Patient Health Questionnaire (PHQ-9), Life Events Scale (LEC-5), Disability Living Allowance (DLA)

5.8.1.1 Missing data

All missing data on CAPS-5 at 12 and 26 weeks and associated factors were imputed using Multiple Imputation by Chained Equations (MICE) under a missing at random assumption. The imputation was based on all variables in the relevant model. The statistician (TP) explored whether the associated factor was associated with the missing CAPS-5 at 12 and 26 weeks. Multiple imputations were undertaken, and exploration suggests that the mechanism was not missing at random.

5.8.1.2 Quantitative validity

Quantitative validity is concerned with whether the means of measurement are accurate and measure what they intend to measure. The quantitative data had high internal validity as the researchers used gold standard clinician-administered interviews and standardised self-report measures to assess the participants. Furthermore, the same measures were used at each time point, and the researchers asked each question systematically to maintain consistency across sessions. The research nurse and I met weekly to discuss scores, to strengthen the validity of the data [343] [344].

5.8.1.3 Quantitative reliability

Inter-rater reliability was not formally assessed. The research nurse and I attended a three-day training program to administer the CAPS-5 and assessed three videos to check for competency. Once researchers reached a threshold and were deemed competent, they were signed off by the PI. Furthermore, the research nurse and I met weekly throughout the trial to discuss ratings and ensure scoring methods remained consistent. Data integrity was assessed by having the data in the excel file independently checked to ensure that this matched the hard copy of the questionnaire for a 10% sub-sample of participants.

5.8.2 Qualitative analysis

Data was analysed from the participant interviews to examine any factors associated with people doing better or worse in treatment. Thematic analysis was selected to examine the qualitative data and produce further evidence to support the factors identified in the systematic review while still considering alternative factors associated with treatment

outcome [345]. Thematic analysis is not theory-driven, and therefore an exploratory approach was adopted to examine within and between cases. The thematic analysis provided detailed and in-depth insight into the participant's experiences [345]. As the qualitative lead and research lead analysed the data for different purposes, stories were developed from the same data set. Despite the research lead not interviewing the participants or transcribing the data, Braun and Clarke's recommendations were followed [346]. This involved spending a lot of time reading and re-reading the transcripts to become familiar with the data [346]. The Consolidated criteria for Reporting Qualitative research (COREQ): a 32-item checklist to report study methods, analysis and results was used [321].

To address the objectives, the qualitative analysis focused on identifying and analysing factors associated with treatment outcome by examining the participant's views and experiences within each case and across the data set [345]. Braun and Clarke [345] provide a step by step guide for researchers to conduct a thematic analysis:

1. Familiarise: Initial thoughts and ideas were noted, which is considered one of the necessary steps of analysis [347]. As it wasn't possible to be involved in the initial stage of transcribing because the research lead remained blind to the randomisation arm. Therefore, as the guidelines suggest after the research lead was unblinded, they immediately immersed themselves in the data by listening to each of the audiotaped interviews as soon as it was practical. The process of "repeated reading" [345] meant reading and re-reading transcripts once they were available to achieve closeness with the data. Notes were made on the key points after reading the veteran interviews. This was particularly important as another researcher conducted the interviews.

2. Generating initial codes: After reading the transcripts, further notes were taken, and codes were developed. The identification of codes was achieved by initially working through each sentence line by line, which was completed using an inductive approach to identify patterns in the data [348]. These codes identified features in the data that was considered pertinent to the research question, such as 'support' and 'relationships', which were shown to be associated with treatment outcome. The complete data set was given equal attention to identifying any repeated or overlap in patterns. The coding was mainly data-driven; however, a within-study design involved the emergence of theories based on agency and structure [349]. It was important to highlight these within the text. My systematic review (Chapter Chapter 3:) found five factors associated with treatment outcome in psychological intervention for PTSD:

PTSD symptom severity, comorbidity with depression, adherence to homework, employment status, and education level. Therefore, the suggested theory was that some of these factors might be present within this dataset. An example of the initial codes generated is shown in Figure 5-1 and the themes in Figure 5-2.

Figure 5-1 Indicates the codes and themes created using QSR

NVivo the Qualitative Data Analysis (QSR) software

Figure 5-2 indicates the themes

Relationships	9	23	KB	08/10/2019 11:54
Research about Trial	2	2	KB	09/10/2019 13:39
Responsibilites	1	1	KB	08/10/2019 19:43
Support	10	36	KB	07/10/2019 22:41
Symptoms	1	1	KB	11/10/2019 20:58
Therapy	11	42	KB	07/10/2019 23:29

During the coding phase, sections relating to treatment outcome were highlighted, and either words or phrases were given to each chosen extract. The data were considered for a second time to group similar sets of words or statements together, which were identified. Mind maps were then created to help decide the final code names and descriptions. Five codes were created deductively: comorbidity with depression, time since trauma, education level, employment status and homework adherence, considering the theoretical propositions (theory-driven). The remaining fourteen codes were produced through an inductive approach (data-driven).

3. Searching for themes: The third stage involved searching for themes; Firstly, coded text were studied for each participant to see the themes relevant to everyone. The purpose of the within-case analysis was to identify themes that were unique to the person. Once these were identified, the data was considered across the participants to determine common patterns

within the data set. Once commonalities were identified, themes were developed. Once the data was coded and themes were identified for each person, the data set was examined again, but this time concentrated across participants. All the relevant themes were then incorporated and examined into a cross-case analysis, which provided information to answer the thesis question of what qualitative factors were associated with the treatment outcome. This helped to consider the relationships between participants.

4. Reviewing themes: At this point, the data was categorised across themes and themes were identified that had insufficient data or were too unique to be categorised. The refinement of themes was conducted in two steps; firstly, it confirmed that the coded information formed clear patterns of themes; secondly, once the themes were developed, it was considered across the whole data set. Reflective writing was utilised, which included statements to identify the overlap between the text and identify themes. This recreated the vital emphasis that some participants placed on treatment outcome. The themes were often emphasised by different aspects of the data, such as periods of repetition. This confirmed that the identified themes correctly reflected the whole data set [345].

5. Defining and naming themes: Further coding was done to ensure no codes had been missed during the earlier stages. Further coding involved revisiting the coded text and exploring any overlap in data and whether correct labelling was used. Once a clear understanding of the code and themes were established, the analysis moved to phase 5. This involved providing detailed descriptions of the themes ready for analysis. As this was undertaken, significant segments relating to the research questions were highlighted. Short names were given to the chosen extracts that indicated the essence of the identified factors. Factors associated with each participant interview and across the data set were identified. The factors enabled me to identify potential themes for consideration more easily. This cross-case analysis, which considered the overlap and relationship of themes across participants, was the most critical part of the analysis. The analysis identified common patterns in reported factors associated with treatment outcome.

6. Producing the report: The final stage involved selecting examples of transcripts to illustrate elements of the themes. The within-participant study design was essential to recognise the relevant themes both within individual participants and across participants. Ayres [350] argues that this is central to data analysis in participant cases. Furthermore, Ayres suggests that researchers explain the information relevant to all participants and identify unique experiences limited to each case. For example, in this study, the participants' levels of support varied. Consequently, the within-participant analysis provided a summary of

each participant's experience. In comparison, the between-case analysis provided overlaps and consistent themes and patterns in the veteran's experiences.

5.8.2.1 Qualitative validity

Validity in qualitative research is defined by objectivity and truth [351]. A strategy to promote validity and improve rigour is that more than one coder codes the data to have minimised conscious and unconscious background bias of interpretation [352]. This was not possible as the research lead remained blind during the trial to what group participants were allocated, so it wasn't possible to participate in the selection, interview or analysis process in time for publication. However, once the last quantitative assessment was finished with the final participant and the study was concluded, it was possible to be unblinded and have access to the qualitative data to conduct the analysis.

To maintain rigour, the qualitative lead and research lead spent time together discussing thematic methodology. This involved in-depth discussion regarding the relationship between themes identified and the data's broader meaning, which provided valuable information in defining and refining coding schemas. The two supervisors also had the opportunity to read the transcripts and share their viewpoints on the data analysis process. Frequent meetings with the qualitative lead and the supervisors were an opportunity to enhance the data's validity and trustworthiness related to factors associated with treatment outcome [353]. The meetings provided useful guidance to independently identify appropriate segments from the data, apply valid codes, and then discuss the selections with other team members. The mentioned steps were taken to improve objectivity, consistency and reduce any conscious and unconscious bias [353].

5.8.2.2 Qualitative reliability

In qualitative research, data quality and accuracy are achieved through strict precision and the value of being thorough [354]. Qualitative rigour refers to the consistency and accurate representation of data over time [355]. Qualitative research is concerned with the reliability and validity of the data, referred to by Lincoln and Guba as "trustworthiness." [356]. Lincoln and Guba highlight the importance of transparency in qualitative research to reduce the risk of bias and improve the quality of analysis [357]. Credible and dependable data is required to achieve rigour in the qualitative analysis [358]. However, considering the time-consuming

nature of thematic analysis and the trial, peer checking of the intercoder reliability was not possible. However, the thematic approach was extensively discussed with the qualitative lead [359], and recoding was practised to enhance reliability [360]. The qualitative lead provided instructions and training to think similarly. The reliability check does not establish that codes were objective, but the same subjective perspective could be applied to the text [361]. Using the same method provided further confidence in the chosen themes [139].

5.8.2.3 Reflexivity

Reflexivity refers to the self-critical examination of thoughts and assumptions during each research stage [362]. Hammersley and Atkinson [54] described the importance of reflexivity for the researcher to become aware of any self-conscious biases in the interpretation of the data [363]. Kleinsasser [364] believes that researchers should participate in reflexivity to achieve quality in qualitative analysis. This process highlighted the impact that each participant potentially had on the data and alerted to any issues concerning personal biases.

During the data analysis process, the research lead kept a journal documenting thoughts and feelings through the qualitative analysis process (Tobin & Begley, 2004). Also, reflexivity helped support self-reflection of feelings, attitudes, and behaviours during the data generation and writing processes (Lincoln & Guba, 1985). Strategies were employed to reduce unconscious bias or subjectivity, such as frequent meetings with the qualitative lead and the principal investigator to discuss the process and rationale for coding different themes. Reflexive notes during the data analysis process enhanced the data and helped meet the research objective. See Figure 5-3 indicates an extract from the reflexive journal below, an extract from the qualitative analysis diary.

Figure 5-3 indicates an extract from the reflexive journal

I was a little disturbed by some of the participants comments and attitudes about other people. He used a lot of unpleasant and derogatory words to describe the Iraqi soldiers and civilians he had encountered in combat. As my father is from Iraq, I couldn't help but be a little offended by some of the words he had used to describe the people. I had met and assessed the participants before, and he had also expressed similar views in our appointments. However, as soon as I became aware of this, I made a conscious effort to spend more time reading and re-reading his interview. This was in order to become less attached from his views and see the text in a more objective manner so I can focus on the research question and ignore the less relevant information. I was then able to start seeing the words and relationship between segments of text, which was relevant to factors associated with treatment outcome. I also expressed my concerns to my supervisor who advised me to take a break from the reading the interview and go back through the text once I had some time to process what I had read.

As the research lead did not interview the participants, they were able to play the outsider role and extract and analyse the data without any concern about influencing the participant. There was a possibility of looking for the pre-selected factors while reading and coding the text; however, the purpose of the analysis was to validate and explore new factors listed as associated with treatment outcome in my systematic review. This reflective approach gave room to explore the viewpoints of the participants and to be more objective. Frequent meetings allowed me to examine the data with the qualitative lead and PI and express multiple viewpoints or feedback towards the data.

5.8.2.4 Anomalies

During data analysis, it was essential to identify unique instances within the data. According to Dey [364], they are called 'singularities' or 'deviant' participants, which are just as crucial as identifying regularities and variations in the data. A systematic coding method created the opportunity to identify deviant cases and similarities once the data was coded. It was essential to identify the single cases that demonstrated unique factors pertinent to that participant's experience. Identification of the singularities provided the opportunity to extend the hypothesis and deepen the within-case analysis. This was done by identifying the overlap between the singularities and associations between different variables. It was then possible to examine the regularities, explaining the variation between each 'deviant' case. Linking up the data provided the opportunity to give a dynamic account of what factors were associated with treatment outcome.

5.9 Summary

This chapter described how the study was undertaken. The chapter contained a justification for using a diagnostic interview, self-report questionnaire measures, and qualitative interviews to collect data. Factors associated with treatment outcome were derived from a systematic review and narrative synthesis of psychological treatment for PTSD. The factors identified were applied to the 3MDR quantitative data to examine whether there were any significant association with treatment outcome. The qualitative interviews used thematic analysis to identify whether any novel factors were associated with participant doing better or worse in treatment. The quantitative design was selected to obtain information about individuals' symptoms to produce objective data. The qualitative interviews focussed on the individuals' experiences, relationships, and perspectives to produce rich and meaningful data [365, 366].

Chapter 6: Quantitative analysis: Exploration of factors associated with 3MDR treatment outcome

6.1 Overview

This chapter presents the main quantitative results concerning factors associated with treatment outcome from a RCT to investigate if 3MDR treatment could reduce symptoms of PTSD to a significantly greater degree than delayed treatment [1]. The analysis presented in this chapter is independent of the main analysis of the RCT data. The RCT results were promising for 3MDR as participants in the immediate arm experienced a significantly greater reduction of PTSD symptoms than those in the delayed treatment arm at the primary endpoint. It is noteworthy that those in the delayed treatment arm also improved, that not all participants who received 3MDR improved and that the degree of improvement varied amongst those who did (Chapter Chapter 4:). It is essential to understand why some participants responded well to the treatment whilst others did not. To date, no studies have considered factors associated with 3MDR treatment outcome. A systematic review and narrative synthesis of factors associated with psychological treatment outcome for PTSD (Chapter Chapter 3:) [124] identified initial severity of PTSD, depression, homework adherence, time since trauma, age, education level, and employment status as the most frequently reported associated factors. The impact of these factors on 3MDR treatment outcome was considered.

6.2 Sample characteristics

As described in the Methods Chapter (Chapter Chapter 5:), all 42 randomised participants were male. The primary traumatic events suffered were: severe human suffering (11, 26.2%), serious injury, harm or death you caused to someone (10, 23.8%), fire or explosion (9, 21.4%), combat or exposure to a war - zone, sudden, violent death, sudden, unexpected death of someone close, and missing data (all 2, 4.8%), physical assault, assault with a weapon, sexual assault (rape, attempted rape), and captivity (for example; kidnapping, abduction) (1, 2.4%).

Table 6-1 Demographics summarises the participants' demographic characteristics and compares those randomised to the immediate treatment arm with those randomised to the delayed treatment arm. The average age of participants was 42 years old, and the mean time since their worst traumatic event was over 19 years. Most participants were white British (95%), and around a third were employed, and a third were unable to work. Almost half the participants had a comorbid depressive disorder.

Table 6-1 Demographics

		Arm						Total*		
		Delayed			Immediate					
		N	%/Mean	SD	n	%/Mean	SD	n	%/Mean	SD
Age		21	44.0	11.97	21	40.2	10.13	42	42.1	11.12
Time since trauma (months)		21	271.4	186.42	21	191.2	145.42	42	231.3	170.05
Ethnic origin	White British	19	90.5		21	100.0		40	95.2	
	Any other Mixed/multiple ethnic background	1	4.8		0	0.0		1	2.4	
	African	1	4.8		0	0.0		1	2.4	
Highest level of qualification	No qualifications	1	5.0		0	0.0		1	2.6	
	1-4 GCSEs or equivalent	6	30.0		7	36.8		13	33.3	
	5+ GCSEs or equivalent	3	15.0		7	36.8		10	25.6	
	Apprenticeship	1	5.0		0	0.0		1	2.6	
	2+ A Levels or equivalent	4	20.0		1	5.3		5	12.8	
	Degree level or above	5	25.0		4	21.1		9	23.1	
	Other qualifications	0	0.0		0	0.0		0	0.0	
Current employment status	Employed	10	50.0		4	19.0		14	34.1	
	Self-employed or freelance	2	10.0		1	4.8		3	7.3	
	Been made redundant	0	0.0		1	4.8		1	2.4	
	Homemaker	0	0.0		1	4.8		1	2.4	
	Retired	1	5.0		3	14.3		4	9.8	
	Volunteering	0	0.0		3	14.3		3	7.3	
	Unable to work	7	35.0		8	38.1		15	36.6	
Diagnosis of depressive disorder	No	12	57.1		11	52.4		23	54.8	
	Yes	9	42.9		10	47.6		19	45.2	

Number (n) Mean (M) and standard deviations (SD) for all participants in both the delayed and immediate arms.

6.3 Summary of 3MDR Trial Results

This section details the main published results of the RCT of 3MDR [302]. Of the Fifty-two military veterans were referred to the study, forty-two participants were randomised, and the retention rate was 83% at 12 weeks and 86% at 26 weeks. Data on the outcome measures were collected at baseline, 12 weeks, and 26 weeks post-randomisation. The groups appeared well balanced according to demographic and clinical symptoms at baseline. The results demonstrated greater improvement for participants in the immediate arm versus delayed arm at the primary 12 weeks on the CAPS-5, PCL-5, GAD-7 and ISI. There was no apparent difference between the arm on WSAS, PHQ-9, EQ-5D-5L, Audit-O and MSPSS.

6.4 Exploratory subgroup analysis of factors associated with 3MDR treatment outcome

This section describes the results of analyses undertaken by me for this thesis. The factors identified in the systematic review (comorbidity with depression, age, time since trauma, adherence to pre-treatment homework, education level and employment status) were applied to the 3MDR data to examine whether they were associated with 3MDR treatment outcome. To look for differences between groups, continuous intention to treat CAPS-5 data was analysed by comparing means using Analysis of Covariance (ANCOVA) with baseline scores as covariates. The hypothesis was that the presence of these factors at baseline assessment would affect treatment outcome.

To investigate the association between the continuous independent variables: comorbidity of depression, time since trauma, and age and the continuous dependent variables: CAPS-5 severity score at 12 and 26-week assessment, multiple regression analyses were conducted. The arm to which participants were assigned was a significant factor in the treatment outcome for individuals in this trial. Given the exploratory nature of these analyses, simple and multiple linear regressions were undertaken. An interaction term with the trial arm variable and a relevant predictor was included to control interaction effects between independent variables and the trial arm. Analyses without the interaction term (but with the trial arm variable still in the model) were also conducted to ensure the analyses provided

consistent results. Statistician TP performed analyses of the published efficacy trial. I performed all other analyses. All analyses were performed at the end of the data collection period using SPSS software for statistical analysis version 20 [338].

6.4.1 Methodological considerations

The examination of factors associated with treatment outcome in RCTs is a subgroup analysis [367]. Subgroup analysis refers to whether a portion of participants responds positively or negatively to a treatment. Although subgroup analysis is considered a secondary study objective, it is essential as misinterpretation can lead to false recommendations. Subgroup analysis can inform treatment choice and inform ways to improve the effectiveness of treatment outcome [368].

There are several benefits to conducting subgroup analysis. One of the main reasons is that regular logistic or regression analysis only considers multiplicative rather than additive analysis. Therefore, only multiplicative variance is considered rather than additive variance. From a treatment outcome perspective, it is crucial to consider the effects of additive variance to understand the benefits of the treatment [369]. A body of research suggests that subgroup analysis helps inform researchers on underlying relationships between factors, which can help inform future treatment choices [370]. Several research studies have recognised problems with the reporting of subgroup analysis. Research by Assman et al. (2000) reviewed 50 RCTs obtained from high impact medical journals to assess the quality of baseline reporting for use in the analysis. Assman et al. found significant inconsistencies and under-reporting of sub-group analysis; 70% of RCTs conducted sub-group analysis, while only 46% reported doing so, and 36% only reported p-values [371]. The research demonstrates a lack of consistency and transparency in reporting subgroup analysis.

Statistical interaction can be assessed in two ways: stratification, which separates baseline factors associated with a subgroup of participants and treatment outcome, and interaction, including the baseline factors and the treatment arm (interaction) with treatment outcome. Due to the small sample size, interaction analysis was used to measure associations between baseline characteristics and treatment arm and treatment outcomes. Interaction analysis is presented separately to illustrate whether the two separate arms were associated with

treatment outcome. Although both groups received the same intervention, participants took different paths to receive treatment. In order to truly understand whether there is any significant association between the independent variables (factors) and the dependent variable (CAPS-5 score), it is considered conservative in RCTs to separate participants by randomisation arm and include this in the interaction to eliminate the risk of drawing false conclusions, from a type I or type II error [372].

Given that the trial collected PTSD symptom severity data at baseline, using the CAPS-5 severity score, all models were adjusted for this factor. For the employment and education variables, categories were collapsed into logical and relevant groups. This was done by evaluating frequency tables in advance of the above-listed analyses to determine which categories that are logically related, when collapsed, would give an equal balance of numbers across the categories to allow for the regression analyses to make reasonable calculations of estimates, 95% confidence intervals, and p-values.

6.4.2 Multiple regression analysis results from the immediate treatment arm

This exploratory analysis employed multiple linear regression that tested whether comorbidity with depression, age and time since trauma, adherence to homework, level of education and employment status were associated with treatment outcome, as measured by the CAPS-5 score at week 12 and week 26. Table 6-2 summarises the numbers of participants (n) within each group for the three identified categorical factors (adherence to homework, employment status and education level) along with CAPS-5 means (M) and standard deviations (SD) at baseline week 12 and week 26.

Table 6-3 Summary of Statistics

Factors	Categories	CAPS-5 Scores								
		Baseline			Week 12			Week 26		
Adherence to pre-treatment Homework		N	M	SD	n	M	SD	n	M	SD
	Yes	9	52.33	5.61	7	38.43	11.94	7	36.86	20.70
	No	12	45.67	9.18	9	24.89	18.72	10	26.50	16.14
Employment	Employed (Full)	4	46.00	6.97	4	16.50	6.12	4	21.25	13.86
	Self-Employed	1	38.00	n/a	1	14.00	n/a	1	5.00	n/a
	Retired	4	50.50	4.79	2	37.50	.707	3	23.33	4.93

	Volunteering	3	50.00	.000	2	46.50	2.12	2	49.00	2.82
	Unable to work	9	49.44	11.33	7	35.00	20.24	7	37.86	20.47
Education	1-4 GCSE or equivalent	7	49.00	8.73	5	34.80	23.40	6	40.83	20.52
	5 + GCSE or equivalent	7	48.43	8.92	6	24.67	17.39	6	23.67	20.56
	2+ A level or equivalent	1	55.00	n/a	1	22.00	n/a	1	33.00	n/a
	Degree or above	4	46.75	11.58	3	34.67	4.93	3	24.67	7.23

Statistical data were not available for sub-categories with only one participant. N/A: not applicable

6.4.2.1 Pre-treatment homework adherence

Pre-treatment homework refers to a two-week diary that participants were asked to complete before baseline assessment. The diary involved the participant monitoring their PTSD symptoms every day for two weeks. Nine people completed their pre-treatment homework, while 12 people did not. No statistical differences were found between groups at baseline (f $(1,19) = 3.678$, P = .070) week 12 (f$(1,14) = 2.761$, p = .119) or week 26 (f$(1,15) = .348$, p = .264) as determined by a one way ANOVA. It is important to note that the participants who did not complete the pre-treatment homework had higher baseline CAPS-5 scores than those who did complete the pre-treatment homework. Pre-treatment homework adherence was not associated with treatment outcome in either group.

6.4.2.2 Employment

Employment was categorised into five subgroups; employed, self-employed, retired, volunteering, and unable to work. The sub-categories were consistent with those used by the NCMH and were originally derived from the Office for National Statistics (ONS). No statistical difference were found between groups at baseline (f$(4,16) = .534$, p = .713) week 12 (f$(4,11) = 1.928$, p = .176) or week 26 (f$(4,12) = 2.105$, p = .143), as determined by one way ANOVA. Participants who were employed, volunteering or unable to work were shown to reduce CAPS-5 scores at week 12 but increased scores at week 26. The two retired and self-employed participants were shown to reduce CAPS-5 scores at week 12 and a further reduction at week 26. It is important to note that due to the small sample size and

inconsistency in the trajectory of CAPS-5 scores, no clinical implication can be made from these results.

6.4.2.3 Education

Education was categorised into five sub-categories: 1-4 GCSE or equivalent, 5+ GCSE or equivalent, 2+ A level or equivalent, or a degree and above. No statistically significant differences were found between any of the sub-categories at baseline (f(3,15) = .209, p = .889), week 12 (f(3,11) = .405, p = .752) or week 26 (f(3,12) = .949, p = .448) as measured by a one way ANOVA. Despite the lack of significant changes, the largest reduction in CAPS-5 scores was seen for the participant who had obtained 2+ A levels or equivalent. It must be noted that this was only one participant, and there was no follow-up data. The results indicate that participants in each subgroup reported a reduction in CAPS-5 scores at week 12. Participants with a degree or above and those with 5+ GCSE or equivalent were reported a further reduction in scores at week 26. Participants with 1-4 GCSE reported an increase in CAPS-5 scores at week 26. The results are inconsistent and underpowered, and no conclusion can be drawn, suggesting further research is required.

6.4.3 Multiple regression analysis results from the delayed treatment arm

Table 6-4 Summary of Statistics shows the participants' descriptive statistics in the delayed arm for the identified factors associated with 3MDR therapy at baseline, week 12 and 26.

Table 6-4 Summary of Statistics

Factors	Categories	Baseline			Week 12			Week 26		
Adherence to pre-treatment Homework		N	M	SD	N	M	SD	N	M	SD
	Yes	8	46.25	6.11	8	37.38	8.733	7	25.71	19.88
	No	13	48.38	7.69	11	43.36	11.82	12	31.67	16.76
Employment	Employed (Full)	10	46.30	8.88	8	41.25	11.88	9	33.00	18.12
	Self-Employed	2	48.00	5.65	2	31.50	2.12	1	11.00	n/a
	Retired	1	41.00	n/a	1	39.00	n/a	1	13.00	n/a
	Unable to work	7	49.71	4.99	7	44.57	11.17	7	32.39	17.98

Education	1-4 GCSE or equivalent	7	42.00	7.14	6	37.00	14.14	5	35.60	14.04
	5 + GCSE or equivalent	4	42.50	5.91	4	37.00	4.32	4	18.75	14.59
	2+ A level or equivalent	4	53.50	3.00	4	47.25	10.34	4	34.75	20.40
	Degree or above	5	51.60	4.72	5	43.40	9.71	5	29.80	22.77

Statistical data was not available for sub-categories with only one participant. N/A: not applicable

6.4.3.1 Pre-treatment homework

Eight people completed their pre-treatment homework, while 13 people did not. No statistical differences were found between the sub-categories at baseline (f(1,19) = .441, p = .515) week 12 (f(1,17) = 1.461, p = .243) or week 26 (f(1,17) = .487, p = .495) as determined by a one way ANOVA. It must be noted that participants who did not adhere to pre-treatment homework reported higher baseline CAPS-5 scores compared to those who did adhere to the pre-treatment homework. Pre-treatment homework adherence was not associated with treatment outcome in either group.

6.4.3.2 Employment

No statistical differences were found between the sub-categories at baseline (f (3,16) = .546, p = .658) week 12 (f (3,14) = .729, p = .552) or week 26 (f(3,14) = .781, p = .524) as determined by a one way ANOVA. Participants in the retired sub-category reported the highest CAPS-5 scores at baseline, followed by participants unable to work sub-category. It is important to note that there were only two participants in each subgroup. Participants in the employed or unable to work sub-category reported a reduction in CAPS-5 scores at week 12 and again at week 26. It is important to note that participants in both the employed and unable to work sub-category reported similar CAPS-5 scores at baseline. The results suggest that the effects of randomisation may have caused participants to be unevenly distributed; therefore, replication within a larger sample is required.

6.4.3.3 Education

No statistical differences were found between the sub-categories at baseline (f (3,16) = 4.609, p = .017) week 12 (f (3,15) = .982, p = .427) or week 26 (f (3,14) = .740, p = .546) as determined by a one-way ANOVA. The results indicate that participants in all the sub-categories reported a reduction in CAPS-5 scores at weeks 12 and 26. It is important to note that there were only 4 participants in the 5+ GCSE or equivalent or 2+ A level or equivalent sub-category. The results suggest that participants in the lowest educational attainment sub-categories: 1-4 GCSEs or equivalent and 5+ GCSE or equivalent reported a similar reduction rate in CAPS-5 scores at week 12 and week 26. Participants in the highest educational attainment sub-categories: 2+ A level or equivalent and a degree or above reported similar reduction rates at weeks 12 and 26. It is important to note that those in the highest education sub-categories reported a greater reduction in CAPS-5 scores at week 12 and week 26 than those in the lower education sub-categories. The lack of consistency across sub-categories and small sample size suggests replication within a larger sample is required.

6.4.4 Regression analysis with interaction and non-interaction arm

The regression analysis with the interaction arm suggests that participants in both the immediate and delayed arm reported similar changes in CAPS-5 scores at week 12 and week 26. To further analyse the data, the regression analysis was performed without the interaction arm. The analysis involved combining the waiting list and the delayed arm group to investigate any significant association between factors and CAPS-5 scores at pre-and post-treatment. The regression analysis calculated a baseline significance level of $\alpha = 0.05$ and 24 p-values, under Bonferroni correction, $\alpha = 0.05/24 = 0.002$. A factor was determined to be statistically significantly related to CAPS-5 if the relevant p-value is $p < 0.002$.

6.4.4.1 Regression analysis including an interaction arm for week 12

The interaction between the trial arm and the treatment outcome was not significant for baseline PHQ-9, age, time since trauma, adherence to pre-treatment homework, employment, or education status with CAPS-5 scores at week 12.

Table 6-5 Interaction between factors and treatment outcome at week 12

Factors	df	F-value	p-value	Partial η^2
PHQ-9	6	1.663	0.236	0.526
Age	4	3.282	0.120	0.354
Time since trauma	5	6.995	0.026	0.875
Adherence to pre-treatment homework	1	1.358	0.253	0.043
Employment	3	1.316	0.263	0.150
Education	3	1.001	0.409	0.107

Patient Health Questionnaire (PHQ-9), degrees of Freedom (df)

Figure 6-1 Interaction between PHQ-9 scores for the active and waiting list at week 12
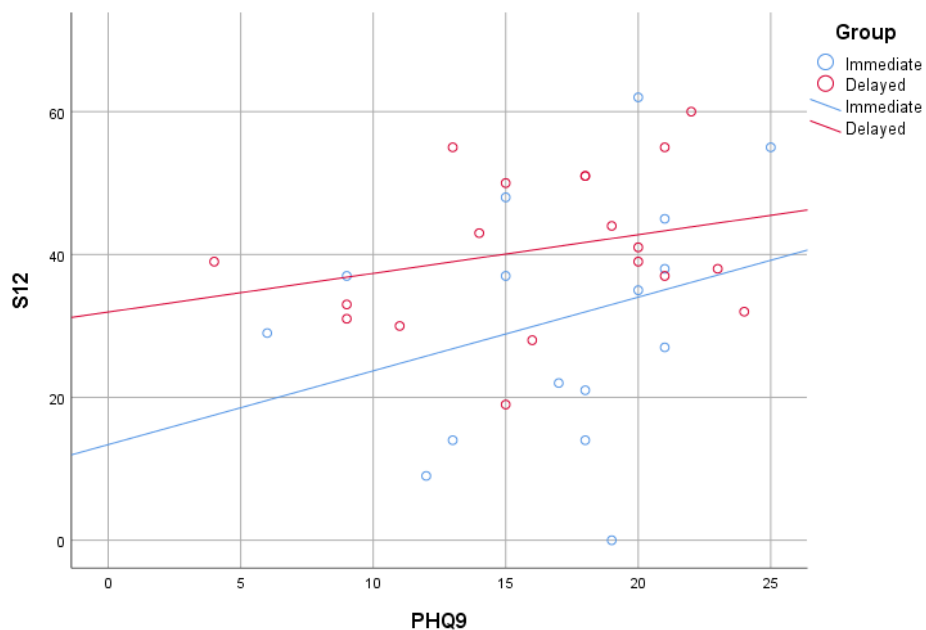
The graph indicates no significant interaction between PHQ-9 and CAPS-5 scores at week 12. The graph shows that participants in the immediate group reported lower CAPS-5 scores at week 12 than those in the delayed arm. Higher PHQ-9 scores were associated with higher CAPS-5 scores in both the immediate and delayed arm.

Figure 6-2 Interaction between Time Since Trauma for the active and waiting list at week 12
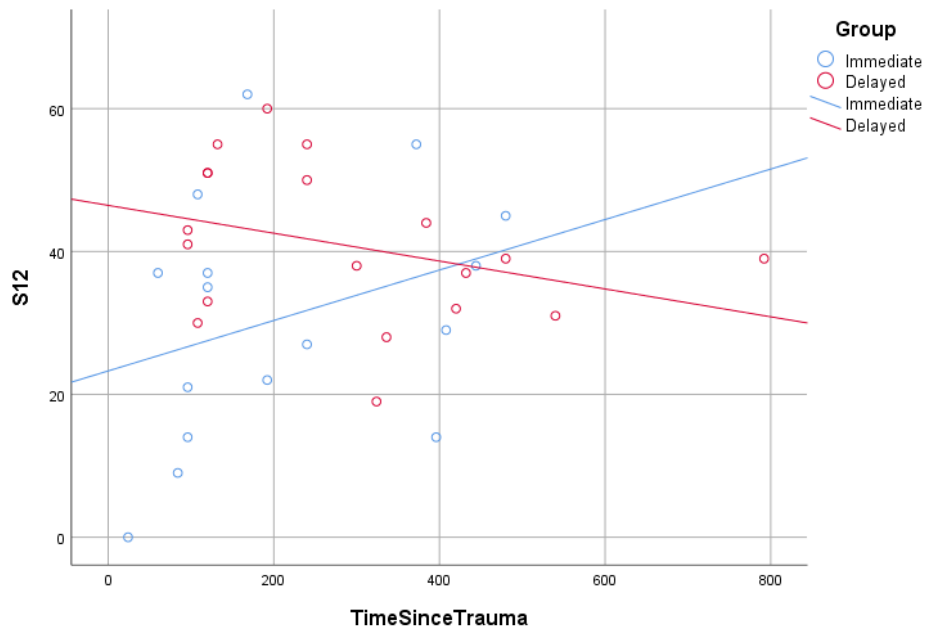
The graph indicated an interaction between time since trauma and CAPS-5 scores at week 12. Despite the lack of a significant main effect, the graph indicates an interaction between the immediate and delayed arm and time since trauma at week 12. The graph suggests that participants in the immediate arm reported lower CAPS-5 scores at week 12 than participants in the delayed arm. Furthermore, a participant in the immediate arm reported lower CAPS-5 scores associated with shorter time since the trauma. Participants in the delayed arm who reported higher CAPS-5 scores were also associated with shorter time since the trauma.

Figure 6-3 Interaction between age for the active and waiting list at week 12
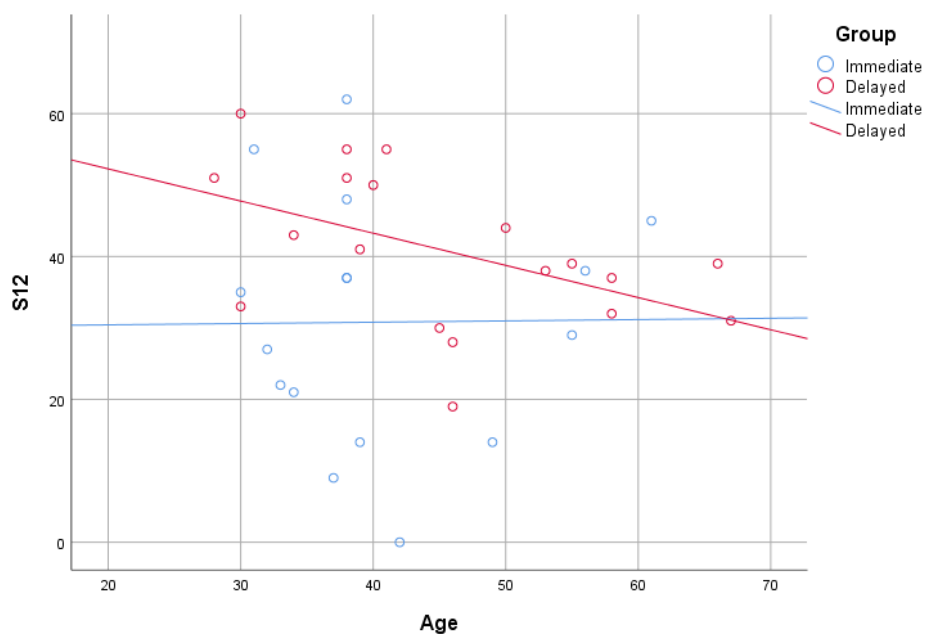
The graph indicated an interaction between age and CAPS-5 scores at week 12. Despite the lack of a significant main effect, the graph indicates a small interaction between the immediate and delayed arm and age at week 12. The graph suggests that older participants in the delayed arm were associated with lower CAPS-5 scores.

6.4.4.2   Interaction arm for week 26

Similar interaction analysis was performed between the trial arm and the treatment outcome, which yielded no significant association for baseline PHQ-9, age, time since trauma, adherence to pre-treatment homework, employment, or education status with CAPS-5 scores at week 26.

Table 6-6 Interaction between factors and treatment outcome at week 26

| Factors	Df	F	p-value	Partial η^2
PHQ-9	17	0.936	0.555	0.499
Age	22	1.600	0.211	0.762
Time since trauma	22	0.657	0.807	0.568
Adherence to pre-treatment homework	1	0.001	0.979	0.000
Employment	4	0.669	0.619	0.087
Education	3	0.908	0.449	0.086

Patient Health Questionnaire (PHQ-9), degrees of Freedom (df)

Figure 6-4 Interaction between PHQ-9 scores for the active and waiting list at week 26
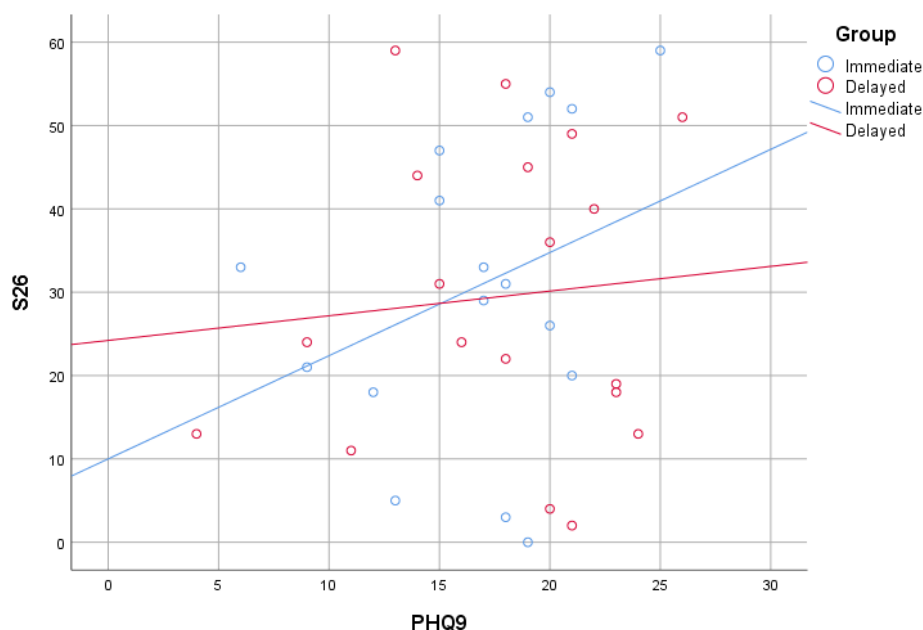
The graph indicates an interaction between PHQ-9 and CAPS-5 scores at week 26. Despite the lack of a significant main effect, the graph indicates an interaction between the immediate and delayed arm and PHQ-9 score at week 26. The graph suggests that participants in the immediate arm reported lower CAPS-5 scores than those in the delayed arm. The graph indicates that higher PHQ-9 scores were associated with higher CAPS-5 scores in the immediate and delayed arm.

Figure 6-5 Interaction between Time Since Trauma for the active and waiting list at week 26
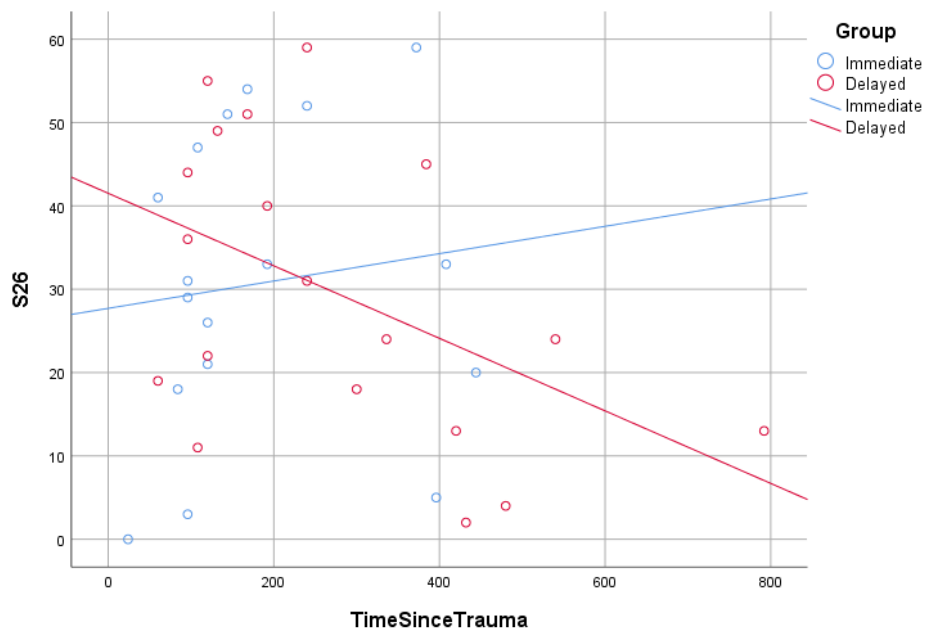
The graph indicates an interaction between time since trauma and CAPS-5 scores at week 26. Despite the lack of a significant main effect, the graph indicates an interaction between the immediate and delayed arm and time since trauma at week 26. The graph suggests that a longer time since trauma was associated with higher CAPS-5 scores for participants in the immediate treatment arm. For participants in the delayed arm, a longer time since trauma was associated with lower CAPS-5 scores.

Figure 6-6 Interaction between age for the active and waiting list at week 26
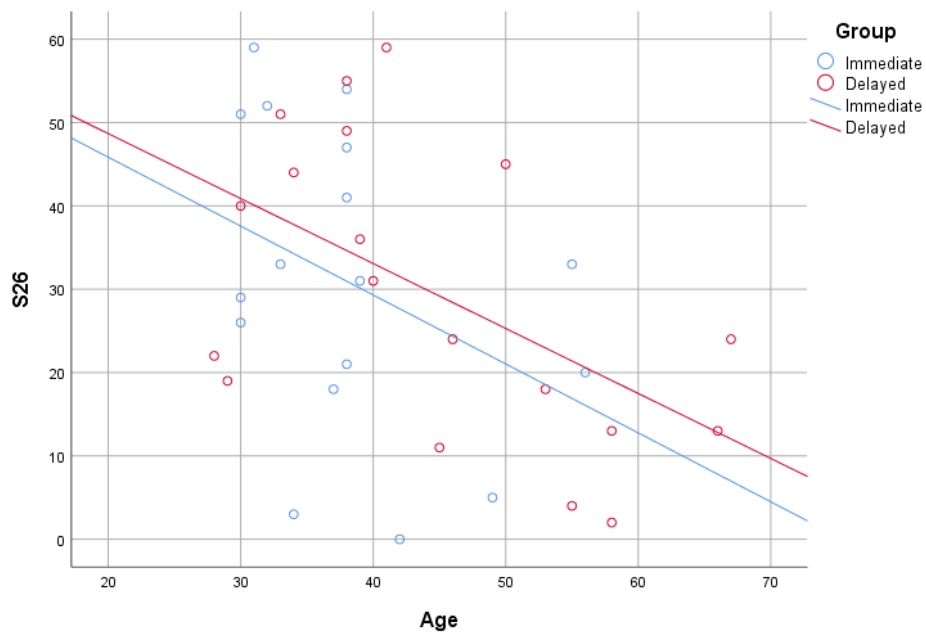
The graph indicates no significant interaction between age and CAPS-5 scores at week 26. The graph suggests that participants in the immediate arm reported lower CAPS-5 scores than those in the delayed arm. The graph indicates that older age is associated with lower CAPS-5 scores in the immediate and delayed arm.

6.4.4.3   Non-interaction arm for week 12

The non-interaction analysis yielded no significant association between baseline PHQ-9, age, time since trauma, adherence to pre-treatment homework, employment, or education status with CAPS-5 scores at week 12.

Table 6-7 Non-interaction between factors and treatment outcome at week 12

Factors	Df	F	p-value	Partial η^2
PHQ	6	0.556	0.755	0.270
Age	22	1.700	0.264	0.862
Time since trauma	6	1.287	0.400	0.607
Adherence to homework	1	0.436	0.514	0.014
Employment	3	0.591	0.627	0.066

Education	3	0.032	0.992	0.004

Patient Health Questionnaire (PHQ-9), degrees of Freedom (df)

6.4.4.4 Non-interaction table for week 26

A similar non-interaction analysis yielded no significant association between baseline PHQ-9, age, time since trauma, adherence to pre-treatment homework, employment, or education status with CAPS-5 scores at week 26.

Table 6-8 Non-interaction between factors and treatment outcome at week 26

Factors	Df	F	p-value	Partial η^2
PHQ	18	0.592	0.858	0.400
Age	22	1.555	0.216	0.740
Time since trauma	22	1.252	0.352	0.697
Adherence to homework	1	0.004	0.948	0.000
Employment	4	1.915	0.135	0.209
Education	3	1.885	0.154	0.163

Patient Health Questionnaire (PHQ-9), degrees of Freedom (df)

6.5 Strengths and limitations

A major limitation of the quantitative analysis was the small sample size which may have made finding a true significant association difficult, due to the inadequate power. ANCOVA was conducted to identify which factors were associated with treatment outcome. Bonferroni correction was applied which further restricted the power of the analysis. However, Bonferroni ensured a conservative approach which minimised the risk of type II error. A strength is the use of data from an RCT which used rigorous methdology [321]. Participants were randomly allocated into one of two groups (the immediate or delayed treatment arm); both groups received the same treatment but were exposed to different treatment pathways [373]. Therefore the participants experience of the trial was different, which may have affected treatment outcome. However, the randomisation process ensured allocation and selection bias was minimised in order to maintain internal validity and accurately examine treatment efficacy.

6.6 Summary

The results indicate that the factors associated with psychological treatment outcome for PTSD in the systematic review (Chapter Chapter 3:) were not shown to have any significant association with the 3MDR treatment outcome. The exploratory analysis of factors associated with treatment outcome is in line with previous literature, indicating limited evidence to support demographic and clinical factors associated with treatment outcome [374]. The results are inconsistent with research suggesting factors such as duration of symptoms, gender, suicidal ideations, type of trauma, history of previous trauma, and time since trauma are associated with poorer treatment outcomes. A key limitation is that the exploratory analysis was underpowered, which may be a key reason for the lack of significant associations [328]. Any indication of pattern or relationship is a risk of a false finding (type II error). No factors were associated with treatment outcome, suggesting that the presence or absence of these factors should not influence treatment advice or clinical decisions. Future research should examine factors associated with treatment outcome in a larger, more general population within routinely collected data, with no forced parameters or categories.

Chapter 7: Qualitative analysis: Exploration of factors associated with 3MDR treatment outcome

7.1 Overview

The first part of the chapter describes the qualitative analysis of data from the RCT regarding factors associated with treatment outcome. This chapter introduces each of the 11 military veterans who participated, summarising their unique characteristics to explore and observe participants experience within their context [375]. A primary view of factors associated with each veteran's treatment outcome and some significant others in their lives also present during the interviews, i.e. family members, friends and partners are described. Descriptions are framed within each transcript, providing 'within case' themes for each veteran and a cross-case thematic analysis to identify common factors across veterans. Factors were unique to each veteran who took part in the 3MDR trial. There were elements of each of their accounts that produced similarities and singularities. The second part of the chapter provides themes that link across the cases in a cross-case thematic analysis. The within-study analysis provides in-depth discussion, following the presentation of all the results generated from the study. Extracts from the entire data set are drawn upon and include specific conversation extracts during the interviews with veterans and their family members and partners [376].

7.2 Sample characteristics

The qualitative lead, Ben Hannigan (BH), is a professor of mental health nursing and an experienced qualitative researcher. BH and the research team purposively selected eleven participants from the 3MDR sample. BH ensured that those selected to participate in the interviews were representative of the study and captured a diverse range of experiences and demographic characteristics. The research technicians Leigh Abbot (LH) and Kate Jones (KJ) sent out invitation letters to some of the participants who had agreed to participate in the qualitative interview and had either completed the trial or those who had stopped attending the treatment sessions. The participants who expressed an interest in taking part in the interviews were forwarded to the qualitative lead. All interviews were conducted by the qualitative lead, who was not involved in any other assessments or therapy sessions. The interviews were conducted at the participant's convenience in their own homes, NHS or

university premises. Interviews took place between November 2017 and October 2018.

7.2.1 Interview schedules, audio recording and transcribing

The qualitative topic guide was developed in advance by the qualitative lead and the unblinded members of the research team. Interviews were semi-structured to allow for discussion, and open-ended questions were used to facilitate conversation between the interviewer and participant.

7.2.2 Characteristics of participants

Below is a summary of the interviews conducted, including the length of each interview, information on the treatment arm, the age of participants, and the reason for selection.

Table 7-1 Veterans taking part in interviews

Name*	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)
Dai	67	Waiting list	First veteran into the trial, traumas dating from the 1970s	63
Rhys	39	Immediate	The first veteran to have 3MDR, traumas from the 2000s	33
Callum	49	Immediate	Trauma not combat-related	25
Terry	59	Waiting list	Multiple traumas, developmental and learning problems	94
Gethin	43	Immediate	Reported significant benefits before the end of scheduled 3MDR sessions, and early discontinuation	35
Chris	45	Waiting list	Intense emotional responses to therapy	47
Duncan	56	Waiting list	Reported unanticipated physical health improvements	31

Berwyn	62	Immediate	Dropped out after initial visit clinic	76
Harry	53	Waiting list	Co-existing physical health problems and disabilities, financial issues	53
Charlie	56	Immediate	Discontinued before the final treatment session, as could not find photos evoking strong enough emotions	48
Tony	57	Immediate	Dropped out early	43

Names* Pseudonyms have been used to preserve anonymity

7.3 Data management and analysis

The qualitative lead conducted two interviews: the first set with the therapists and the second with the participants. The transcripts were read and anonymised by the qualitative lead (BH). I was blind to randomisation, so after the final follow-up assessment, all transcripts were uploaded onto NVivo 10, a Qualitative Data Analysis (QDA) package created by QSR International [337] (Chapter Chapter 5:), where I was able to access them and familiarise myself with the data. I only used the participant data and conducted my analysis, separate from the qualitative lead.

Braun and Clarke's thematic analysis was adopted to identify any qualitative factors associated with treatment outcome [345]. This involved examining the differences and similarities between participant interviews to identify any relationships or singularities associated with individuals doing better or worse in treatment. This included becoming familiar with the text by reading and re-reading each interview and identifying important sections within and between cases to identify relationships within the text. The results are presented in three sections. The first section describes each participant in detail (within-case analysis), highlighting specific factors associated with treatment outcome, as measured by the CAPS-5. The second sections integrate the data across the participants (between-case analysis), highlighting each participants similarities and differences. The third section combines, contrasts and concludes the main factors associated with better or worse treatment outcome, defined by a reduction in PTSD symptom severity score. The aim of combining the quantitative and qualitative analysis was to develop a deeper, more meaningful understanding of factors associated with treatment outcome [377].

7.4 Within case analysis

The purpose of the within-case analysis was the detailed study of each participant within their context to develop an in-depth understanding of their experiences to discover what individual factors were associated with participants doing better or worse in treatment [378-380]. Each individual reported different perspectives and experiences; therefore, it was crucial to analyse the data in its context to identify unique factors associated with the individual. It provided insight into their personal story. I will summarise each transcript below and highlight the factors that emerged from the data, associated with people doing better or worse in treatment. A detailed case analysis of each veteran is presented below.

7.4.1 Case 1 - Participant 1: Dai

Table 7-2 A Summary of participant 1: Dai

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks
P1	67	Waiting list	First veteran into the trial, traumas dating from the 1970s	63	41	39	13

Motivated and Committed to helping others: Dai was very enthusiastic about taking part in 3MDR therapy: *'anything that can alleviate the symptoms I was getting and make it better to live with, I was up for it'*. He was mainly motivated by the thought of helping other veterans with a PTSD diagnosis: *'Oh yeah, yeah, if it helps you've got to go, you've got to get involved with it, and if it helps, the fact that I'm on this course and I'm on interview here today it felt if it helps young men and young women get through it and get better and that's obviously what I had.'*
Support from friends: Dai reported sharing the news of being involved in the 3MDR treatment with fellow veterans who *'were quite eager to know how it went'*. He spoke about having a good relationship with the veterans and felt comfortable sharing his experiences: *'I had four good workmates I'd worked with for quite several years, twenty-odd years and everything was okay.'*
Support from a healthcare professional: He also reported the support and help he had received from a General Practitioner (GP) who helped him overcome certain hurdles and provided him with alternative methods of support and care. Furthermore, ahead of meeting his treating therapist for the first time in the 3MDR context (though they had met before), he was *'obviously a bit apprehensive'* but said how he *'put me at ease straightaway'*. Ahead of his first treatment session, he had 'a couple of bad days' but was supported by his wife, who offered to share the journey.
Support from Family: He also reported being very open and honest with his family and felt incredibly close to his wife and daughter. He reported that his daughter encourages him to stay committed to the 3MDR therapy and his wife played a crucial role in his recovery, saying *'The shove has always been there you know, not that I needed it but just in case I wanted it, she was there.'*

The positive experience of 3MDR therapy: The time and effort finding images and the associated trauma was incredibly difficult. Dai's wife reported the process as a *'a terrible thing'*, and he reported *'I managed to get quite a bit of information on, pictures and I was quite surprised at what was out there you know and it was quite a traumatic experience for me just getting these pictures.'* Of his first visit, he said, *'I was very impressed when I got in the room, it was like NASA'*. He felt the process was very immersive, and it was what was required to confront his fears. *'……everyone was including yourself, your good self, at ease, you're put at ease that's the main thing.'* Later, talking about a second traumatic event, he said how, *'it brought back a lot of the actual, you could see faces [...]'.* However, later on in the trial, he felt overwhelmed by the experience: *'oh gosh I shouldn't have done this, I shouldn't have come because you felt, you felt closed in, you were into that, pushed into that tunnel'.* Even following his journey home, he felt affected, saying how *'I must have been as white as a sheet'* although his wife encouraged him to continue *'if this is what it's going to take'.*

Positive attitude towards treatment: Dai reported staying committed to the therapy, despite sometimes feeling anxious: *'Anything was better than just carrying on the way we were.'* He also reported feeling obligated to those that had supported him to stay committed and see things through. Overall Dai felt very positively about 3MDR and his experiences in the trial. He reported feeling better: *'I can handle situations a lot more now, a lot better than I could.'*

Figure 7-1 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 scores for Participant 1: Dai
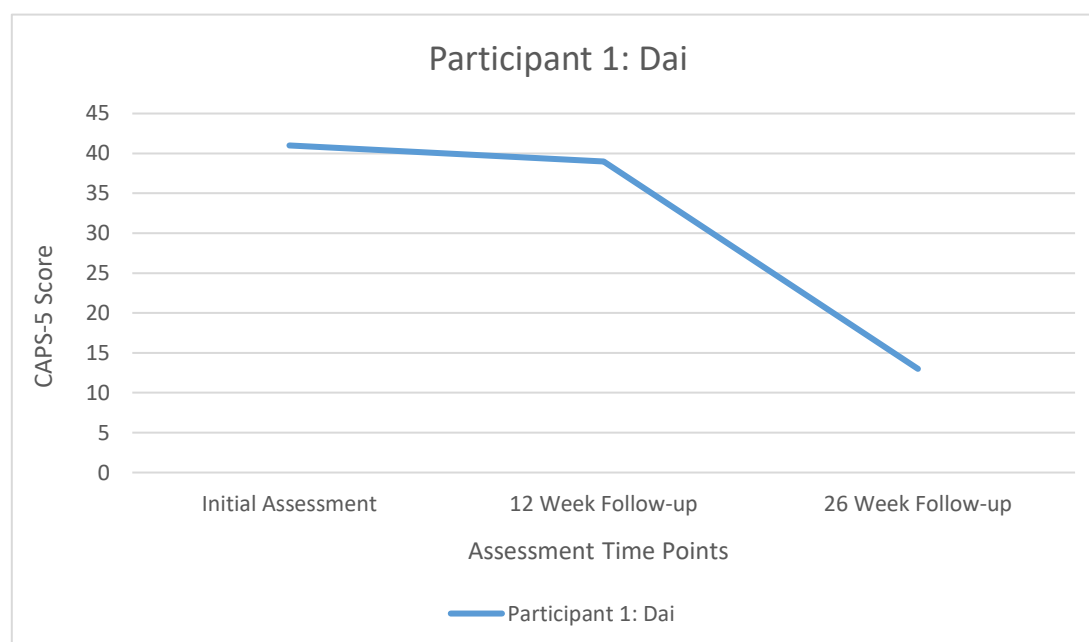
7.4.2 Case 2 - Participant 2: Rhys

Table 7-3 A Summary of participant 2: Rhys

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks

| P2	39	Immediate	The first veteran to have 3MDR, traumas from the 2000s	33	50	48	47

Positive attitude to treatment: Rhys was open to any form of treatment that could help him eradicate his symptoms: *'Well I'm of a mind that I'm willing to try anything if it's going to improve my life or the lives of my family.'* He was prepared for the challenge of therapy: *'I would probably have a little bit of a rough patch, but again in the military, you're used to going through the tough to get out the other end'.*

Motivated and Committed to helping others: Rhys felt very committed to improving the quality of his own life and the life of his family: *'I don't quit anything. I'm still very military-minded you know, I've always been quite set in my way, I don't like letting people down so once I start something, I'll see it through.'*

The positive experience of 3MDR therapy: He described having a positive outlook on the treatment and was impressed by the set-up of the trial, stating *'I thought it was great, well I've been in gait analysis rooms before, so I know that it's purpose-built for it and I was impressed with the set-up.'* Rhys reported finding some difficulty with selecting the images, describing the process as '*really, really hard'*, and talked about a night of searching and selecting and telling his wife, *'look this is so bad trying to get my experiences, ones that really affect me and move me and reduce them down to their bare bones'*. He reported finding selecting the music a lot easier and less anxiety-provoking due to its positive connection with his family: *'one of the songs that I sing in the car with the kids when we're having fun'*. He felt that no other therapy had affected him in the same way: *'like physically and mentally it really burnt me out, you know, there weren't any easy sessions I don't think'* and each therapy day was met with a sense of dread.

Support from family and healthcare professional: Rhys felt supported during the trial. He reported feeling relieved that he knew his treating therapist before and had built a good rapport: *'it probably would've had to have been a longer process.'* if he had not known the therapist. He felt exhausted after each treatment session and reported experiencing flashbacks whilst travelling home. Talking with his therapist led to the conclusion that *'I was still processing stuff.'* Rhys explained that he was very close to his wife '*I spoke to my wife and, you know, gave her the outline, and you know, as always she fully supported me.'* Overall, Rhys felt optimistic about 3MDR and would recommend it to others. He found parts of the therapy challenging and uncomfortable but felt it was a necessary part of the treatment. Although he felt that he might never stop experiencing PTSD symptoms, he felt glad to have participated in the trial: *'the way I look at it, with every treatment I try if I get an incremental improvement it's just going to improve the quality of life for me and my family.'*

Figure 7-2 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 scores for Participant 2: Rhys
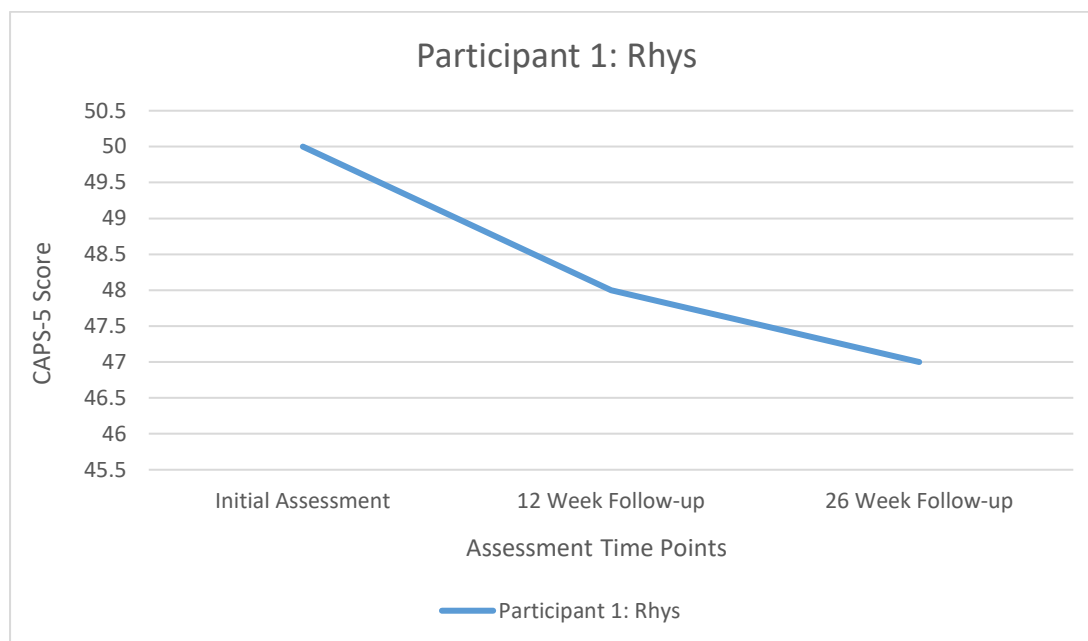
7.4.3 Case 3 - Participant 4: Callum

Table 7-4 A Summary of participant 4: Callum

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks
P4	49	Immediate	Trauma not combat-related	25	38	14	5

Motivated and Committed to helping others: Callum felt motivated to help other veterans: *'if it don't help me it might help someone else and you needed participants, so I agreed to give it a go.'* He also explained that he would stay committed to the trial *'It's a military thing. You aren't going to find many people dropping out unless they have a really bad experience.'*

Isolated: He explained that he did not speak to many people about his experiences *'I'm a private person.'* He reported that he would say very little about his day to his wife, and only express whether it was a good or bad day and would never elaborate *'I always keep things to myself.'*

The experience of the 3MDR therapy: Callum's reaction to first seeing the clinic was, *'This is different'*, and his experience of the therapy was of an immersive experience: *'I didn't know what to expect it was just it was quite overwhelming the whole 3-D experience on the treadmill because you do get sucked into it when you're there and the screen is virtually surrounding you yeah you sort of get sucked in to the, you're in that picture.'* He reported being *'in a complete daze'* on his way home. Callum felt that 3MDR therapy *'has done a lot of good'* but also that *'only time can tell.'*

Figure 7-3 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 scores for Participant 4: Callum
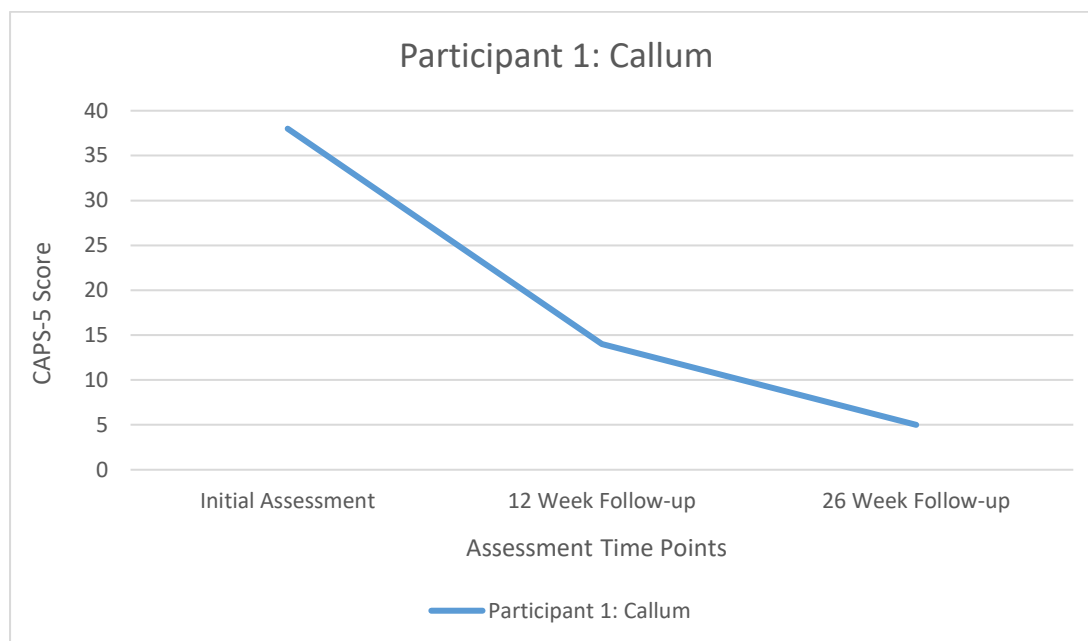
7.4.4 Case 4 - Participant 8: Terry

Table 7-5 A Summary of participant 8: Terry

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks
P8	59	Waiting list	Multiple traumas, developmental and learning problems	94	51	32	13
Support from his partner: Terry had experienced a lot of different psychological treatment for his PTSD. His attitudes towards treatment were that *'anything is better than nothing'*. He was encouraged to take part by his wife who was present during each treatment and assessment session: *'Yes, yes, I mean she said go for it, go for it you know because anything is better than nothing, you know.'* Terry's wife drove him for most sessions, but not all, including one time where his drive home was characterised thus: *'I was driving home, it was like either side of the road I could, I could see ahead of me the road that I was driving on but it was like as if, if you'd have pinched me I wouldn't have felt it but either side, like [name of wife] said, the images but of the Falklands one side, Bosnia next and it was like as if you were driving looking at a television either side on the roadside'.* The experience of 3MDR therapy: He also reported feeling *'apprehensive'* ahead of commencing treatment. However, he felt confident and reassured during each treatment session because of his pre-existing relation and rapport with his allocated therapist, who he felt played an integral part in his recovery. *'Yeah and I think [therapist] being there initially because I was confident with [name of therapist] and I knew [name of therapist], her being there as the therapist during the 3MDR helped.'*						

Activities after 3MDR therapy: His first three or four therapy sessions saw a worsening of his difficulties, characterised by nightmares, feeling drained: *"didn't know where I was, I used to walk out of there and it was like feeling as if you were still there"* and felt that he was *'reliving what I'd gone through.'* His wife was key to getting him back to his next session, driving him, herself in the face of him saying how he did not wish to continue. Being on the treadmill he described as causing a *'tunnel effect, the tunnel effect was absolutely brilliant.'* Terry and his wife planned and went on several enjoyable activities, such as walks and lunch after each 3MDR session, to help Terry deal with the aftermath *'Yes one time we went to Porthcawl…. and Barry Island.'*

Dyslexia: Terry explained that his dyslexia made certain parts of the 3MDR trial difficult: *'Yes, because I was doing, because of my dyslexia obviously [therapist] was getting me to do different forms, you know there, now, when now, and I was getting totally confused and it was making me feel worse.'*

Terry felt generally positive about the trial; however, he reported that individual parts could be improved or changed to make the experience less complicated, such as substituting static images with moving pictures to make for a more realistic experience. He also recommended family members sitting in on sessions.

Figure 7-4 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 for participant 8: Terry
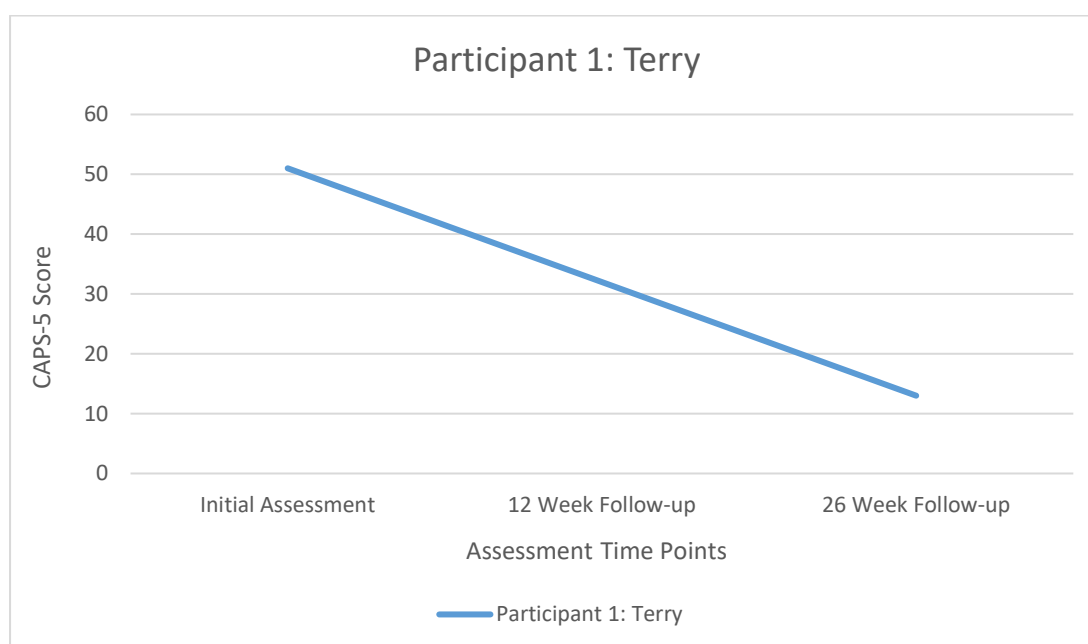
7.4.5 Case 5 - Participant 9: Gethin

Table 7-6 A summary of participant 9: Gethin

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks

| P9 | 43 | Immediate | Reported significant benefits before the end of scheduled 3MDR sessions, and early discontinuation | 35 | 38 | 0 | 0 |

Motivation to participate: Gethin reported feeling very excited and enthusiastic about taking part in the 3MDR trial:*'So I jumped feet first in and expected what I was given, and what I was given experiencing all the way through, I needed to do it.'* He found YouTube information on the therapy, and talked about possible participation with his mother, then partner and with other veterans but was still *'a bit hesitant to start with.'*

Positive experience of 3MDR therapy: Of his first visit to the clinic he said: *'It was like walking into a, what I would, what I would call a spaceship, because when you walk into the room you've got those cameras everywhere, even though they don't, they're not for the actual therapy itself like, because it's like a physio room, and then where I was looking at the treadmill and see this big screen around you, I thought, huh, it's like a PlayStation now isn't it, like a big screen on a PlayStation, but when you actually walk on there, and you see it for the first time and it is, it's an amazing bit of equipment, it is'.* Later he referred to this as an *'encasement.'*

He found the sensory stimulation quite difficult, reporting *'Yes. The images were very distressing for me at the beginning, because I had to look and trawl the internet for key……… Yeah, it is significant for therapy I think.'* Selecting a song associated with his trauma was also challenging, *'because it made, it was like how I felt at that time'* though the second track was much easier to select.

Communication: Although he did not know his therapist until starting in the trial, he had trust in his therapist, saying how, *'when [therapist] stood next to me on the treadmill talking me through these pictures [therapist] has that sound, that voice, that reminds me of my [therapist gender] as such, and that's why I trusted [therapist].'* His then partner helped, but *'each one brought tears to my eyes, and it was just horrible, to look for it, but as you see them from time to time they become more easy to look at.'*

Support from family and partner: *'so I was there explaining to them about this new study, this new thing that's come on over here, and I was there sort of like selling it to them as well, and I think one of the guys over there now is actually looking into it.'* He also spoke to his veteran friends who encouraged his participation in 3MDR: *'They were excited for me, for me to actually do something which would hopefully, that's how I thought, would make me better. And it is going well.'*

The positive experience of 3MDR therapy: *'This has been the best therapy that I've ever responded to, in my eyes. This has done wonders to me wonders with a resolution of nightmares, and no more drinking.'*

Figure 7-5 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 for participant 9: Gethin
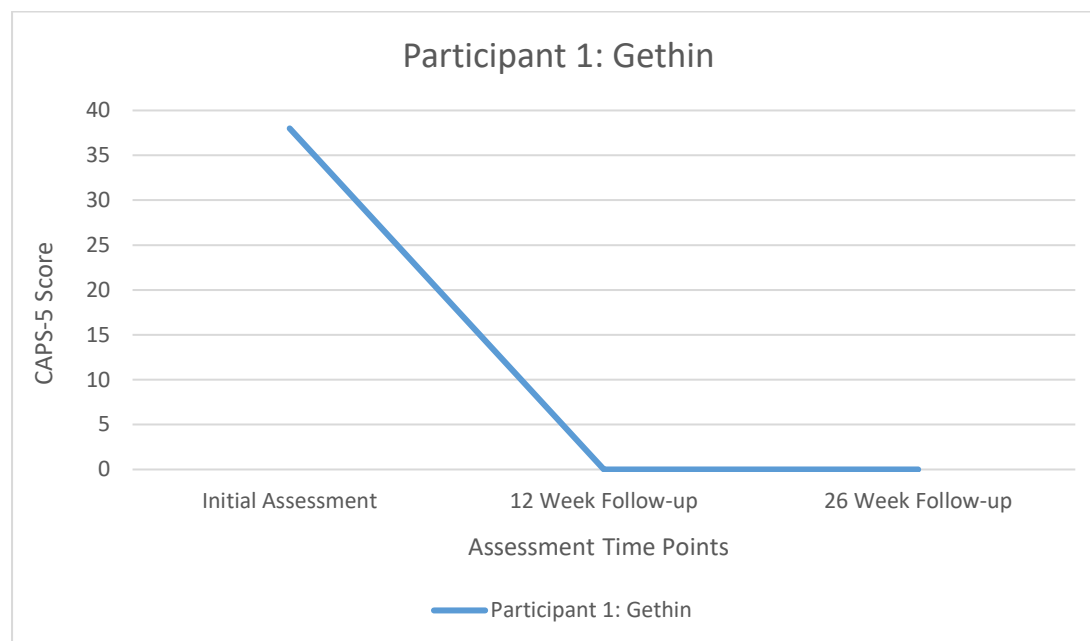
7.4.6 Case 6 - Participant 10: Chris

Table 7-7 A summary of participant 10: Chris

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks
P10	45	Waiting list	Strong emotional responses to therapy	47	52	30	11
A positive attitude about participation: Chris reported feeling very enthusiastic about taking part in 3MDR: *'so I was keen if there was an opportunity to get better because it's been five, six years so I was to some extent almost excited really for the potential of me actually getting a little bit better.'* He reported not to have researched 3MDR before starting, because *'I wanted to come in with a complete open mind on the whole thing'*, but was also fearful *'because I knew they'd be unlocking a lot of bad things inside me.'* Motivated and determined: *'not going to leave any stone unturned.'* His music choices included music which would *'get all the crying out of me, so I won't come in through the door crying.'* He arrived in tears to his first clinic visit, describing himself as *'vulnerable.'* He had good explanations of the set-up from his therapist and the RA, but said: *'it reminds me of 28 Days Later and fucking chimpanzees tied to a thing and you think bloody hell you know, an experiment at Porton Down.'* Therapy continued to be deeply affecting, and images triggered a *'horrendous reaction.'* Walking was slow (*'my knees are knackered'*), and whilst session one was challenging the experience intensified over time: *'the first, probably about halfway through and I started to feel exhausted and up to the end of it feeling almost like you're feeling a collapse, the second and some of the sessions after that were worse than that but I was feeling utterly exhausted on that first session but the second one got a lot*							

worse from there on.' The music, the images, the talk all combined: *'I never felt like this before in my life.'*

Positive rapport with the therapist: Having a consistent therapist across sessions was necessary, and this therapist he knew and trusted, *'No I've known [therapist] for years so she's very good, she's the best person I know, I've had and she's very attuned to me so it's good.'* Furthermore, he felt supported by his work*: '… they said look do whatever and they'll make adjustments for my work so they were very supportive.'*

Support from family and friends: Encouraged by his wife to have 3MDR, *'because she's living with someone who's mentally ill'*, but had no close friends. However, he spoke very little to family or friends during his therapy sessions *('I just didn't really talk too much. I did say it was horrendous to people and I said look that's it but I didn't really talk much about it'*).

Motivated and Determined: Despite the difficulties, he was determined to get through: *'I would have died for any of my soldiers, I was determined, that's why, because I've seen people kill themselves and you know, just turned to alcohol, shit and I'm not going to be one of those people.'* His work was on a contract basis, and the company he worked for knew he had been ill and were able and willing to make adjustments.

Positive 3MDR experience: *'It's definitely helped me without a shadow of a doubt, more than other therapy I've had, it's been the hardest therapy but it has definitely helped me.'* Specifically, he described improvements in his sleep and a reduction in his intrusive thoughts.

Figure 7-6 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 for participant 10: Chris
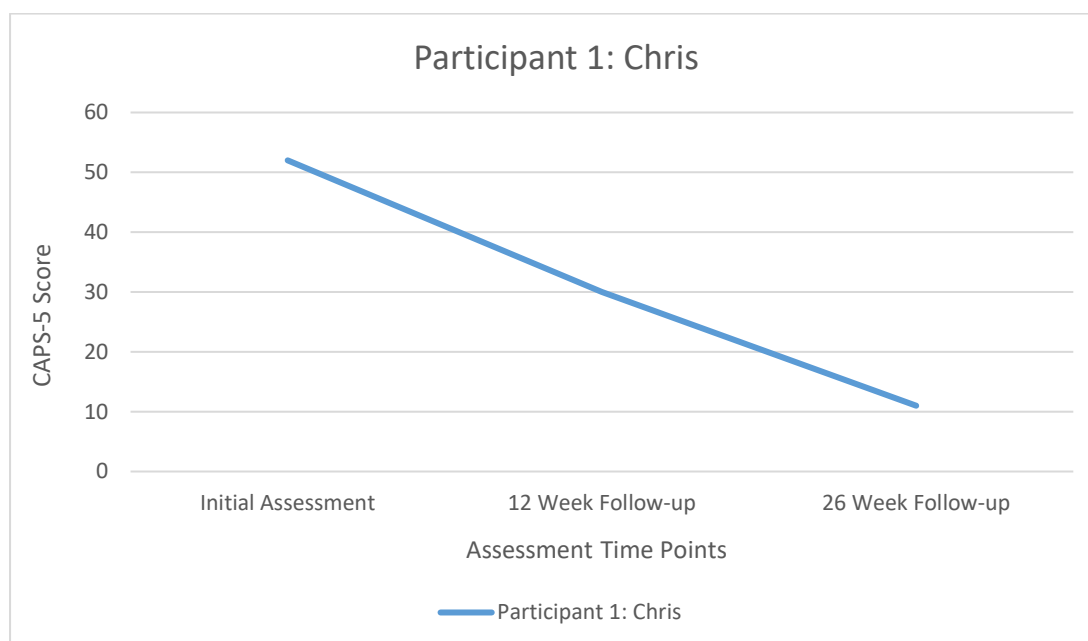
7.4.7 Case 7 - Participant 12: Duncan

Table 7-8 A summary of participant 12: Duncan

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks
P12	56	Waiting list	Reported unanticipated physical health improvements	31	55	39	4

A positive attitude about participation: Duncan reported that he is *'interested in new things.'* He decided to join the study without consulting family or friends, saying how *'My wife doesn't get involved with anything like that.'* His initial thoughts were that he *'was quite wary'*, and *'Yeah and a bit anxious, you know nervous like you know because I'm, I didn't know what it was going to be like or you know.'* On first visiting the clinic and seeing the set-up he said how *'I didn't think it was going to work, you know, I had some doubt but I'm quite good at entering a thing with an open mind.'*

Duncan reported that picking out the images was incredibly difficult, as he *'wanted ones that really upset me, like I don't know why just you know, there was a point, I thought it was pointless going there with photographs that weren't going to do anything.'*

Negative feelings towards waiting list: His first clinic visit involved an explanation of the clinic set-up, with harness and heart rate, followed by an unwelcome wait until the commencement of therapy. The therapy itself, he found helpful and described swapping photos in and out over sessions and that during 3MDR *'the penny dropped'*, during sessions 2 and 3 specifically.

Communication: He reported not speaking to any family or friends during the therapy period.

Avoidance of treatment: He a described *'a blip'*, wherein between sessions he *'was on a bit of a downer'* and thought he was slipping back: *'……..I think it was about bloody Sunday or something but anyway, you know something that was very prominent in my mind..'* Scheduling therapy he described as straightforward and involved driving to and from the clinic.

Positive 3MDR experience: *'I've got to be fair after the second or third session I felt, it was a bonus, I felt fantastic, you know, I really did […] I know the answer, it just came like that, like a eureka moment, you know.'* He reported to have benefited from the 3MDR treatment describing himself *'a better person […] happier.'*

Figure 7-7 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 for participant 12: Duncan

Participant 1: Duncan
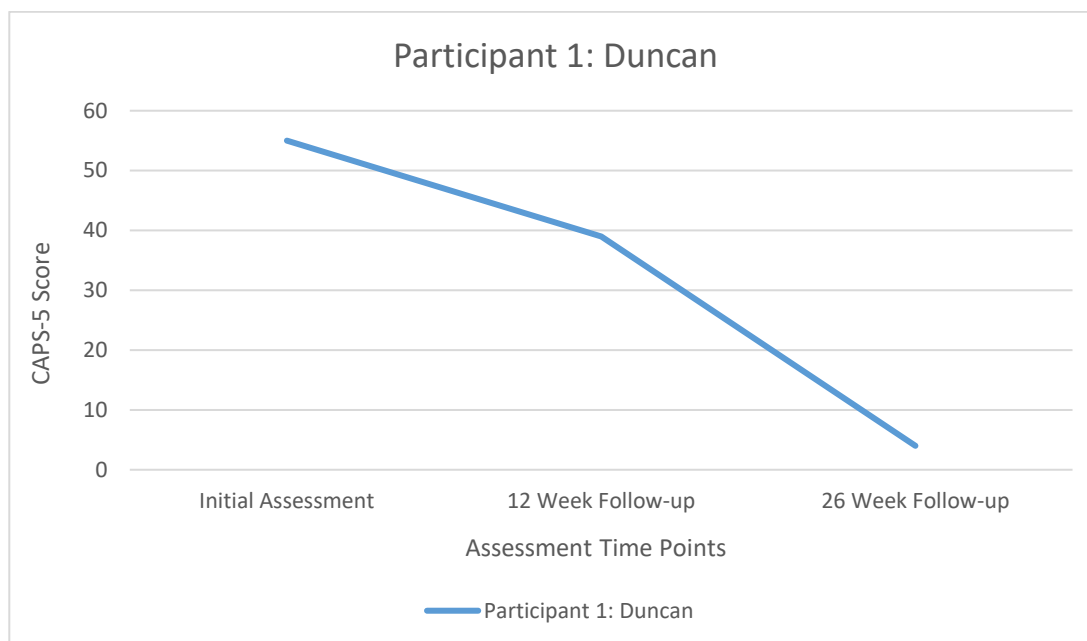
7.4.8 Case 8 - Participant 16: Berwyn

Table 7-9 A summary of participant 16: Berwyn

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks
P16	62	Immediate	Dropped out of treatment sessions after the initial visit to the clinic.	76	50	45	Not completed
Motivated and committed to helping others: Berwyn wanted to try *'almost anything'* to get better, and was motivated too by the idea that others might benefit in the future: *'I'm more than happy to take part in trials and experiments, whatever you like to call it because my thoughts are not for myself but by taking part others might benefit.'*							
A negative experience of pre-treatment activities: Berwyn assumed 3MDR was being offered through the veterans' services and so *'it would have been safe.'* Searching for images, he described as *'triggering'*: *'the big thing that went wrong is I took it very seriously and I spent quite some time selecting images that would trigger me so you know, if you're asked to select something that's going to trigger you, what's going to happen? It will be triggered, okay?'* A clear view he expressed was that selecting images should be done with someone with whom a relationship was already in place, such as							

a known and trusted therapist, rather than being done alone and then needing to be explained to a previously unfamiliar practitioner. Selecting music he described as having been even harder than selecting images, reflecting on his experience in the military as a musician.

Experience within the military: Berwyn explained that he entered the army as a very young boy and felt underprepared and overwhelmed with his role. *'I put my first pair of boots on, army boots on and from that time on I was ordered to do this, ordered to do that and very, very quickly I was ordered to handle very dangerous machinery, I could kill.'*

Negative attitude towards self-report measures: He disapproved of filling in the self-report questionnaires as he felt it was not an accurate reflection on how and what he was feeling: *'..... it appeared a bit of a joke really, a box ticking exercise completely disregarding anything else that might be going on and completely missing the wider picture.'* He described the process as *'triggering'* and doubted the reliability: *'you kind of think well you know, if I didn't sleep last night I'm going to fill it in one way but if I had the best night ever I'm going to fill it in another.'*

Difficulty attending treatment sessions: He found trips to the Hadyn Ellis Building for assessment and the University Hospital of Wales for treatment difficult and anxiety-provoking. His friend/partner present during the interview also added that parking caused further difficulty and funding to cover travel costs would have helped. The journey home was challenging: *'that journey home on the motorway, I mean I was going to commit suicide.'* He immediately met with his friend, and during the interview, the conversation turned to the value of having support from the 3MDR team to check safe return home following a difficult meeting.

Unfamiliar treating therapist: His treating therapist was not his usual therapist, and the first meeting with the former took place in the clinic following his second trip to Cardiff, again made on his own. He arrived in Cardiff in a state of anxiety, having continued looking for images until midnight the day before and having had problems parking. Not knowing the therapist, he described as a problem, and many of the images he had selected to represent his sense of moral injury ended being edited out.

Moral Injury: Berwyn explained that he disagreed with the diagnosis of PTSD and that he felt very strongly about the term *'Moral Injury'* as he felt this better explained his symptoms and what he had experienced in the military. *'I kind of got the opinion that I was actually teaching [name of treating therapist] about moral injury rather than being able to, responding to it.'*

Lack of support: Berwyn did not have any friends but was close to his parents, although he did not see them very often. He had no social network of friends and was isolated from any form of interaction other than his partner who was unable to attend all treatment sessions: *'I think possibly [name of original therapist] did say about taking someone with me and you would normally have come but you were working.'* Berwyn also reported trust issues with the military and related staff: *'I still don't trust don't, we all collectively don't trust the militia, not that we trust civilians.'*

A negative attitude about 3MDR treatment: Berwyn was against recommending the therapy to others. He felt overwhelmed when he first saw the MOTEK machine. He did not feel that it was a comfort or at all welcoming. *'Based on my experience I would, no I won't do this again, I probably won't ever do this again but if I was being considered doing it again I wouldn't do it without being an inpatient.'*

Berwyn left the study following these three initial meetings, and key factors from the interview included therapist continuity, support during the selection of pictures and music and travel arrangements.

Figure 7-8 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 for participant 16: Berwyn
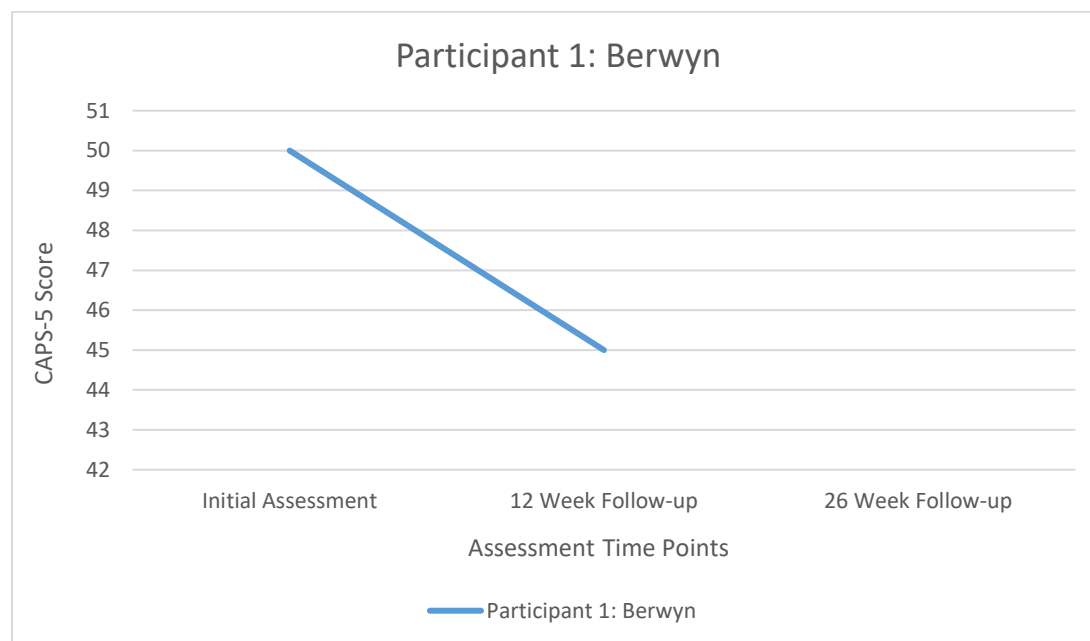
7.4.9 Case 9 - Participant 18: Harry

Table 7-10 A summary of participant 18: Harry

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks
P18	53	Waiting list	Co-existing physical health problems and disabilities, financial issues	53	41	38	18
Positive attitude towards treatment: Harry was recommended to take part in the treatment by his trusted therapist, and he reported, *'I thought you know, instantly I thought wow, that's, for me personally.'* He viewed a YouTube clip but did not talk with family or friends before deciding to join. He felt that he was a unique position and wanted to take full advantage of participating in a new therapy designed for military veterans.							
A positive experience of 3MDR therapy: He described his first visit to the clinic thus: *'I was gobsmacked, I thought what am I, is this like NASA, you know, what's going on here you know? It was just unexpected, totally unexpected because it's such, for me it's such a contrast between going into an old classroom or whatever […].'* Images were generally selected at the start of each session, with the most emotionally charged one tending to be used at the end of the session modified by some random shuffling, in some sessions, of the ordering of the selected pictures.							

A negative experience of 3MDR: Harry thought of dropping out following one tough session: *'I think it was about halfway through or just after and I was pretty close thinking mmm, because I think it was just that particular day that you know, felt like a kick in the teeth like and because I felt so shit and drained and all the rest of it I just thought how much more, am I going to put up with this [...]'*. However, he felt the therapy sessions provided him with a routine and something productive *'I found it quite fulfilling really because it gave me something to get up and do and it was a challenge as well, and it was sorting out times and things.'*

Support from friends: Harry did not speak to many people, but he felt that he could speak to a few close individuals, namely a veteran that lived close by, as well as the treating therapist. *'....well I spoke to, you know I've got a friend up the road he's ex-army and when it was a bad day I suppose sometimes I used to just say you know, go for a beer, or what you've had a shit day have you?'*

Difficulty travelling to and from 3MDR sessions: Travel to and from the clinic (from home over 40 miles away) was via public transport, and finding the clinic on the first occasion was not easy for him. The feeling of being physically and mentally drained, he described as sometimes lasting for days, but at the end of the therapy, he would have continued had the option been available.

Figure 7-9 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 for participant 16: Harry
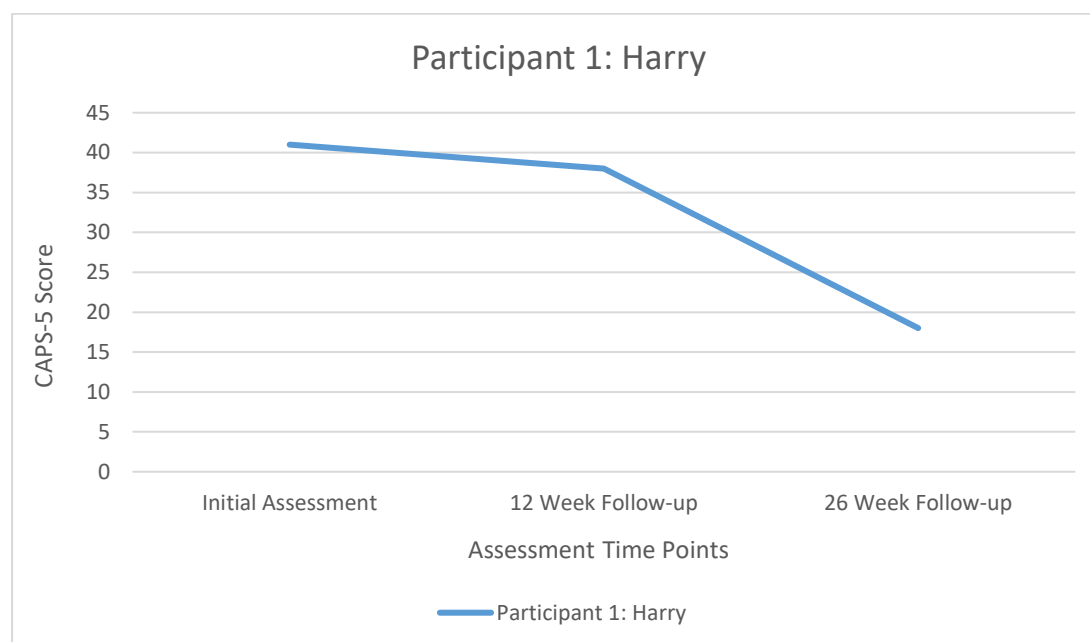
7.4.10 Case 10 - Participant 25: Charlie

Table 7-11 A summary of participant 25: Charlie

ID	Age at interview	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks
P25	56	Immediate	Discontinued before the final treatment session, as could not find photos evoking intense enough emotions	48	30	29	33

Motivated and committed to helping others: Charlie felt a great connection to veterans and taking part in the trial was an opportunity to give back to the community *'...the fact that I've been given a couple of opportunities to help other veterans start up groups and has made me feel self-worth again.'*

Stigma: Charlie felt there was still a lot of stigmas attached to a PTSD diagnosis, and he struggled to deal with some of the emotions associated with the disorder. He explained that he had received support, to help with some of these emotions, through combat stress. Ahead of having 3MDR he was *'shit scared, plain and simple, you know, and I made that known to [name of therapist] as well, that I was you know, shit scared of what it might bring up'*. He entered therapy with *'a badge of shame attached to me, and guilt.'*

Discovering important document: Searching for images with therapist help was a revelation. Alongside finding online, *'difficult'*, pictures of aeroplane crash sites and RAF police, he also found a 'top of the mountain' document, the existence of which he had not previously been aware, which recorded an official judgment that the trauma he had been involved in was down to pilot error and not to his negligence. This had been the position taken by investigators at the time. Finding this was a tearful event, which *'sent me on a huge roller coaster of emotions',* and this single *'document took over so much.'* His music *'was a godsend really'*, both being important and selected because they were very different and because both words and music were meaningful.

The positive experience of 3MDR therapy: Charlie explained that 3MDR helped evoke some of the memories and emotions that he found difficult to recall, as he confronted them head-on. *'Various pictures came up which were difficult, some hit me straightaway because they took me back to 1979 which is when my SH1T started if you like.'* He liked the fact that the therapy was personalised as he felt this made the participant central to the treatment. He also explained that he had accepted certain aspects of the PTSD, and the therapy had made him more confident to deal with other aspects of emotions: *'Has it helped me, I'm going to say yes because that, red ball tick-tick-tick blew my mind and it's helped me to deal with the (unclear) that I had ten/twelve weeks ago and so yes it has.'*

Support from family and friends: Charlie explained that the support received from his family members who took him to the therapy and research sessions was beneficial *'Again, by having so many people, [name] basically and [name] who in turns took me in there, that was fantastic.'*

He spoke to friends who encouraged him to continue attending the treatment sessions in order to reach a sense of closure: *'I wanted to give it a 110%, I know that I'm damaged and if I could get some help myself then I wanted that and again you know, let's see what happens over the year.'* Charlie explained

the importance of his friends within the military. He described them as *'Brothers'*, and they were the only people who could understand what he had experienced.

Positive rapport with the therapist: He saw the location of services for veterans as necessary: *'friendly to the eye, friendly to the smell, friendly to the touch'*, and his first clinic visit involved taking the set-up in: *'so it's going to be up there and you're going to walk so I was, going through the motions I suppose.'* His 3MDR therapist was new to him, and his referring therapists recommendation was important. At the start of therapy, *'It started off a little bit gingerly'*, but the relationship grew, and he appreciated the therapists permission to be open: *'if you need to fucking well swear you fucking well swear'* and genuine interest. Walking *'warmed my arthritis up'* but was important because it meant *'you're given a chance to confront your demons and some of it I did sort of head-on.'*

He felt that he built a connection and an excellent professional rapport with his allocated therapist, who supported him. *'Yeah, she came across with you know, really good you know, professional attitude but also it seemed to be that the lady genuinely cared and if she didn't then she hid it very well but that's how she made me feel and all credit to her for that.'*

A positive experience of 3MDR therapy: *'I know a little bit more now about myself, about my character than what I did prior. That's as much as I can really say on that really.'* He thinks it too early to recommend to others, saying first *'I'd like to see what becomes of this'* in, perhaps, a year.

Figure 7-10 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 for participant 25: Charlie
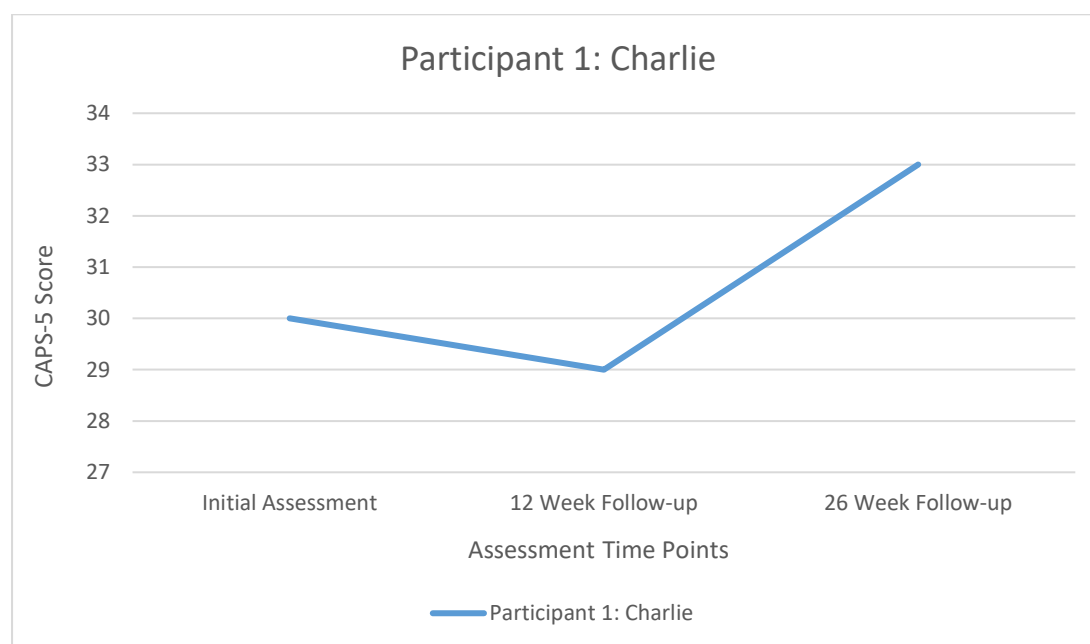
7.4.11 Case 11 - Participant 26: Tony

Table 7-12 A Summary of participant 26: Tony

ID	Age at in2tervie w	Arm of study	Reason for sampling	Length of the interview (minutes)	CAPS-5 outcome scores		
					Initial Assessment	12 weeks	26 weeks

P26	57	Immediate	Dropped out after three sessions	43	54	38	20

Partner's attitude about participation: Tony explained that his wife was slightly hesitant about his participation in the trial. However, he felt that he wanted to try something new as other existing therapies were not working for him: *'My wife was a little, little bit dubious because she thought I would be like a guinea pig.'* Introduced to 3MDR by his usual therapist, who was not directly involved in the trial, who referred him in because *'I wasn't progressing as well as I should have been.'*

Difficulty travelling to and from 3MDR sessions: Tony explained that his journey from home in West Wales to assessment was anxiety-provoking, *'because Cardiff being three quarters of an hour away from me I'd got time when I was driving up, dwelling on what's going to happen so there was, I did feel a bit apprehensive, nervous and unsure what was going to go on so I had a lot of time to think about it really'*, but was nonetheless *'welcomed and it was, you know they settled me down.'* He was *'uneasy'* when he first arrived at the clinic *'because there was nobody on the desk to receive me and I was just wandering around the building trying to find out about so I had to stop somebody and they pointed me in the right direction.'*

His wife accompanied him to sessions but could not drive, and on his way home, he felt lacking in concentration, meaning he learned to stay longer (having coffee, for example) before heading off. Parking at the clinic site was a problem during his second visit, as it had been on the first, but the session was different: *'.....but there was a problem with the parking and my wife is disabled and we had problems finding disabled spot so she couldn't walk so she couldn't go into the centre.'*

Difficulty sourcing images: Before the treatment session began, he found it challenging to source the images for the session which meant the photographs were *'really didn't send me right back to where I was so I think the actual feeling when I was given the treatment, I didn't feel that I was there, you know, fully into what I was doing.'* His images continued to be problematic: *'but there was nothing there to relate that because of the experience that I had so that was quite difficult really because I didn't feel any relation to that at all.'* Tony reported feeling cynical about the randomisation process as he felt it would be biased: *'I was expecting maybe I would be the one that was going to be on the back burner because of my age and the experiences.'*

Father's Day trigger: Following a problematic weekend, he rang the clinic and asked for a week off, telling his therapist it had *been 'as if the whole world had just sort of caved in.'* His third treatment was followed by a problematic weekend: *'it was unreal, you know I just blew at everything really, so I wasn't nice to be around and the experiences were there and I just couldn't get rid of them any more you know.'* His sleep was disturbed, his memories intrusive, and he felt like killing himself. Tony felt that the therapy had resurrected some of his trauma which made him feel he was back in a *'bad place.'* *'Anger, suicidal thoughts, especially that Sunday and my wife was really concerned, I was sitting on the side of the bed just crying my eyes out and I just felt like killing myself.'*

Lack of support: Tony's experiences included the difficulty of travelling long distances, and having to drive home post-therapy, and the lack of back-up out of hours: *'I think there should be someone there because they referred me to the mental health, the crisis team which is [name] who's here but I didn't feel that if I rang those people they would be aware of what was going on with my case, I would have to go through things again and I might end up in hospital somewhere but I felt there should be somebody I could just pick up a phone and say can I have a chat.'* Looking back over his experience, he sees some good, insofar as *'I've been able to talk to my family, my wife, my son about what I experienced.'*

A negative attitude about 3MDR treatment: Tony explained that he felt 3MDR was not suitable for his type of trauma. He felt that he had too many traumatic experiences, and 3MDR was not suitable to deal with all of these experiences. *'....I didn't think it was fair for your team to have me on board giving false, what I would say readings, because I'm having issues not just the two, but, so to me I would say*

that maybe the treatment is geared towards somebody who's had treatment recently.....' He felt there was a lack of support from the research team as they were not able to be accessed 24/7: *'I didn't feel there was sufficient back up, I didn't feel like I could pick up a phone and ring somebody on the team because they were in Cardiff and not in Swansea and it's a weekend.'*

Figure 7-11 The Clinician-Administered Post Traumatic Stress Disorder Scale for DSM-5 for participant 26: Tony
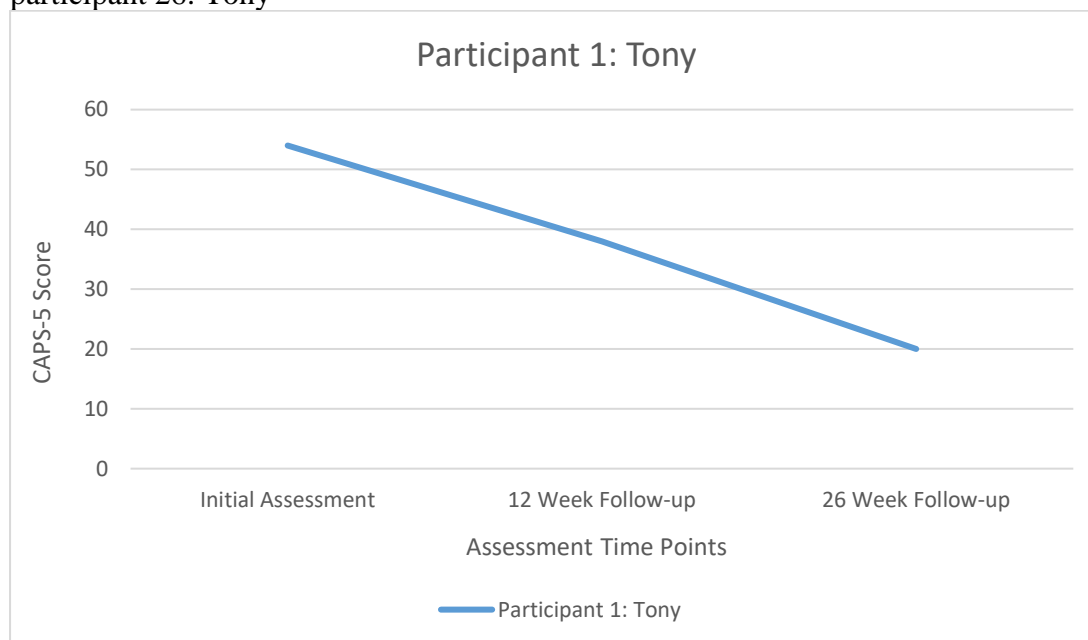
7.4.12 Within-case synthesis

The within-case analysis produced single case summaries, primarily descriptive and considered factors that shaped the veterans' individual experiences. This took advantage of the data set's richness and did justice to the complexity of these veterans' experiences. To assess the similarities and differences within the data, veteran transcripts were compared to one another to identify the full range of themes within the sample [379, 381]. Similarly, interviews were compared across veterans to develop the sub-themes that reflect variations in how a theme manifested across the veteran's experience. These themes and sub-themes arose from the initial analysis of individual cases and conceptual building blocks for the overarching themes. The process involved coding and categorising the data to highlight relationships between the factors associated with treatment outcome [345, 378, 379].

7.5 Between-case analysis

The second phase of analysis involved moving to a thematic analysis of the total participant interview data set. This method helped identify several additional themes based on case

differences among how individual veterans defined or perceived their experiences. Across-case analysis contributed to identifying themes and relationships among themes that characterised the veterans' thoughts and feelings across a broad range of experiences. The individual veteran account was formalised by narrative case summaries, whereas across-case comparisons were developed using NVivo, to quantify the number of recurring themes. A grid display was used to manage sub-theme categories to identify similar thematic patterns comprising distinct experiences. This process resulted in the identification of three main themes. To describe each theme's content in a way that communicated the complexity of veterans' experiences, summaries of the three main themes in the context of the individual veteran transcript are detailed below.

Three main themes are presented, which describe factors associated with treatment outcome among military veterans. The themes are *attitudes and motivations, expectations and experiences, and relationships and support.* Each central theme is made up of sub-themes, which are:

1. Attitudes and motivations: Participation, Altruism and Military Experience.

2. Expectations and experience: 3MDR Set up and views on treatment outcome.

3. Relationship and support: Friends, Family and Health care professionals.

7.5.1 Theme 1: Attitudes and motivations

7.5.1.1 Participation

Veteran participants had varying attitudes towards 3MDR treatment. Some explained that they felt very fortunate to be part of a novel study designed for military veterans, which was associated with positive treatment outcome, measured by a reduction in PTSD symptoms. Others showed fewer positive attitudes about taking part in the trial and felt that the therapy was not suitable for them or their trauma, associated with participants doing less well in treatment. Participants explained two primary motivators for taking part in the 3MDR trial: an attempt to try something new to improve their symptoms and an opportunity to potentially help fellow veterans and further research in PTSD. The following sections present an analysis of this sub-theme in detail.

Table 7-13 Between case analysis of sub-factor: participation

No. of Participants	Identified Factors	The direction of association with treatment outcome	Example Extract 1	Example Extract 2
9	Attitude about the trial.	Positive association: decrease in PTSD symptoms as measured by the CAPS-5 scores.	*Harry: you were lucky to get picked to go and do something like this you know, because there are only forty-odd people that get a chance to do it out of the whole country, out of the whole UK*	*Duncan: To be honest with you I was quite wary, you know, I'm more of a technology and all this type of thing, and when [name of therapist] said I was interested because of the, it was something new, and I'm always interested in something like that*

7.5.1.2 Altruism

Seven participants reported feeling altruistic towards veterans and motivated to improve the lives of their loved ones and the lives of fellow veterans. For example, most of them indicated they stayed committed to the treatment despite finding it difficult because they were not prepared to let their family, friends, or research staff down. The results indicate that those who expressed motivation to help others were associated with better treatment outcome, as indicated by a reduction in CAPS-5 scores (see individual graphs above). In the following extracts, the participant acknowledges the difficulties and the possibility that he might not fully benefit from 3MDR treatment but was willing to continue so that others could benefit from his participation.

Table 7-14 Between case analysis of sub-factor: altruism

No. of Participants	Identified Factors	The direction of association with treatment outcome	Example Extract 1	Example Extract 2
4	Motivated and committed to helping others.	Positive association: decrease in PTSD symptoms as measured by the CAPS-5 scores.	Callum: *I'd made a commitment. If I hadn't been happy I'd have dropped out, but there was nothing that bad that I needed to and the fact that from the beginning I thought the process was if it doesn't help me it might help someone else.*	*Rhys: ....the way I look at it, with every treatment I try if I get an incremental improvement it's just going to improve the quality of life for me and my family, so I'm willing to jump through whatever hoops put in front of me.'*

7.5.1.3   Military experience

Participants reported feeling obligated to try and better their lives for the sake of the friends, family and health care professionals that have helped them with their PTSD symptoms. They also believed that their time in the military had helped them stay committed to the treatment, as they had developed an ethos not to give up and stay committed to whatever they had started. The CAPS-5 results indicate that those who expressed a commitment to the trial were associated with better treatment outcome, as defined by a reduction in PTSD symptoms. In the following extracts, the participants describe a commitment to the trial and loyalty to others were due to time spent in the military.

Table 7-15 Between case analysis of sub-factor: military experience

No. of Participants	Identified Factors	The direction of association with treatment outcome	Example Extract 1	Example Extract 2
7	Commitment to a task, obligation to fulfil a role and the camaraderie that was developed whilst in the military.	Positive association: decrease in PTSD symptoms as measured by the CAPS-5 scores.	*Dai: Well if I said to someone I'll carry through, I'll do it., a lot of people are going to a lot of trouble for me, Veterans' health, a lot of people are going to a lot of trouble to you know, my GP, my wife, family, GP..... I don't want to waste their time.*	*Callum: Yeah exactly, it's a military thing, it is a military thing, you don't join the military in the first place unless you want to help somebody else.*

7.5.1.4 Summary

Overall, participants reported positive attitudes about taking part in 3MDR. The results indicate that those who expressed a positive attitude and motivation to participate in the trial had better treatment outcomes, as measured by a reduction in PTSD symptoms. However, five participants reported feeling anxious, worried, or afraid about participating in the treatment and felt doubtful about the treatment outcome. This did not have any significant association with treatment outcome as participants continued to improve.

Participants reported two main reasons why they chose to participate in 3MDR. Firstly, three participants reported they were motivated to help other veterans, as it was a chance to improve mental health support and provide alternative treatment options for this group. Secondly, three participants reported that their military experience made them feel more committed to the trial as it was not in their nature to give up or give in. Consequently, the participants' attitudes and motivations shaped the other sources or themes of factors associated with treatment outcome, which will be discussed in the following sections.

7.5.2 Theme 2: Expectations and experience

There was a consensus among the veterans that the 3MDR treatment was impressive, and they felt lucky to have had the opportunity to participate in a novel treatment tailored to veterans. Some participants also reported the added value of having a known therapist by their side during the treatment sessions, making them feel comfortable and safe. Some participants reported feeling cynical about the randomisation process and that the set-up was not suitable for their trauma. A detailed account of the sub-themes is reported below.

7.5.2.1   3MDR set-up

Most of the participants reported a positive outlook on the 3MDR treatment. They expressed gratitude for participating in the novel intervention, which was associated with veterans doing better in treatment, as measured by their CAPS-5 scores. Furthermore, participants also reported feeling impressed and excited when they first saw the 3MDR lab because the treatment encouraged participants to be active and face their fears as they walk towards their trauma. For example, in the following extracts, the participant feels enthusiastic that the treatment involves physical exercise and that it is different from the usual sit-down methods of treatment. The following two extracts describe the participants feeling overwhelmed and frustrated with the trial process.

Table 7-16 Between case analysis of sub-factor: 3MDR set-up positive experience

No. of Participants	Identified Factors	The direction of association with treatment outcome	Example Extract 1	Example Extract 2

3	Impressed and enthusiastic about taking part in the treatment	Positive association: decrease in PTSD symptoms as measured by the CAPS-5 scores.	Dai: *Well I saw the treadmill, being a runner, you know, I enjoy my run as well, treadmill so it'll save me doing my training when I get home.*	*Rhys: I thought it was great, well I've been in gait analysis rooms before, so I know that it's purpose-built for it and I was impressed with the set-up*

A few participants found the 3MDR experience quite difficult, particularly certain aspects of the treatment sessions. For example, in the extracts below, the participants described finding the 180º degree screen quite overwhelming and the pendulum ball a draining exercise that caused them to become slightly dizzy. They also reported frustration about filling in the self-report questionnaires. Some participants felt more hesitant than others; however, as highlighted above, their motivation to improve their quality of life encouraged them to take part and stay committed to the treatment.

Table 7-17 Between case analysis of sub-factor: 3MDR set-up negative experience

No. of Participants	Identified Factors	The direction of association with treatment outcome	Example Extract 1	Example Extract 2

| 4 | 3MDR treatment sessions and assessment requirements. | Negative association: Participants didn't improve and or dropped out before the start of treatment. | *Rhys: I mean, don't get me wrong I found it pretty horrendous at times but again I've gone through so much, you know, I know if you just keep pushing through you eventually get to the end, you know, it doesn't mean I wasn't happy to finish the treatment, I was, because it took a lot out of me, but like I say there was no way I was going to stop* | *Berwyn: 'Extremely frustrating because it [forms] seems so silly, these are the sheets you fill in to, over time, to establish the difference between the beginning of a study and the end of it, so there are some demonstrable achievement, outcomes.'* |

7.5.2.2 Views on treatment outcome

Many participants reported entering the study with an open mind and a neutral outlook on their views on treatment outcomes. For example, in the following extracts, the participants explained that they wanted to enter the trial with no preconceptions about treatment outcome. The participants explained that he was going in with a willingness to confront his fears.

Table 7-18 Between case analysis of sub-factor: treatment outcome

No. of Participants	Identified Factors	The direction of association with treatment outcome	Example Extract 1	Example Extract 2

3	Various views on treatment outcome.	Positive association: decrease in PTSD symptoms as measured by the CAPS-5 scores.	*Chris Yeah, you know I went for it, it's interesting I looked at it, but I didn't want to look too much about the therapy.....I want to remove that bias, so I wanted to come in with a completely open mind on the whole thing.*	*Duncan: To be quite honest with you I didn't think it was going to work, you know, I had some doubt, but I'm quite good at entering a thing with an open mind, you know, and saying yeah unless I've done it, I'm like that, that's the type of person that I am, you know.*

7.5.2.3   Summary

Veterans reported several experiences and expectations associated with the trial. Firstly, overall, they felt positive towards the 3MDR experience despite long and tiring sessions; they felt it was a necessary part of treatment. Expression of disappointment at the process was associated with minor improvement. Several negative experiences associated with the treatment sessions were reported, namely, travelling to and from appointments. Several sub-themes related to experience and expectations emerged, such as participants' perceptions and characteristics. All participants had experienced at least one TF therapy before starting 3MDR and either did not respond or did not engage. This might have influenced their expectation for treatment outcome. Consequently, it is challenging to ignore close relationships and support that might affect their capacity and perception.

7.5.3 Theme 3: Relationship and support

Veterans explained their different relationships and support networks, or lack thereof. They explained how this contributed to their participation and completion of the trial. Others

explained how they had isolated themselves and had not engaged in conversations about the treatment experience. The following sections present an analysis of each sub-theme in detail.

7.5.3.1   Friends and Family

The main consensus was that friends and family were generally supportive of their participation in 3MDR. Participants reported speaking to their partners and children and reported feeling encouraged to continue with treatment. In the extract below, the participant expressed gratitude to his daughter and wife for supporting him through treatment. However, some participants also reported having little or no one to speak to during the treatment or had no encouragement or support from friends or family. For example, in the below extract, the participant describes only speaking to his wife. The results indicate that there is evidence to suggest that speaking to family and friends is associated with better treatment outcome, but participants who chose to not speak to friends and family also significantly improved. However, further evidence suggests that a more extensive support network was consistently associated with better treatment outcome.

Table 7-19 Between case analysis of sub-factor: friends and family

No. of Participants	Identified Factors	The direction of association with treatment outcome	Example Extract 1	Example Extract 2
8	Participants who chose to communicate their feelings to their partners and family or friends during treatment.	Positive association: decrease in PTSD symptoms as measured by the CAPS-5 scores.	*Dai: Yes, oh yes, yes, she's been absolutely brilliant, I don't think if it wasn't for my wife I think I'd have been a hopeless case with my problem, yeah.*	*Gethin: Yeah, I spoke with my mother obviously, because she knows everything, my partner at the time, and there's, where I used to live in the city, there is another block opposite me with ex-forces veterans in there as well*

7.5.3.2   Health care professionals

Most veterans reported that they had been supported by health care professionals within and outside the 3MDR research team, which was strongly associated with treatment outcome. However, results indicated that significant improvement was associated with participants who reported a support network, with multiple friends, family members, and health care professionals who supported their recovery journey compared to those who reported only having support from their partner. Some reported feeling comfortable with a new therapist and welcomed the new interaction and input. However, most veterans reported feeling relieved to be allocated and supported by their known therapist, who had built a trusting, long-standing rapport. Many of the participants reported that this was an integral part of their recovery. For example, in the extract below, the participant reports that he felt relieved and supported. He was allocated his therapist that he had known for years, which helped him be honest and open in the therapist sessions.

Table 7-20 Between case analysis of sub-factor: health care professionals

No. of Participants	Identified Factors	The direction of association with treatment outcome	Example Extract 1	Example Extract 2
5	A good relationship with the therapist	Positive association: decrease in PTSD symptoms as measured by the CAPS-5 scores.	*Terry: That was important yeah because I think when you meet someone for the first time, I've met you before so I know you, so you've broken the ice as we say, but if you meet someone for the first time, especially in a situation like that, you cannot open up, I don't believe you can open up*	*Chris: I've got a good relationship with her, she understands all my background, and so she can, she can ask me questions too, in therapy to actually, because she knows what sort of response, what I get and stuff so I think that was really important*

7.5.3.3   Summary

The results indicate that positive experience and attitude was associated with better treatment outcome. Veterans reported several different relationships or lack thereof and supportive and unsupportive interaction during the treatment sessions. Nine of the veterans felt supported in at least one way, either by friends (5), family or partner (3) and the therapist/research team (7). Ten of the participants reported feeling reassured or comforted by the therapist and researchers. Five participants reported feeling relieved that they were being treated by their referring therapist, who had developed long-standing, trusting relationships and professional rapport. Two participants reported that they felt alone when they chose not to speak to their family and friends about their experiences. One participant reported feeling under-supported when they felt the research staff could have provided out of hours support. One participant discussed having trust issues and found it difficult to confide in anyone and trust their intentions.

7.6   Strengths and limitations

There are several strengths to the thematic analysis approach. The main strength is that it provides accessible guidance on how to conduct and review qualitative semi structured interviews. Furthermore, thematic analysis is data driven which therefore provides the opportunity to explore novel factors that have not been pre-determined. This form of analysis best suited the aim of the study to investigate perspective and experiences, as it was important to demonstrate within and between factors that could be associated with treatment outcome.

There are limits to the generalisability of the qualitative findings, as there were only 11 participants interviewed. This was further exacerbated by the within case analysis which considered participant themes on a case-by-case basis. A further limitation to the analysis is that if themes are not accurately interpreted and grouped into well matched themes, there is a risk of overlap, making the themes less reliable [381]. Furthermore, the identification and grouping of themes are limited by researchers language to describe and label the data, which limits the interpretation [346]. A mismatch between the data and the labelled themes is another pitfall as if the themes lack sufficient data or essential information, and the interpretation is considered less reliable [382]. However, regular consultations with the

qualitative lead and supervisory team during the data analysis process reduced the risk of inaccurate data interpretations.

Another limitation is the risk of quantifying themes identified in the thematic analysis [382]. Gibson warns that themes should not be developed by only paying attention to the repetition of terms, identifying commonly reported ideas, and forming relationships between common concepts in the data [382]. To avoid this shortcoming, I considered the data very carefully to understand the various concepts within the data and grouping these into themes instead of focusing on specific terms. I also worked very closely with the qualitative lead to discuss any concerns and improve the quality of the analysis through adherence to rigorous methodology.

7.7 Summary

Three groups of themes were identified that may be associated with veterans doing better or worse in treatment outcome, defined by CAPS-5 PTSD scores: 1) veterans attitudes about 3MDR treatment and motivation for taking part; 2) expectations about taking part in the trial and experience before, during and after treatment sessions; and 3) relationships with friends, family and research staff and support received or lack thereof. Within these factors, some sub-factors were identified that might be related to treatment outcome. A detailed summary of the themes and sub-themes identified are listed in the below table.

Table 7-21 A summary of findings across all veteran interviewees:

Factors	Descriptions	Association
Attitudes and Motivations	- Participant feeling anxious yet excited about the prospect of 3MDR treatment outcome - Managing the feelings and attitudes of friends and family members. - Managing personal experiences of PTSD	- Positive attitudes associated with better treatment outcome - Negative attitudes associated with small improvement and drop out. - The stigma around PTSD diagnosis

	• Helping fellow veterans • Contributing to Research	associated with worse treatment outcome.
Expectations and Experiences	• Learning about 3MDR and initial reactions • Discussing with family, friends and other veterans • Experiencing 3MDR as immersive and exhausting • Re-experiencing trauma • Travelling to and from treatment sessions • Managing physiological responses after 3MDR. • Benefiting from therapy • Recommending/not recommending to others	• Positive expectations were shown to be positive associated with treatment outcome. • Negative expectations were associated with small improvement. • External stressors associated with worse treatment outcome.

Relationships and Support	• Relationships with different friends and family members • Relationship with the research team • The rapport between veteran and therapist. • Social Network	• Strong supportive relationships were associated with better treatment outcome • A more extensive network of support better treatment outcome. • A good long-standing relationship with therapist better treatment outcome.

A wide range of individual characteristics differ between participants and could have helped or hindered their response to treatment. However, there was considerable overlap between what participants reported as factors associated with treatment outcome. The results indicate that a more extensive network of support from family, friends, and healthcare professionals is critical and positively associated with treatment outcomes than those with smaller support networks. The results also indicate that those who chose to speak to only their partner or no one also improved, indicating that other factors could have influenced treatment outcome. While 3MDR may help some people and could be considered an effective treatment, other factors outside of the therapy sessions may have played a part in the therapy's effectiveness.

Chapter 8: Discussion

8.1 Main findings

The first aim of this thesis was to explore factors in the literature associated with the outcome of psychological treatment for PTSD (Chapter Chapter 3:). The systematic review found six factors associated with treatment outcome: PTSD symptom severity, comorbidity with depression, time since trauma, employment status, education level and homework adherence. The second aim was to apply the factors identified by the systematic review to the quantitative results from an RCT of 3MDR to examine any association with treatment outcome (Chapter Chapter 6:). None of the factors identified from the systematic review were significantly associated with 3MDR treatment outcomes. The third aim was to conduct an exploratory analysis of the qualitative semi-structured interviews from the RCT to explore factors associated with treatment outcome (Chapter Chapter 7:). The qualitative analysis found three themes associated with treatment outcome: attitudes and motivations, expectations and experience, and relationships and support.

The systematic review examined 126 RCTs that explored factors associated with treatment outcome from psychological therapies for PTSD, measured by the severity of PTSD symptoms post-treatment and recovery or remission. There was insufficient data to undertake a quantitative meta-analysis; therefore, a narrative synthesis approach was employed. The review found 25 papers that reported on factors associated with treatment outcome. Collectively, these papers suggested that a comorbid diagnosis of depression and higher PTSD symptom severity at baseline were associated with poorer treatment outcomes. Conversely, higher education, adherence to homework tasks, and recent trauma were associated with better treatment outcomes. The review revealed that limited research had explored the factors associated with treatment outcome in psychological therapy for PTSD and, to the best of our knowledge, no research on treatment outcome in 3MDR [107].

The quantitative analysis examined data from the 42 military veterans recruited for a phase II RCT of 3MDR. The aim was to conduct an exploratory analysis to examine whether any of the six factors identified by the systematic review were associated with treatment outcomes. A multiple regression analysis was conducted to test whether the severity of PTSD symptoms

as measured by the CAPS-5. Comorbidity of depression measured by the PHQ-9, age, time since trauma, pre-treatment homework adherence, employment status, and education level was associated with treatment outcome. The results indicated that none of the factors was significantly associated with treatment outcome. Despite the lack of significant findings, the quantitative data indicated a potential association between higher education and better treatment outcomes.

The quantitative results are inconsistent with the systematic review, which reported a small number of RCTs that found a significant association between factors and treatment outcome. Notwithstanding the small sample size, the lack of significant findings may suggest that the factors considered may not be relevant to the TR veteran population. However, the factors were identified in a systematic review, providing a clear and comprehensive overview of the literature and the most likely factors associated with treatment outcome. Participants from the RCT were all military veterans with TR-PTSD, with a high probability of symptom complexity.

Qualitative analysis and a mixed-methods approach were employed, whereby the quantitative CAPS-5 scores were considered alongside the qualitative data to produce a more comprehensive set of findings. The aim was to examine whether any factors within the semi-structured interviews were associated with treatment outcomes. The qualitative analysis examined data from 11 military veterans recruited for semi-structured interviews for the phase II RCT of 3MDR. The aim was to conduct a thematic analysis to identify any emerging factors related to treatment outcome, as measured by the CAPS-5 [381]. The choice of methodology was carefully considered with the supervisory team. Braun and Clarke's framework [345] was followed. A within-case analysis was conducted to examine each participant interview in detail, and a between-case analysis to examine the themes across the data set.

There are both positive and negative critiques of both methodologies. In a quantitative design, the data is restricted and does not explore the deeper meaning of an individuals' perspective. However, quantitative analysis often requires larger sample sizes, which allows for more power and generalisability of the data, enhancing the quality of the findings [359]. Furthermore, the statistical methods employed for analysis are often considered accurate and reliable, with no interpretation or researcher bias.

The qualitative analysis of the semi-structured interviews provided some insight into unexamined factors associated with treatment outcomes. Unlike the quantitative analysis, there was no preconceived hypothesis. The qualitative analysis provided more flexibility and allowed the data to guide the results. However, the qualitative interviews were not designed to examine treatment outcomes; important information may have been missed in data gathering. The qualitative analysis suggested three additional factors to consider in future research: attitudes and motivations, expectations and experience, and relationships and support. A summary of the findings from each chapter is provided in Table 8-1.

Table 8-1 Summary of the main findings from this thesis

Aims	Design	Chapter number and Title	Main findings
Study Aim Addressed: Aim 1	Design: Systematic review and narrative synthesis	Chapter 3: A systematic review of factors associated with the outcome of psychological treatments for PTSD.	Comorbid diagnosis of depression and higher PTSD symptom severity at baseline assessment was associated with poorer treatment outcomes. Conversely, those in full-time employment, higher education, adherence to homework, and experience of a more recent trauma were associated with better treatment outcomes.
Study Aim addressed: Aim 2	Design: Sub-trial multiple regression analysis of the RCT data.	Chapter 6: Quantitative analysis: exploration of factors associated with 3MDR treatment outcome.	None of the factors identified in the systematic review was significantly associated with 3MDR quantitative treatment outcome.
Study Aim addressed: Aim 3 and 4	Design: Thematic analysis of interviews of eleven participants from the 3MDR RCT.	Chapter 7: Qualitative analysis: Exploration of factors associated with 3MDR treatment outcome.	Three themes were associated with treatment outcome: attitudes and motivations, expectations and experience, and relationships and support.

Post Traumatic Stress Disorder (PTSD), Randomised Control Trial (RCT), Multi-Modular Motion-assisted Memory Desensitisation and Reconsolidation (3MDR)

8.2 Factors associated with treatment outcome

The presence and absence of significant associations may be for several reasons. First, the data was derived from a relatively small sample, as there were only 42 participant in the study, resulting in insufficient statistical power to detect any true effect. Therefore, the lack of significant association between factors and treatment outcome is likely due to inadequate power. Second, the homogeneous sample of military veterans with TR-PTSD may have restricted the chance of detecting any significant associations due to the lack of variation in demographic characteristics between participants. Third, the restricted range of target factors due to the exclusion criteria may also have compromised the possibility of detecting effects. Finally, caution must be taken to use these results only to interpret the clinical importance of this RCT as an effective treatment for TR-PTSD and not with the recommendations of factors to help select the best PTSD treatment. Overall, the literature suggests a limited number of studies that have examined the association between PTSD and treatment outcome. This suggests further research is required in a larger, more heterogeneous population of routinely collected data to test whether efficacy translated into effectiveness before making clinical implications.

8.2.1 Symptom severity

In the systematic review, there was some evidence to suggests that PTSD symptom severity at baseline was associated with benefiting less from treatment, but this was not a uniform finding, and therefore premature to conclude any precise associations from the review. In the 3MDR quantitative analysis, symptom severity was not shown to have any association with treatment outcome. A possible reason for not finding an association is that symptom severity has been associated with high-burden impairments across several psychological and social functions [188]. Therefore, measuring PTSD symptom severity alone may underestimate the impact of the trauma on the individuals' functioning. The lack of association is inconsistent with some literature suggesting that symptom severity is associated with poorer treatment outcomes [384]. Several studies found no association between baseline symptom severity and treatment outcome. It has been suggested that significant avoidance can interfere with the processing of traumatic experiences due to the lack of engagement in therapy [66, 73]. The association of higher levels of avoidance of thoughts and feelings pre-treatment with higher rates of PTSD symptom severity post-treatment supports this claim [385-387].

In the qualitative analysis, the three themes identified were considered alongside PTSD symptom severity, as measured by the CAPS-5. The results indicated that those who were more supported by family, friends, and healthcare professionals, together with a more positive outlook on treatment, improved in 3MDR treatment. However, a positive outcome was not restricted by these themes, as those who were not considered supported also improved in treatment. As the qualitative analysis was considered alongside the quantitative analysis, inadequate sample size continues to be a problem. However, the qualitative themes also provide some insight into other factors that could be significantly associated with treatment outcomes.

8.2.2 Comorbidity of depression

The systematic review revealed some evidence to suggest a positive association between comorbidity with depression and treatment outcomes. However, due to the lack of consistency and strength in the findings, caution should be taken when interpreting the results. Comorbidity of depression with PTSD was not shown to be significantly associated with 3MDR treatment outcomes. A mentioned above, the main reason for the absence of association is the small sample size, making it challenging to identify a genuinely significant association. Another possible reason is that depression and PTSD share multiple overlapping symptoms, resulting in the under-diagnosis of depression, creating difficulty finding associations [388]. In the DSM-5 criteria for PTSD, both the D and E symptom clusters examine negative emotions and beliefs about oneself or the world and other symptoms, which are relevant or could be confounded by the presence of depression [389].

An interaction between clinical characteristics and social factors must be considered when understanding the underlying causes and triggers of mental health comorbidities; however, measuring this complexity would likely require a sophisticated methodology. Although comorbidity was not considered in the qualitative analysis it is important to note that other confounding factors such as socioeconomic status, environmental influences and social support may also be associated with the onset and the duration of depressive symptoms [175]. Haagen et al. speculated that comorbidity of depression might act as a destabilising factor that creates further difficulty in prognosis and treatment of PTSD [175]. The research

indicated that comorbidity of depression might create an increase in symptom burden, which creates a complex manifestation of symptoms.

The association of comorbidity of depression with poor treatment outcomes is recognised [28], although the exact mechanism is unknown. One possible explanation [48] considers emotional processing theory, whereby the emotionally charged traumatic memory is altered by activating the feared stimuli through exposure and subsequent habitation [316]. In order to experience habituation, the individual must emotionally engage with the traumatic memory. However, for those who are depressed, active engagement of emotions may prove difficult and lead to under activation of the feared stimuli, and habituation may not occur. Rumination and over-generalisation may result in an over engagement for those who experience comorbid depression and risk becoming overwhelmed by the emotional intensity of treatment and reduce its efficacy for PTSD [76]. It is essential to recognise that psychiatric comorbidity might impact treatment planning and outcome.

8.2.3 Age

Age was not a factor that was considered in the systematic review or the qualitative analysis but was considered a relevant factor to include in the quantitative analysis of 3MDR. There was some evidence in the literature to suggest an association with treatment outcome [96]. Age was not shown to be associated with 3MDR treatment outcomes. Although the sample age ranged from 28 – 67 years old, many of the participants were on the older end of the spectrum. It could be speculated that their PTSD symptoms may not have been recognised or present during or after combat exposure. Therefore, older age may be associated with longer time since trauma as age could indicate when participants sought support and psychological therapy for their PTSD. Research indicates that a long time between trauma and seeking support may be associated with poorer treatment outcomes due to further complexities and the likelihood of symptom burden [390].

The lack of association with treatment outcome is inconsistent with the literature, indicating that the trajectory of PTSD symptoms is worse in older adults with PTSD than in their younger counterparts [391]. Research suggests that older participants were more likely to have been exposed to more trauma and secondary social consequences of enduring mental health difficulties making treatment of more chronic conditions more complex [392].

Participants were all diagnosed with TR-PTSD and were likely to present with severe symptoms, making treatment less likely to be effective. Despite the age of the participants, they were likely to have experienced similar combat-related trauma, which reduces the chances of finding as many factors associated with better or worse treatment outcomes.

8.2.4 Pre-treatment homework adherence

In the systematic review, there was some modest evidence to suggest homework adherence was associated with better treatment outcomes, and therefore again caution should be taken when interpreting the results from the review. Pre-treatment homework adherence was not found to be associated with the 3MDR treatment outcome. However, unlike other psychological therapies such as CBT, which encourage and monitor homework throughout the therapy process, the pre-treatment homework in this study was considered a self-monitoring activity. It was not analysed data or part of treatment but rather a pre-request to map the trajectory of symptoms over two weeks. The homework was not encouraged, and receiving therapy was not contingent on completion. It may be suggested that homework requires motivation and mentoring to complete work outside the therapy sessions. Therefore, it could be argued that it was not a good proxy for homework adherence as defined in other studies.

Despite the difference in homework types, the results are inconsistent with previous research, suggesting that homework adherence was associated with better PTSD treatment outcomes [152]. A meta-analysis of eight RCTs of EMDR and CBT investigated the effects of homework adherence from session to session therapy, and improved PTSD symptoms were associated with stronger adherence [393]. It is likely that homework adherence was associated with treatment outcome, whereas in the 3MDR quantitative analysis the pre-treatment behaviour may not be a good proxy to measure treatment outcome. People with PTSD vary significantly in their ability to complete homework assignments due to various factors, including a mismatch between the homework assignment's ability and difficulty or motivation/commitment on the person with PTSD or the therapist. Strategies for improving homework completion may increase the likelihood of completing homework exercises to enhance treatment outcomes [28].

Completing homework may cause distress, leading to a direct re-experiencing of the traumatic event and symptoms such as hypervigilance. Furthermore, completing homework involves subtle reminders and triggers of the traumatic event, particularly within the military population, exposed to repeated activation of the fear and stress symptoms. Therefore, a lack of homework adherence could reflect the individuals' general avoidance of therapy. It could be speculated that this avoidance is an underlying aspect of PTSD, which may also be the main factor limiting participants seeking and recovering from their symptoms, particularly within the military veteran population [394].

8.2.5 Time since trauma

In the systematic review, more recent trauma was associated with better treatment outcomes. The evidence for associations was weak and therefore it would be premature to make any definitive conclusions from these results. Time since trauma was not associated with 3MDR treatment outcome. The military sample was considered TR; therefore despite the broad age range, participants were likely to have similar trauma types which may have made it difficult to identify significant differences between groups. Research suggests that a long time since trauma may increase vulnerability to developing comorbid physical and psychological conditions [395], which has shown to be associated with increased symptom burden and problematic functioning [396]. Therefore, trauma may not have been a good proxy for treatment outcome in a small homogeneous sample of male military veterans.

The lack of significant findings might also be because a broader understanding of the complexity of PTSD is required. Time since trauma may be a proxy for the severity or complexity of PTSD symptoms [71] which may be associated with secondary psychosocial consequences and other adverse events (unemployment, loss of housing and social isolation) [397]. These events themselves can lead to low mood, psychological distress, and further mental and physical problems. For example, studies have observed an increase in alcohol and drug use after the experience of a traumatic event [398], which can increase the likelihood of relapse and clinical worsening of symptoms.

A long time since trauma has been associated with comorbid conditions, and characteristics exaggerated characteristics of PTSD such as startle and related hyperarousal. Several studies have demonstrated that greater time since the trauma is associated with additional adversity

and comorbidities since conflict and, in turn, more unsatisfactory treatment outcome [34, 399]. A meta-analysis has examined similarities and dissimilarities of time since trauma in PTSD treatment outcome [400]. However, the research was limited to 12 RCTs and, unlike our review, only included studies that directly compared one type of treatment with another.

8.2.6 Employment status

Employment status was not associated with treatment outcome in the systematic review or the 3MDR quantitative analysis. However, the quantitative results indicated some evidence to suggest that full-time employment was associated with better PTSD symptoms post-treatment. A lack of association is inconsistent with the literature, which suggests employment is associated with improved mental health [401], which is also associated with better treatment outcomes. Savoca's research found that a PTSD diagnosis after treatment was associated with a 50% increased unemployment risk [402]. Some of the research suggests that participants in full-time employment were associated with better treatment outcomes than unemployed participants [403]. Similar factors that are associated with PTSD symptoms may also be associated with employment status outcomes. Unemployment has been associated with unhealthy eating, smoking, and alcohol use, leading to other physical and mental health conditions [404].

The relationship between employment and PTSD is complicated, specifically within the military population adjusting to civilian employment. The small indication of an association between employment status and treatment outcome is worth exploring in a larger sample size. An explanation for a better treatment outcome is that full-time employment may have raised aspiration and self-efficacy, associated with better mental health [403] which may mediate the relationship between employment status and treatment outcome [405]. Veterans may have valid concerns about the financial impact of full-time employment on access to benefits. Veterans in the 3MDR trial may not have accurately reported their employment status or income to protect their current personal circumstances such as benefits and council housing [406]. Therefore, it is vital to explore what factors are associated with employment, such as an increased sense of purpose and improved quality of life, to better understand the effects of employment on treatment outcomes.

8.2.7 Education level

In the systematic review, there was some indication that higher education may be associated with better treatment outcomes, although caution is advised when interpreting the results. However education was not shown to have a significant association with 3MDR quantitative treatment outcomes. Research indicates that higher education could be associated with cognitive ability in adulthood [407]. This could be due to the impact of educational background on understanding psychological interventions and engaging in them fully. For example, TF-CBT requires written homework, and more advanced literacy skills may facilitate better outcomes [393]. Moreover, research has suggested that low educational status is a precursor to poor treatment outcomes in PTSD. It can cause difficulty interpreting the interventions' content, resulting in a lack of motivation to adhere to treatment [408].

The quantitative results are inconsistent with previous research, which shows that higher-educated individuals respond better to treatment than those with lower education [188]. This could be because people with PTSD often struggle with concentration, motivation, and other positive behaviours associated with higher education [239]. However, it could also be argued that poor language skills could result from lower education attainment. In addition, veterans who joined the military from a young age may have done so to avoid academic pressures and classroom setting restrictions. Therefore, it is likely that the skills needed to complete the treatment (i.e., complete self-report measures) may not be present in all people with lower educational attainment [409].

Participant Intelligent Quotient (IQ) or cognitive ability was not formally assessed; therefore, a participant may have underlying and undiagnosed difficulties, which may have impacted their understanding and performance on the self-report measures or the therapy tasks [407]. Future research into the relationship between treatment outcome in 3MDR therapy and psychological therapies, in general, must attempt to consider neuropsychological tests that measure working memory, speed of processing, verbal and visual learning, and social cognition [396]. Understanding how brain functions are associated with PTSD and other behaviours can help identify associations between better or worse treatment outcomes and help identify the best treatment choice.

8.3 Additional factors impacting treatment outcome

Several authors have highlighted that the relationship between people with PTSD doing better or worse in treatment may be due to various factors [96]. The absence of a significant association between target factors and 3MDR treatment outcome could be because other unexamined factors were at play, some of which will be described below.

An additional factor associated with treatment outcome could be avoidance. It is likely that avoidance impedes recovery as individuals avoid seeking support and, in turn, may experience further symptom burden, which could make available treatment less effective [66, 73]. The retention rate suggests that avoidance of traumatic reminders and engagement with therapy was overcome through 3MDR, which may have been a critical factor in better treatment outcomes [73]. Therefore, it is essential to consider avoidance coping as a factor that may impact treatment outcomes in the future. However, examining these factors among non-veterans should be applied cautiously as different coping strategies may play within the general population [306, 386, 410].

Another factor influencing treatment outcome is previous childhood adversity, implicated in CPTSD and PTSD [411]. Keller et al. suggest that individuals who have experienced childhood adversity may benefit less from PTSD treatment in adulthood [315]. As the participant sample was all considered TR-PTSD, it could be suggested that participants would likely have fulfilled the CPTSD diagnostic criteria.

Research indicates other factors that have secondary effects on treatment outcomes, such as family relationships, parental attachment, or physical and domestic violence in the home, manifest in a wide variety of symptomatic behaviour [412]. In addition, Kilpatrick's research found that exposure to childhood trauma was associated with a higher rate of Major Depressive Disorder (MDD) [413]. This could mean that comorbidities associated with childhood adversity may also contribute to treatment outcomes. As the current literature around childhood sexual abuse and PTSD remains inconclusive, it is essential to examine how childhood adversity is associated with treatment. Therefore, trauma history may be worth examining in the future when identifying factors associated with treatment outcomes. Information regarding the presence of childhood traumatic experiences may help clinicians and therapists select and adapt the treatment to target any depression and trauma.

8.4 Strengths and limitations

8.4.1 Systematic review

The systematic review provided an overview of factors associated with psychological treatment outcomes in PTSD. Although the review did not yield many significant associations with treatment outcome, it was understood that this was due to the lack of consistent reporting factors associated with treatment outcome. The review highlighted the lack of data and urged methodological guidelines to include treatment outcome factors as standard methodology and result reporting.

There are some issues with the included studies that limit interpretation. For example, they adopted strict inclusion criteria, which often excluded patients with active substance dependence, acute suicidal ideation, and MDD, all associated with greater severity of PTSD [414-416]. This may have resulted in excluding participants from more vulnerable and, potentially, TR populations, limiting the generalisability. Although more practical inclusion criteria may enhance generalisability, it may be challenging to determine the actual effects of the intervention and to whom the results apply. Finally, I alone extracted and synthesised data from studies that may have resulted in essential studies being missed. However, data extraction followed the standardised criteria for narrative synthesis [123], thereby ensuring a standardised process across studies. Frequent meetings with the review team were held to discuss progress and interpretation of the results.

Overall, it is difficult to draw firm conclusions from this review due to the limited strength and consistency of evidence for assessing specific factors with treatment outcomes. For example, a depression diagnosis and homework adherence were only predictive in two studies, although the evidence was consistent. This contrasts with PTSD symptoms severity, where only one of eight studies found an association with poorer outcomes. Further research is required to determine the true nature of the associations found in this review. As the systematic search is over 18 months old, an updated review may also provide additional information.

8.4.2 Quantitative analysis

The quantitative statistical analysis was based on a small sample of 42 participants from the Phase II RCT. A lack of adequate statistical power is a severe concern in this study and research in the field of psychological therapy [367]. In addition, the correlation between predictors and outcomes is often small and requires adequate power to identify change mechanisms [417]. The absence of significant associations between factors and treatment outcome is not consistent with the systematic review results, which revealed a limited number of factors associated with treatment outcome. Therefore, it would be better to examine factors associated with treatment outcome in a larger, more extensive RCT and investigate other unexamined factors which may be at play. Furthermore, the systematic review provided only week evidence to support the identified factors that were applied to secondary data from a phase II RCT. Therefore, it is essential to consider that the results may be an accurate indication that the factors identified in the systematic review had no association with treatment outcome.

The statistical analysis applied Bonferroni correction. Previous research has suggested that Bonferroni correction fails to measure the correct hypothesis when both treatment groups are identical and only considers the family-wise error [1]. It has also been suggested that Bonferroni correction creates a strict restriction, which unnecessarily underpowers data [2]. Due to the small sample size, the Bonferroni correction threshold of claiming significance was restricted (p < 0.002), but no significant association was found at p <0.005, which suggests no observed effects were undetected. An explanation for the lack of significant findings is the small sample size, and potentially the use of Bonferroni correction resulted in a low probability of finding actual effects [418]. Despite its limitations, under the guidance of the statistician (TP), it was considered appropriate to apply Bonferroni correction to the data to reduce the risk of type II error. An alternative method to examining factors associated with treatment outcome is a large cohort of routinely collected data, in which all participants receive the same treatment and treatment pathway [419].

A further strength is that the factors were derived from a systematic review and narrative synthesis. The strict methodology is likely to reduce the risk of bias. The restricted range of factors due to the exclusion criteria may have compromised the possibility of detecting

significant effects. Although the multivariate analyses considered confounding factors such as age and number of traumas, other variables may have influenced the relationship between factors and treatment outcome, such as medication use or exposure to life stressors. A strength of the analysis is that data were derived from the CAPS-5, a gold-standard clinician-administered measure. All but two of the factors (age and pre-treatment homework adherence) were calculated from self-report measures. Self-report measures may not accurately reflect a participants' actual characteristics due to under or over-reporting, reflecting the individuals' own biases. However, well-validated measures alongside clinician-administered interviews ensured that the data gathered was as accurate and reliable as possible.

8.4.3 Qualitative analysis

One of the main strengths of the qualitative analysis is that the data set was analysed by two people, which meant two perspectives. Although the purpose of the analysis was different, similar themes were identified in both analyses. A limitation is that only one person analysed the data to identify factors associated with treatment outcomes. Therefore, discussions with the supervisory team also aimed to reduce the impact of bias, ensuring all avenues had been adequately explored. Another limitation of secondary analysis is that I was not involved in the data collection process, unlike the research lead. Therefore, I missed the opportunity to be aware of any signs and indicators such as changes in the tone of voice or body language that may have been important to interpreting some of the specific factors associated with the outcome. However, careful examination of the data by repeatedly reading each transcript reduced the likelihood of missing critical information. Furthermore, working closely with the qualitative lead and engaging in frequent meetings provided an opportunity to discuss any uncertainties in analysis, which helped increase the accuracy and validity of the grouping of themes.

An advantage of the qualitative data collection was that the qualitative lead conducted purposive sampling, which meant participants at various stages of treatment were included in the sample. The participant sample included those who had completed and dropped out of treatment to account for anomalies or 'deviant' cases. This form of data collection provided the maximum level of heterogeneity, which helped distinguish extreme outliers within the cohort, and helped identify unique factors within each case. As the sampling method is based

on researcher judgement and data interpretation, it is highly prone to researcher bias. However, as the sample was derived from a rigorous RCT with strict inclusion criteria and a clear theoretical framework, the risk of research bias was minimised.

A significant limitation to the secondary qualitative analysis is that the data was not collected to address the thesis question. Therefore, it is likely that more relevant data could have been obtained if the researcher had tailored their questions towards factors contributing to treatment outcome. An alternative method could have asked additional questions at the end of treatment specific to my research question. However, due to the in-depth information in the data, the supervisory team and I considered it unnecessary to add additional questions at that moment in time. Furthermore, the research lead explored each participant's thoughts and feelings about the treatment and covered a wide range of topics around the therapy. Therefore, it is unlikely again that important information was missed, although additional questions could have helped make the interview more focussed on treatment outcome.

Another strength of the qualitative analysis was using the computer software programme NVivo to help categorise and code data [420]. Yin highlights that the purpose of these types of software is to assist in the analysis [421]. Silverman highlights the advantages of using qualitative software packages as an analytic strategy. He suggests that the software package enables the researcher to identify patterns, code data and efficiently apply themes [422]. A significant amount of data was produced in this study because of the lengthy semi-structured interviews and the participants' generous input. Using the NVivo software package to identify relevant extracts was extremely helpful during the analytic stage of the study. The within-case analysis was then examined in a cross-case analysis to identify the reported themes and the overlapping factors that were considered to have hindered or helped treatment outcome. This resulted in a detailed description of the entire data set, giving an accurate account of the factors associated with treatment outcome. At each stage of the analysis, the qualitative outcome was discussed with the supervisory team for feedback. Regular meetings ensured a collaborative process of analysis and refinement of data.

The main disadvantage of 3MDR qualitative analysis is that the sample was not always selected with generalisability in mind. Therefore, the results cannot be applied to a broader group of people. However, in contrast to most existing research on factors associated with treatment outcome, this thesis used a mixed-method approach by comparing and combining

quantitative and qualitative measures. The mixed-method approach provided further insight into the individual differences between participants and any unique factors that influenced treatment outcomes. Only a small number of participants were required to be interviewed to provide enough valuable and relevant insight. As I was not involved in the interviews, my interpretation of what was significant and essential in the data may differ from the lead researchers interpretation of the data. Despite the disadvantages, the qualitative lead provided me with training and supervision to accurately interpret the participants' data [423].

8.5 Clinical implications

The results of this thesis suggest that no one should be excluded from receipt of treatment due to the presence of the factors considered. Therefore, the evidence presented in this thesis may provide some clinical suggestions, but no recommendations can be made until further research is conducted in a larger routinely collected PTSD sample [424]. Other factors not considered in this thesis, such as neuroimaging and cognitive testing, in addition to routinely collected clinical characteristics, may provide a 'person with a PTSD signature' that illustrates specific factors that predicts response or non-response to different treatments.

In the systematic review, the findings that higher education was associated with better treatment outcomes suggest that particular care should be taken to make treatments fully accessible to people with PTSD with different education levels. The 3MDR quantitative analysis revealed a small indication of a positive association between longer time spent in education and better treatment outcome. Veterans with higher education could potentially better process information to better detect and report symptoms. Therefore, it is plausible that collaborative efforts between educators and the military may encourage pursuing academic qualifications to improve their cognitive skills to help equip them later in life. Higher education's potential mental health effects could counterbalance employment prospects and help veterans be more equipped with transferable job skills after their time in the military. Education level may affect different treatment stages (i.e., adherence to homework or completion of self-report measures), which may help identify where changes need to be made to improve treatment outcomes. It may be that tailored support for military veterans with lower education is required during treatment to facilitate optimal outcomes [425]. If

clinicians consider education level when treating people with PTSD, they could offer extra support with more cognitively challenging aspects of treatment.

It may be that where treatment is ineffective alternative strategies are required, such as the provision of additional support or adoption of models that minimise cognitive demand while maximising the active processing of new information. For example, on the basis that comorbid depression was found to be associated with poor treatment outcomes in the systematic review, clinicians should pay particular attention to adapting treatments to individuals' specific needs, including whether the initial targeting and treatment of PTSD symptoms will subsequently reduce depression symptoms or whether it is necessary to prioritise the reduction of depressive symptoms before starting PTSD treatment. This could determine the best approach for the most significant improvement of both disorders. For example, the use of an adapted form of EMDR to suit the individuals' cognitive and emotional functioning levels may also be recommended [426]. This involved a short explanation of the treatment, visual cues instead of abstract language to represent feelings, and physical gestures to help communication.

Personalised treatment in healthcare aims to create a unique approach to treating individuals and considering each person's variability in their clinical, demographic, social and personal preferences in treatment [427]. It should inform the clinician on adapting treatment goals and guide patients to achieve personal goals [428]. 3MDR is one of the first psychological therapies that adopts a personalised form of treatment for veterans with TR-PTSD [259], allowing them to be at the centre of the treatment sessions [78]. This aimed to increase engagement and reduce avoidance, which is considered a pervasive characteristic in military veterans with PTSD. The results indicated that a more tailored approach was successful with those who had previously not responded or engaged with existing treatment. However, the results highlighted that the treatment did not help everyone and the need to identify factors associated with treatment outcome to inform treatment decisions is vital. Increasing our understanding of factors associated with treatment outcomes can help clinicians identify the most effective treatment for each individual. In addition, information on factors could provide information about the underlying mechanism of psychological therapy and help develop a treatment for PTSD and other related conditions.

The qualitative analysis identified veterans who had researched the trial and started with an overall positive attitude was associated with positive treatment outcomes. This may be an important consideration for clinicians before they start work with participants in the future, to concentrate on building a rapport and encouraging a positive outlook on treatment outcomes. Commitment to continuity may be helped by increasing awareness of the impact of the research and its potential to help others. Furthermore, it could also be considered helpful to match therapists already known to veterans, but preferences might differ. Veterans' description of how challenging travelling to and from sessions suggests a potential for specific support with transport to ease stress around parking and concentrating on driving home. Allocated parking arrangements, accurate information on the clinic location and being accompanied to and from treatment sessions would be advisable.

Participants also described specific factors that may have affected their attitudes about the treatment and their reason for not continuing with the treatment or missing sessions. For example, a participant felt that the treatment was not suitable for him or his trauma as the research did not target what he struggled with the most. Researchers should understand that suitability is essential and revisit their inclusion criteria or make participants fully aware of the treatment aims before starting sessions. Out of hours support that was available out of the typical working day was essential to some veterans, particularly those experiencing psychosocial crises, and therapists observed how some people dropping out included those whose personal lives were complicated.

Identifying which factors are associated with better treatment outcomes may allow for a personalised approach to healthcare, allowing the opportunity to target symptoms or match participants with effective treatment. Treatment may consequently be adapted to focus on specific needs, such as improving low mood to reduce the likelihood of poorer treatment outcomes. Also, unlike predictor factors considered relatively stable, formulating a list of more malleable factors when designing and executing a trial can provide a foundation for better outcomes. For example, whether underlying characteristics such as a participant's attitudes before starting treatment reduce the likelihood of adherence. Treatment outcomes could be enhanced by active encouragement and support throughout the treatment process.

8.6 Research implications

A clear research implication from this review is the need for further work into the association of factors with PTSD treatment outcome and the reasons for these associations. A more rigorous approach for developing consistent reporting of factors associated with treatment outcomes is needed. The lack of reporting on such a vital treatment area may reflect that the available interventions are not appropriately developed. As such, it is difficult to determine the quality and effectiveness of treatment and reduce adversity.

To better appraise the quality and effectiveness of treatment outcomes, I recommend that a universal reporting style must be adopted to improve the quality of factors associated with treatment outcomes. The CONSORT [321] guidelines were specifically developed to eliminate inadequate reporting. However, the guidelines do not address other facets of reporting that may require attention, namely factors associated with treatment outcome. As the CONSORT checklist provides guidelines to improve the completeness of the study, we suggest that the following additional factors are considered for inclusion: a) characteristics of the participants (age, gender, and ethnicity); b) clinical characteristics (severity, chronicity, comorbidity, and prior treatment exposure); c) social and economic variables (income, employability, living arrangements); d) self-efficacy and social support (relationships, family and friends). Factors should be documented at baseline, during, and after treatment to understand their association to treatment outcome at every stage.

There is also a need to develop more multidimensional standardised measures of treatment outcome. Traditionally, and importantly, trials have focused on the reduction of PTSD symptoms and rates of remission. Factors associated with treatment outcomes in people with PTSD need to be explored at multiple units of analysis, which combine clinical and demographic characteristics to understand clinical input better. Measures of the acceptability of the treatment are also required, such as a) adherence (consisting of attendance to therapy and homework completion); b) retention rates (the reasons people continued with treatment or withdrew); and c) attitudes to treatment (to identify patient experiences and perspectives through semi-structured interviews). The aim to improve treatment outcome must evolve from further knowledge of participant-specific factors and collecting biological, psychological, and environmental factors associated with treatment outcome.

These additional measures will facilitate consistent reporting and a greater understanding of factors likely associated with treatment outcomes. Adopting similar strategies to examine factors associated with treatment outcomes has the added benefit of international collaboration and data sharing, which will help improve current and future interventions. Reporting guidelines can help reduce inconsistency and ambiguity and ultimately improve the quality of care. If reporting guidelines are not developed appropriately, their guidance may be of little use to improve existing and developing treatment. A collaborative approach between researchers, clinicians, and patients is worthy of consideration, particularly when identifying factors that may help or hinder their recovery.

Another research implication of this thesis is that data derived from an RCT is not the best method for establishing factors associated with treatment outcome. Further analysis could be considered in a larger sample of routinely derived data, in which participants receive the same treatment simultaneously. This would enable more statistical power to examine factors associated with treatment outcomes. It is also important for the population to be specified a priori and matched against study aims and hypotheses. Different trauma types and histories equate to different diagnoses (PTSD or CPTSD). For example, It is unknown whether current established treatment for PTSD provides optimal outcome for CPTSD, considering the usually prolonged and repeated nature of trauma in CPTSD and additional symptoms of DSO [411, 429]. The systematic review found a study that considered elements of DSO in the context of comorbid BPD, research is required to examine DSO in the context of individuals with a diagnosis of CPTSD for further understanding of the effects of the additional symptoms on treatment outcome.

Future research is required to address the discrepancy between the potential factors underlying the relationship between PTSD and treatment outcome using sophisticated analysis, such as Structural Equation Modelling (SEM) and hypothesis testing rather than exploratory analysis. The analysis could examine PTSD severity at the symptom level and explore how coping strategies, such as avoidance, affect the intensity and frequency of symptoms. A hypothesis based on the findings of this thesis could be applied to a larger sample to examine the direct or indirect association between factors and treatment outcome. SEM can detect the interaction between observed and unobserved (i.e., latent) variables. Based on this association, SEM can determine whether the model accurately fits the data

[430]. The lack of consistent examination of factors associated with treatment outcome has resulted in limited knowledge in the effectiveness of new and existing treatment for PTSD.

The analysis highlights a crucial first step in research to inform and improve 3MDR treatment outcomes. Future research could use a mixed methods approach and use qualitative semi structured interviews to identify potential risk factors and protective buffers to treatment outcome. The factors identified can be tested through quantitative analysis to further validate what factors are the most pertinent to the patients success in treatment. A lot more research is required to identify more definitive association between factors and treatment outcome before any recommendations can be made with confidence.

8.7 Conclusion: a step towards precision in treating PTSD

The notion of precision healthcare was first explained by Archibald Garrod, who described a clinicians' role as someone who applies scientific knowledge to accurately match patients with effective treatment while avoiding side effects [433]. Even though psychological medicine is considered somewhat personalised, efforts are required to help bridge the translational gap between medicine and healthcare sciences to improve treatment outcomes. Examining factors associated with treatment outcome provides the opportunity to deliver three key benefits to patients; 1) identify specific client groups achieving poorer outcomes in order to tailor treatment to their need, 2) identifying areas to target in treatment through working collaboratively with patients, and 3) assessment of suitability for specific treatment approaches. The findings from this thesis represent an important step towards discovering which treatments work best for whom. The findings highlight the need for more research in this area to develop better treatments, inform better treatment decisions, and ultimately achieve better outcomes.

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