INterventions for Complex Traumatic Events – INCiTE

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1. Title: INterventions for Complex Traumatic Events – INCiTE

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2. Background

2.1 What is the problem being addressed?

Trauma and stressor related disorders, also known as reactions to severe stress and adjustment disorders, are mental health problems directly related to exposure to a traumatic event or series of traumatic events. Post-traumatic stress disorder (PTSD) is among the most common mental health disorders to occur after experiencing (or witnessing) a major traumatic event. Typical symptoms include involuntary re-experiencing the traumatic event in a vivid and distressing way (e.g. flashbacks, nightmares), avoidance of activities reminiscent of the trauma, persistent numbness, emotional blunting and detachment from other people and previously significant activities, along with hyperarousal in the presence of reminders of the trauma (including hypervigilance, difficulty sleeping, irritability, poor concentration, and an exaggerated startle response). People with PTSD may also experience comorbid psychological problems including substance use disorders, depression (with increased risk of suicide), and other anxiety disorders (e.g. panic disorders), and functional somatic syndromes which can further impair social, educational and occupational functioning.

PTSD can occur at any age and is relatively common with a lifetime prevalence of 7.8%,[1] 12 month prevalence ranges from 3-4%.[2] Rates vary depending on the type of stressor experienced: for example physical assaults in women are associated with a lifetime prevalence of 29%; combat experience in men is associated with a lifetime prevalence of 39%; and 15.4% in people exposed to war and displacement.[3]

It is argued however that the PTSD symptom clusters described in the current and previous versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and ICD-10 do not adequately capture the full range of clinical symptoms exhibited by those who experience complex trauma (i.e. developmentally adverse interpersonal trauma such as prolonged domestic or community violence, childhood abuse, torture or exploitation).[4] People who experience complex trauma, especially, but not exclusively or necessarily in formative periods, are more at risk of other psychiatric disorders. Complex PTSD (CPTSD) and Disorders of Extreme Distress Not Otherwise Specified (DESNOS) are labels that have been used to define syndromes that involve, in addition to core PTSD symptoms: pathological disassociation, emotional dysregulation, somatisation, and altered core schemas about the self, relationships and sustaining beliefs.[5]

Recent empirical work using latent class analysis in people exposed to different types of acute and chronic stress has gone some way to endorse the distinction (to be included in ICD-11)[6] between PTSD and CPTSD, with the CPTSD class scoring highest for symptoms related to affective dysregulation, negative self-concept, and interpersonal problems.[7 8] The symptom profile of CPTSD is thus characterised by the loss of emotional, social, cognitive and psychological skills, either because their development has been interrupted during a formative phase or they have been seriously impaired owing to exposure to complex trauma. Beyond the prototypical case of childhood sexual abuse complex trauma experiences have also come to embrace 'other types of catastrophic, deleterious and entrapping traumatisation occurring in childhood and/or adulthood, such as repeated domestic violence, trafficking and exploitation, and being forcibly displaced.[9] Compared with single event PTSD, complex trauma is characterised by sustained or repeated instances of trauma of an interpersonal nature that are 'extremely threatening or horrific and from which escape is difficult or impossible due to physical, psychological, maturational, family/environmental, or social constraints.'[10]

However a counter argument favours conceptualising PTSD as a trauma spectrum disorder from simple to complex, with the complex variant sharing significant symptom overlap with PTSD and other diagnoses such as Borderline Personality Disorder (BPD).[11] Studies that have compared CPTSD with PTSD conclude that the difference is more about symptom severity rather than a difference in associated symptoms, and the new
DSM-V criteria for PTSD adopts this approach,[12] making the distinction between CPTSD and PTSD less clinically meaningful.[13]

Whether CPTSD and PTSD are distinct clinical entities that can be separately diagnosed is contentious.[11] However beyond this diagnostic debate what is of relevance is whether treatments that are effective for people with single event PTSD are equally effective for people exposed to complex traumatic events who have significantly greater psychological

comorbidity and functional impairment. Standard cognitive and behavioural therapies and exposure based treatments for PTSD might have limited utility and might be harmful if used prematurely for people with psychological problems following complex traumatic events.[14] Many people with CPTSD have high levels of disassociation and psychological comorbidities that might limit their capacity to engage in exposure based therapies and findings from effectiveness studies in single event PTSD cannot be generalised to people with complex trauma.[15] Compared with brief trauma focussed treatments, phased based approaches or sequential interventions which first focus on stabilisation (ensuring individuals' safety, resolving symptoms – including dissociative symptoms – and increasing emotional, social and psychological competencies), followed by processing unresolved aspects of individuals' trauma, with an emphasis on consolidation of treatment gains to facilitate re-engagement with social, educational, or occupational relationships can be effective in more complex presentations of PTSD following childhood sexual abuse.[16]

This expert consensus is however built on a non-systematic review and did not include an effectiveness review of pharmacological interventions. Existing international clinical guidelines (including NICE guidance) for PTSD do not extend to people whose main problems are 'enduring personality change after catastrophic experiences', CPTSD or DESNOS.[17] In the absence of evidence based guidelines it is unclear whether patients who have experienced complex traumatic events and who have trauma symptoms and/or substantial psychological problems will benefit from existing treatments for single event PTSD, or if alternative psychological and/or pharmacological approaches are warranted. Nor do we know enough about acceptability of interventions across all populations with different types of complex trauma histories. Owing to these uncertainties the first step is to undertake a broad systematic review of experimental evidence about treating mental health in populations exposed to complex traumatic events. The purpose of this review is to then identify candidate interventions that warrant further testing as part of future definitive cost-effectiveness evaluations.

2.2 Why is this research important in improving the health of the public and/or to patients in the NHS?

Mass conflict, persecution, generalised violence and human rights violations pose a critical threat to global mental health. By the end of 2014, 59.5 million people across the world were forcibly displaced (19.5 million refugees, 1.8 million asylum seekers, 38.3 internally displaced persons) and this figure has certainly been surpassed owing to exceptional numbers fleeing conflict in the Middle East.[18] Asylum trends show that there has been a huge increase in applications in industrialised countries with 80% being lodged in European countries (82% of these in EU countries); the UK has seen a 5% increase in asylum applications from 2013 to 2014.[19]

PTSD affects 30.6% of forcibly displaced people; reported torture is consistently the strongest population risk factor associated with PTSD in this group.[3] Depression is also very common among this population, affecting 30.8% of refugees, especially those exposed to prolonged life threatening political terror events.[3] Similarly, human trafficking (i.e. recruitment and movement of individuals by force, coercion or deception for exploitative purposes) is associated with high levels of physical and mental health problems.[20] Worldwide, up to 2.5 million are known to be in conditions of forced labour and are exposed to high levels of physical and sexual violence, economic restrictions and controlling behaviour.[21] The risk of depression, anxiety and PTSD are significantly higher in women who have been exploited for 6 months or more,[22] and higher in women trafficked for sexual exploitation compared with women trafficked for labour exploitation.[23] The impact of complex trauma in all these cases goes beyond PTSD however. Refugees for example face challenges associated with resettlement and acculturation, including social isolation unemployment and discrimination, and on-going social and legal insecurity that might demand using phased or multimodal treatment strategies.

Other critical cases of complex trauma of relevance to this funding call are associated with child abuse. Although underreported (1 in 3 cases are not reported) 1 in 20 children have been sexually abused in the UK.[24] Victims of child abuse are three times more likely to experience PTSD over their lifetime. Rates of PTSD and alcohol dependence are especially high in women who have experienced childhood abuse and related interpersonal violence. In total the cost of physical and mental health (depression and PTSD) and substance abuse to the UK is estimated to be £3.2 billion a year, in part owing to under- and unemployment and high spend in the criminal justice system as well as costs attributed to use of mental health services.[25] Stigma, discrimination and depression similarly affect victims of childhood abuse and severely impair their quality of life.

In line with current NICE guidance people with PTSD would normally be expected to be referred to high intensity therapy, typically CBT in Improving Access to Psychological Therapies (IAPT) services. However referrals for PTSD

only make up 1% of all referrals to IAPT based on diagnosis using ICD-10 criteria; the recovery rate is only 36.5%.[26] The reasons for such low referral rates and poor recovery rates are unclear. However it may well be that cases of PTSD referred to IAPT are more complex and require different and more effective treatments than CBT. A recent observational study of patients referred to an urban IAPT service (63% to high intensity treatments) showed that a high proportion of patients presented with complex mixes of psychiatric comorbidity (72% met criteria for ≥2 current diagnoses), personality disorder traits (including definitive BPD), and high rates of childhood trauma (67% reported at least one form of childhood abuse).[27] The presence of comorbid personality disorders is known to negatively impact treatment outcomes for patients attending IAPT services for depression and anxiety.[28] Equally, high levels of complex psychopathology may also negatively affect treatment outcomes for people with trauma disorders, including increased drop out from therapy. Additionally, existing services are not well placed to refer and effectively treat people who have experienced complex traumatic events. Health professionals working in secondary care and mental health services lack the knowledge, training and confidence to identify and respond appropriately to victims of human trafficking for example.[29 30]

The increased prominence and relevance of complex trauma to the NHS along with evidence that existing mental health services are not well equipped to appropriately manage patients with complex trauma suggests that there is a need to identify effective treatments for this group. This review will make a critical contribution to improving the lives of people with a history of complex traumatic events by identifying candidate interventions that can be assessed as part of robust trials, with a view to shaping recommendations for effectively and safely treating this underserved population.

2.3. Why is this research needed now: a brief review of the evidence of treatments of mental health problems in people with complex trauma histories

We did a scoping search (22/03/16) in MEDLINE, PsycINFO, CDSR/DARE, and PILOTS - Published International Literature on Traumatic Stress for systematic reviews and meta-analyses on treatment of mental health problems in people with a history of complex traumatic events but excluding cancer survivors and trauma related to physical injuries (complex adj2 trauma$; complex PTSD.ti,ab; DESNOS.ti,ab; Stress Disorders, Post-Traumatic). We summarise the key findings here to highlight why our proposed review will address outstanding questions.

A Cochrane review (70 trials; n=4761) found that individual trauma focused CBT (TFCBT) and eye movement desensitisation and reprocessing (EMDR) therapy are more effective than waitlist/treatment as usual (TAU) groups for reducing core symptoms of PTSD; TFCBT and EMDR may be more effective than non-TFCBT over the short term; there was less evidence for using stress management, relaxation or group CBT.[31] Drop out in active treatment groups in trials included in this review was higher. Methodological limitations of included trials (risk of bias, small sample sizes and underpowered analyses, lack of follow-up data) limit the conclusions that can be drawn from this review, especially applications in people with complex trauma history and longer term benefits.

Another but older Cochrane review (35 trials; n=4597) showed that medication, compared with placebo, is more effective for reducing PTSD symptom clusters (including depression), with the most convincing evidence in favour of SSRIs.[32] Hoskins et al have since updated this analysis and similarly concluded that SSRIs are superior to placebo for reducing PTSD symptoms; they also found no difference in the number of participants leaving trials early, suggesting medications are well tolerated and acceptable. [33]A small Cochrane review found no difference between combined psychological and pharmacotherapy and the use of either interventions alone.[34] Medication treatment effects for PTSD are small by comparison with psychological therapies and there is international consensus that psychological trauma focused therapies should be used as first line therapy for PTSD;[17 35]medications might be preferred where psychological therapies have failed or are not available.[36]

Existing international guidance makes no distinction between more complex variants of PTSD and recommends the use of trauma focused therapies for people with comorbidities and PTSD. However many of the trials included in existing systematic reviews (upon which NICE guidance is based) were done in North American or Western European countries where the type and severity of trauma experienced by participants may not be comparable to settings and scenarios with a higher risk of prolonged exposure to complex interpersonal trauma. And the WHO guideline excluded reviews based on trials of treatment of PTSD in refugee populations. Treatment recommendations for complex PTSD draw heavily on an

expert panel survey and a non-systematic review of the literature that identified nine studies of phase-based trauma treatment in populations with a history of childhood abuse.[16 37] The expert consensus treatment guidelines recommend that complex PTSD be treated first with a stabilisation phase aimed at ensuring patient safety through improvement in psychosocial and environmental resources followed by a focus on trauma memory processing and consolidation of treatment gains.

A recent critical appraisal suggests however that the evidence for CPTSD guidelines is methodologically weak: 2 studies were not RCTs; only 3 included an active control and none included head to head comparisons with trauma focused therapies; 3 studies did not follow-up participants; and all 9 included participants exposed to childhood abuse and no other types of complex trauma – limiting the validity and generalisability of the conclusions.[13] Indeed, patients with a history of complex traumatic events might benefit from existing evidence based psychological and pharmacological treatments. Crumlish et al identified 10 trials (n=528) in a review of psychotherapy for refugees and asylum seekers.[38] CBT and narrative exposure therapy (NET) emerged as candidate interventions for reducing core PTSD symptoms but small sample sizes, inadequate allocation concealment, and use of different comparisons limit conclusions. Similarly, Palic et al in a review of 25 experimental and non-experimental studies (n=1113) of psychosocial treatments for PTSD among refugees identified CBT as the most effective therapy for reducing PTSD symptoms.[39] Trauma focused therapies such as CBT and narrative exposure therapy (NET) appear to be equally efficacious across different types of trauma too, including repeated traumatisation. Powers et al in a review of 13 trials (n=675) showed that there was no significant difference in effect sizes for prolonged exposure therapy across types of trauma (combat/terror, childhood sexual abuse, rape, mixed: p=0.14).[40]

More complex presentations of PTSD include psychiatric comorbidities and there is growing evidence that existing non-phased based approaches are effective in this group. A wide ranging review with meta-analysis that included 148 anxiety-disordered treatment samples (47 in PTSD; combined n=3534) showed that effect sizes at post-treatment or at follow-up were generally unrelated to psychiatric comorbidity (for comparisons with active and non-active psychological or pharmacotherapy treatments.[41] However, in cases of PTSD there was a positive association between presence of comorbidities and treatment outcome – people with comorbidities did better. More specifically, there is emerging evidence that PTSD symptoms in patients with comorbid dissociation, depression, substance abuse, and/or mild BPD can be successfully and safely treated with existing evidence based trauma focused therapies and their outcomes are comparable to patients without these comorbidities.[42] CBT is also possibly the most effective approach for PTSD symptoms when compared with multimodal interventions that seek to first address additional social and psychological problems in refugees.[43]

Additionally, consistent with NICE guidance, trauma focused therapies that target PTSD symptoms can positively impact comorbidities. A review of 93 studies with 116 comparisons showed that there was a strong correlation between effect sizes for PTSD and depression outcomes, suggesting that psychological and pharmacological therapies are equally efficacious for PTSD and depressive symptoms.[44] There is however less good evidence of effectiveness of trauma focused therapies for PTSD and comorbid substance abuse disorders. Roberts et al in a Cochrane review (14 trials; n=1506) found that individual trauma focused therapy with a substance abuse adjunct were more effective than treatment as usual at post-treatment for PTSD symptoms, but only reduced substance abuse at long-term follow-up.[45] However the effects were small, follow-up short, and studies were typically at high risk of bias. Additionally, people with complex presentations e.g. psychiatric comorbidities, were excluded from trials in this review limiting generalisability to people with complex trauma histories.

Co-applicant Barbui is a co-author of an on-going review of psychological and pharmacological interventions for refugees and asylum seekers with PTSD.[46] That review is however exclusively about people in high-income countries (HIC) and there is scope for a review that assesses effectiveness of interventions in all settings – treatments that are effective in LMIC countries might be effective in HIC for example. Purgato et al aim to review psychological therapies for mental disorders in LMIC affected by humanitarian crises, but that review is not sufficiently focused on people with complex traumatic events.[47] Also, as part of a comprehensive review, new knowledge about novel interventions (e.g. trauma focused mindfulness, combined psychotherapy and pharmacotherapy)[48 49] for treating people with complex trauma histories needs to be captured along with greater understanding about acceptability and adverse events of treatments in this population.

In summary there is an expert consensus that phased based approaches effectively treat symptoms associated with CPTSD in adults, but evidence upon which this consensus is based is methodologically weak and exclusively based on studies that recruited participants with childhood abuse; findings might not translate to other populations with complex trauma histories. These consensus guidelines also did not review evidence about effectiveness of pharmacological interventions in CPTSD. The weight of available evidence suggests that evidence based trauma focused psychological therapies can reduce PTSD symptoms in people exposed to complex traumatic events who have psychiatric comorbidities. These treatments can also reduce comorbid illness in people with PTSD and can be used safely without a stabilisation phase. However existing reviews of the use of trauma focused therapies in people with complex trauma histories have focused on narrowly defined population sub-groups and we still do not how effective psychological therapies are across all populations with complex trauma. Comparative effectiveness of psychological interventions for mental health outcomes is also unknown for people with complex trauma histories in all settings. Acceptability of psychological interventions, either phased based or trauma focused, has been less well studied. There are also no comprehensive overviews of effectiveness of pharmacological interventions in people exposed have complex traumatic events. As such there are remaining uncertainties and questions about which interventions warrant further evaluation by NIHR HTA which this review seeks to address.

We propose therefore to conduct a broader review that will provide:

- Informative and clinically meaningful estimates of the effectiveness of psychological and/or pharmacological interventions for **mental health problems** in people with trauma and stressor disorders following exposure to complex traumatic events
- Analysis of comparative effectiveness of psychological and pharmacological interventions
- Analysis of adverse events/harms associated with different types of psychological and pharmacological interventions
- Easily understandable summaries for patients and stakeholders about the acceptability of psychological and/or pharmacological interventions
- Stakeholder consensus about which interventions are leading candidates for further evaluation by NIHR HTA

3. Aims and objectives

The aim of this review is to provide a broad synthesis of evidence about the effectiveness of psychological and/or pharmacological interventions to treat mental health problems (with or without PTSD symptoms) in people exposed to complex traumatic events. Additionally, where feasible, the review will identify and synthesise qualitative and quantitative evidence about the acceptability and uptake of delivering mental health interventions for people with a history of complex traumatic events. Together these syntheses will provide estimates of the clinical effectiveness and acceptability of existing and novel treatments and describe uncertainties about the strength of this evidence to inform a broader understanding about what interventions are likely to be candidates for testing in future definitive trials. Service user and provider input will make a critical contribution to the research prioritisation exercise. More specifically this review will include:

i. Descriptive synthesis: Provide an overview of existing randomised and non-randomised controlled trials of psychological and/or pharmacological interventions for mental health in people with history of complex traumatic events (as defined in PICOS) with specific reference to participant characteristics, intervention format and content, and outcomes measured.
ii. Clinical effectiveness: Narratively and quantitatively, with meta-analysis if feasible, report the clinical effectiveness of interventions delivered to adults aged 18 and over with trauma and stressor disorders after exposure to complex traumatic events. Effectiveness will be measured against all available primary and secondary outcomes.
iii. Comparative Effectiveness: Where data are available, provide evaluations of comparative clinical effectiveness of psychological interventions (e.g. phased based versus conventional trauma focused therapies) and different pharmacological interventions using network meta-analysis
iv. Acceptability and feasibility: Identify, appraise and synthesise narratively qualitative and quantitative data that addresses service user and provider perspectives about the acceptability and feasibility of using

psychological and/or pharmacological interventions to treat mental health problems after complex traumatic events, with specific reference to professional competencies and training, intervention uptake, adherence, and service experience.

v. Research priorities: In partnership with service users and providers with expertise and experience of delivering trauma focused therapies we will use the results of this review to identify candidate interventions that could be feasibly tested and used in the NHS and make recommendations to the HTA programme about future research priorities.

4. Research Plan

We propose an evidence synthesis of published and unpublished literature which will be undertaken following guidance produced by the Centre for Reviews and Dissemination (CRD)[50] and the Cochrane Collaboration,[51] with specific adaptations to reflect innovations in assessing risk of bias in non-randomised trials,[52] and in prioritising research.[53] The project will be undertaken in conjunction with service users and providers.

4.1 Inclusion and exclusion (clinical effectiveness)

4.1.1. Population

To answer the questions posed by the NIHR HTA funding brief it will be important to adopt a clinically meaningful and feasible approach to identifying studies of relevance. Practically it will not be feasible to undertake a review of evidence using a search strategy that hinges on differential diagnostic criteria for PTSD and CPTSD. Neither DSM-IV or ICD-10 distinguish between PTSD and CPTSD. DSM-V does include a dissociative sub-type, but it is unlikely many studies have yet been conducted using this approach. ICD-11 criteria that will include CPTSD will not be published until at least 2018. Our goal is therefore to identify studies based primarily on trauma history rather than diagnostic criteria.

Therefore our population of interest will be adults aged 18 or over exposed to complex interpersonal traumatic events defined as a "…deliberate and premeditated event or series of events of an extreme and prolonged or repetitive nature that is experienced as extremely threatening or horrific and from which escape is difficult or impossible due to physical, psychological, maturational, family/environmental, or social constraints".[54] This will include adults exposed to childhood physical and/or sexual abuse, being a victim of or witnessing domestic violence, forcibly displaced persons (refugees, asylum seekers, internally displaced persons), torture survivors, recruitment into armed conflict as a child, on-going armed conflict and combat, and relocation through human trafficking.

Complex interpersonal trauma can be distinguished from single event impersonal trauma such as a road traffic incident or a natural disaster. Traumatisation following complex interpersonal trauma is typically more severe and associated with greater psychological and functional impairment than traumatisation following impersonal and single event trauma. In line with the remit of the funding brief we will therefore exclude studies that only include participants with a history of exposure to single and non-interpersonal traumatic events. However we anticipate that some studies will include a mix of participants with a history of single event non-interpersonal trauma and complex interpersonal trauma. We will therefore include studies of mixed populations if we can determine that 75% of the participants have a history of complex trauma. If studies include less than 75% of participants with complex trauma but present data separately for this sub-group we will consider inclusion if these types of mixed population studies meet the other PICO criteria.

In this review we will take a broad approach to including trauma-and stressor related disorders and reactions to severe stress and adjustment disorders, but symptoms should be present for >1 month in people with a history of complex interpersonal trauma defined above. The trauma disorders of interest include:

i. PTSD according DSM-IV (APA 2000), DSM-V (APA 2013), or ICD-10 (WHO 1992) criteria, by means of a structured interview and/or a self-rated psychometric assessment tool with validated cut-offs for caseness.

ii. Complex PTSD (also known as Disorder of Extreme Stress Not Otherwise Specified [DESNOS]) which is characterised by the core symptoms of PTSD (i.e. re-experiencing of an extremely traumatic event accompanied by avoidance/emotional numbing, negative cognitions and mood, and hyperarousal) PLUS

identification by a structured clinical interview (i.e. Structured Interview for Disorders of Extreme Distress [SIDES])[55] and/or a self-rated psychometric assessment tool with validated cut-offs for caseness of at least one symptom from each of the following disturbances in self-organisation: (1) severe and pervasive affective dysregulation (e.g. violent outbursts, excessive crying, anhedonia, self-destructive behaviour, dissociation, or emotional numbing); (2) persistent negative self-concepts (i.e. perception of a diminished or defeated sense of self that can arise from the experience of a trauma, and is characterised by the presence of persistent negative beliefs about oneself along with feelings of guilt and shame); and (3) persistent interpersonal problems (i.e. an inability to build or maintain close and intimate personal relationships/bonds).[5 56]

iii. Dissociative PTSD as defined in DSM-V (APA, 2013).

In recognition that people exposed to complex trauma may not have PTSD but present with combinations of common mental health problems and interpersonal relationship and emotional regulation difficulties we will take a broad approach to inclusion than that used in previous reviews of PTSD. We will therefore not restrict this review on the basis of psychiatric comorbidities (i.e. depression, anxiety, panic disorder, borderline personality disorder and other personality disorders of relevance, functional somatic disorders) except for psychotic illness, or on the basis of substance misuse disorders.

While the aetiology of psychological problems in adults associated with complex traumatic events can be developmental in origin, occurring in childhood for example, this review is focused on interventions to improve outcomes in adults. We will therefore exclude all studies of children and adolescents under 18 years of age. Acute stress disorders will also be excluded because of their transient, self-correcting and essentially non-complex clinical presentation.

Because this review is focused on treating adults with existing psychological problems following complex traumatic events we will exclude studies of adults exposed to complex interpersonal trauma but who have not yet developed a mental health problems but focus on preventive therapies.

4.1.2. Interventions

4.1.2. Psychological interventions

This review will include studies that evaluated any first or second line psychological therapy aimed at improving symptoms (including comorbidities) of trauma-and stressor related disorders either delivered to individuals or in a group. In-keeping with the classification used by NICE[17] interventions to be considered are:

i. Trauma-focused CBT that includes one or more of the following types of treatment techniques: exposure, cognitive therapy, stress management.
ii. Eye movement desensitisation and reprocessing.
iii. Other psychological treatments used to treat trauma survivors and victims but use predominately non-CBT techniques: supportive therapy and non-directive counselling; psychodynamic therapies, including inter personal psychotherapy (IPT); hypnotherapy; mindfulness and compassion focused therapies; acceptance and commitment therapies; accelerated resolution, and sensorimotor therapies.

Where possible we will include as part of sub-group analyses consideration of the following interventions:

iv. Group trauma-focused CBT
v. Group non-trauma focused CBT

4.1.2.2. Pharmacological interventions

In the UK only two drugs are licensed for the treatment of PTSD: paroxetine and (in women only) sertraline. However this review will consider all drug treatments subjected to experimental testing in the context of treatment of mental health

problems in people with a history of complex trauma. Categories of pharmacotherapy to be considered are: SSRIs, SNRIs, tricyclic antidepressants, anxiolytic medication, mood stabilizers, atypical antipsychotics.

4.1.3. Comparators

4.1.3.1. Psychological interventions versus

i. Waitlist
ii. Treatment as usual
iii. Symptom monitoring
iv. Repeated assessment or other minimal attention control group akin to psychological placebo
v. Alternative psychological treatment
vi. Pharmacological treatment

4.1.3.2. Pharmacological interventions versus

i. Placebo
ii. Other medication
iii. Psychological therapy

Comparisons of two or more active interventions or of an active treatment with a 'no treatment' comparator will be included. Differences in comparators will be taken into account during data summary and analyses. Network meta-analyses will be conducted to provide comparisons of all interventions within a connected network (including comparisons of active interventions not originally evaluated in included trials).

4.1.4 Outcomes

There is growing evidence, from studies in women, that compared with single event or non-interpersonal trauma, exposure to repeated interpersonal trauma is associated with depressive and anxiety disorders other than PTSD,[57] and that somatisation, dissociation and affect dysregulation symptoms can occur after exposure to complex trauma irrespective of the presence of PTSD.[58]

To capture outcomes relevant to exposure to complex traumatic events we will divide the review into outcomes for core symptoms related to trauma and stressor related disorders and outcomes associated with psychological and psychiatric comorbidities even in the absence of PTSD.

4.1.4.1. Primary outcomes

i. Reduction in severity of traumatic stress symptoms as measured using a validated and standardised clinician rated scale.
ii. Reduction in symptoms of difficulties with emotion regulation (e.g. Difficulties with Emotion Regulation Scale [DERS])[59] and interpersonal relationship problems (e.g. Inventory of Interpersonal Problems [IIP]).[60]

4.1.4.2 Secondary outcomes

i. Severity of self-reported traumatic stress symptoms using a standardised measure (e.g. Modified PTSD Symptom Scale (MPSS-SR)[61]
ii. Reduction in depressive and/or anxiety symptoms measured using validated clinician-rated instruments (e.g. Hamilton Depression Rating Scale), or validated patient self-reported instruments (e.g. Hospital Anxiety and Depression Scale)
iii. Reduction in symptoms of panic disorder

iv. Reduction in symptoms of disassociation
v. Reduction in symptoms of functional somatic syndromes
vi. Reduction in substance misuse
vii. Acceptability measured in terms of intervention uptake, adherence and withdrawal (drop-outs)
viii. Adverse events and harms from trial data (e.g. worsening of traumatic stress symptoms); for psychological interventions we will code these in-keeping with latest typologies of adverse events of psychological therapies.[62]
ix. Suicidal ideation, attempts, and completion
x. Functioning and disability and quality of life measured by validated clinician-rated scales (e.g. Global Assessment of Functioning) or validated self-reported scales (e.g. SF-36, Sheehan Disability Scale).

4.1.4.3 Qualitative acceptability syntheses

For qualitative evaluations embedded within a RCT the inclusion criteria for population, intervention, and comparisons will be largely unchanged from that used to identify studies for the effectiveness syntheses. Additionally, to ensure that we identify non-trial based qualitative evaluations of acceptability of psychological and/or pharmacological interventions we will also include standalone studies not specifically linked to RCTs.

4.1.5. Studies and settings

4.1.5.1 Experimental studies

We will include RCTs and cluster RCTs (if relevant); non-randomised controlled studies will be included to capture data on emerging treatments and treatments tested in more pragmatic settings. Single group before and after studies, uncontrolled observational studies, case studies, opinion papers, descriptive studies, editorials will be excluded. Studies undertaken in any country and setting (i.e. LMIC and HIC) are eligible for inclusion across all phases of the review.

4.1.5.2 Qualitative studies

For the purpose of our review, qualitative research will be defined as those studies that collect data using specific qualitative techniques such as unstructured interviews, semi-structured interviews or focus groups, either as a stand-alone methodology or as discrete part of a larger mixed-method study, and analysed qualitatively. Studies that have collected data using qualitative methods but then analysed these data using quantitative methods will therefore be excluded.

4.1.6. Search strategy

A two-step search will be employed to identify evidence relevant to the effectiveness synthesis and the qualitative acceptability synthesis.

4.1.6.1 Effectiveness synthesis

To ensure maximum but targeted coverage of studies relevant to this review search strategies will be employed for the period from 1992 to the present, which includes the inception of ICD-10[63] and DSM-IV[64] (i.e. 1992 and 1994 respectively). We will include electronic database searches, journal hand searches, reference list searches, targeted author searches, grey literature searches (including material generated by service user-led organisations), research register searches, and forward citation searching. No language or other restrictions will apply. In partnership with our Advisory Group we will make judgements about the relevance of international literature to the UK health setting against our stated inclusion criteria.

Search terms relating to the population characteristics and interventions will be identified by scanning the background literature, browsing the MEDLINE medical subject heading (MeSH) thesaurus and via discussion between the research team and the Advisory Group chair (Bisson).

We will run searches of general biomedical databases (e.g. MEDLINE, Embase, PsycINFO, CINAHL, Science Citation Index as well as specialised databases such as International Pharmaceutical Abstracts and PILOTS – Published International Literature on Traumatic Stress. We will liaise with the Advisory Group to identify grey literature not indexed in medical databases.

Co-applicant Wright will check the project search strategies by using a test set of database records identified from the included studies of the reviews conducted by co-applicant Barbui (co-author of a review about PTSD treatments in refugees and asylum seekers in HIC),[46] and by collaborator Bisson (author of Cochrane reviews on PTSD). We will also have access to the list of studies excluded by the Cochrane reviews led by Bisson and also Barbui to screen these for eligibility for our review

4.1.6.2. Qualitative acceptability synthesis

We will run a separate search to identify qualitative evidence that addresses our aim to explore service user experience of treatments for people with a history of complex traumatic events. Search terms relating to qualitative designs will be developed based on our previous meta-syntheses [65] and terms relating to user experience of therapies will be developed by scanning the background literature, browsing the MEDLINE medical subject heading (MeSH) thesaurus and via discussion between the research team.

Additionally, while screening effectiveness studies for eligibility we will flag qualitative process evaluations that are associated with clinical trials. From this source we will develop a test set of search results to determine if the qualitative search is able to identify published qualitative evaluations that address the implementation of treatments for people with a history of complex traumatic events.

4.1.7. Data management and extraction

All potentially eligible records will be imported into a bibliographic referencing software program (Endnote versionX6) and duplicate references will be identified and deleted. We will then use Covidence (www.covidence.org) to manage screening of citations. Covidence is a Cochrane recommended web-based software platform that offers functions to share citation screening within the review team and resolution of discrepancies and agreement on final consensus data. Two reviewers will independently screen titles and abstracts for relevance, using the inclusion criteria outlined above. Where both reviewers agree on inclusion, or where there is disagreement, the full text article will be retrieved. The two reviewers will independently assess the full text of the articles against the inclusion criteria. Any remaining disagreements will be resolved through discussion with other members of the team. We will record inclusions and exclusions throughout this process to enable us to complete a PRISMA flow chart [66] and produce tables of 'Characteristics of included studies' and 'Characteristics of excluded studies'.

Data extraction and validity assessment will be performed by one reviewer and independently checked by a second. Discrepancies will be resolved by referral to the original studies and if necessary through arbitration by a third reviewer. Data extraction will be guided by a pre-specified data extraction sheet detailing key features of the study sample, setting, methods, intervention, control (if appropriate) and recorded and reported outcome measures. Short-term (post treatment to six months), long-term (7-12 months) and very long-term data (> 12 months) will be extracted and analysed separately.

4.1.8. Critical appraisal

4.1.8.1 Quantitative synthesis

Included RCTs will be assessed for risk of bias using the Cochrane Collaboration Risk of Bias (RoB) assessment tool for randomised controlled trials.[67] A judgment will be made for each domain into one of three categories (low, unclear or high risk of bias). We will tabulate risk of bias assessments alongside other details about the included studies, using ratings about random sequence generation, allocation concealment, and blinding as the primary markers of quality in sensitivity analyses due to evidence of their relationship with study results.[68]

Non-randomised controlled trials are increasingly used where there is access to linked administrative databases and health records with large populations and the means to control for confounding. Additionally non-randomised studies tend to offer more pragmatic or 'real-world' assessments of interventions and their inclusion can thus add value to systematic reviews and meta-analyses by providing a broader assessment of evidence.

There is less agreement however about the ability of non-randomised studies to produce unbiased estimates of effect even if these types of studies tend to be larger and more powerful than controlled trials. We will therefore assess risk of bias in non-randomised studies separately using the newly developed Cochrane Risk of Bias for Non-Randomised Studies of Interventions (ROBINS-I)[52 69] which has proven utility in assessing internal validity in non-randomised studies of medical and non-pharmacological interventions.[70 71]

4.1.8.2 Qualitative acceptability synthesis

Critical appraisal of qualitative research is recognised as a controversial issue.[72] Following the lead established by the GRADE Working Group (www.gradeworkinggroup.org) and the Cochrane Qualitative and Implementation Methods Group (cqim.cochrane.org) we will adopt the CerQual (certainty of the qualitative evidence) approach to assess both the methodological limitations of individual studies and the coherence of our review findings. CerQual is similar to GRADE[73] in that both approaches aim to assess the certainty of (or confidence in) the evidence, and both also rate this certainty for each finding across studies rather than for each individual study. Unlike GRADE, which is only relevant to evaluations of effectiveness, CerQual offers a framework to evaluate the certainty of evidence that address questions beyond effectiveness of interventions, such as acceptability. As per the approach taken by Glenton et al.,[74] methodological limitations will be assessed with the CASP checklist.[75] Coherence of the review will be assessed by identifying patterns across the data contributed by each of the individual included studies, for example, where findings are consistent across multiple settings or different sub-groups. Certainty of evidence in each individual study will be rated as high, moderate or low, ranked according to the methodological limitations and coherence of each finding of our review.

4.1.8. Data synthesis

4.1.8.1 Clinical effectiveness of psychological and/or pharmacological interventions versus control

We will conduct meta-analyses pooling data relating to psychological and/or pharmacological interventions where the interventions, populations and study contexts are sufficiently similar to make such analyses appropriate and interpretable.[76] We will explore statistical heterogeneity thoroughly through use of appropriate statistics such as I^2.[77]

If cluster trials are identified, they will be analysed appropriately, which may involve reducing effective sample size through calculation of the 'design effect'.[51] Studies including multiple treatment groups will be analysed including each relevant pair-wise comparison separately, but with shared intervention groups divided out approximately evenly among the comparisons to avoid double counting.[51]

Where studies report multiple outcomes within one of our categories (e.g. two depression scores), we will use one, based on a decision rule that maximises comparability between studies in the review (i.e. including measures which are used frequently by other studies in the review) or take a median in cases where the decision rule does not apply.

We will apply measures of effect (such as the standardised mean difference) so that the results of different interventions can be compared by decision-makers to assess their relative value. In recognition that the outputs of reviews need to be accessible and relevant to wider range of audiences including service users and professionals,[78] we will, where certain assumptions for the variance of effect are met,[79] back-transform standardised effects into mean differences, and to translate standardised effects into clinical meaningful metrics such as number needed to treat.

4.1.8.2 Subgroup analyses

To answer whether treatments are more effective than other treatments for specific population sub-groups we will perform subgroup meta-analyses for the primary and secondary outcomes of critical importance to mental health. The population subgroups will include victims of specific types of trauma:

- Exposure to sexual abuse as a child
- Exposure to sexual abuse as an adult
- Refugees and asylum seekers
- Trafficking and exploitation

We will adopt the methods and approaches used by the US Agency for Healthcare Research and Quality in their comparative effectiveness review of psychological and pharmacological treatments for PTSD in adults.[80] Data for subgroup analyses will be captured from: 1) individual studies that report subgroup analyses of effectiveness of interventions for a particular trauma type or comparative effectiveness studies that compared two or more treatments within a group of subjects all with the same trauma type, and 2) subgroup analyses (stratified analyses by trauma type) of our meta-analyses for primary and secondary outcomes related to PTSD and mental health outcomes. We will restrict stratification by trauma population to interventions that favour the experimental group and have sufficient number of studies to warrant the stratification.

4.1.8.3 Comparative effectiveness of psychological interventions – network meta-analysis

Traditional reviews often focus on overall benefit of interventions compared with usual care, and lack rigorous comparisons between interventions. This is especially problematic in areas where there is uncertainty about the relative effectiveness of interventions. Psychological therapies are recommended as first line therapy for people with trauma and stressor disorders but there are no direct head to head comparisons of phase based psychological interventions and brief trauma focused psychological interventions for people with complex trauma. This is seen as a critical deficit in the evidence base. Where data permits our proposed network meta analyses will allow the full consideration of the relative effectiveness of all psychological interventions, including those that have not been directly compared.

The structure of the network meta-analyses will be informed by clinical considerations, ensuring that the pooled estimates are clinically meaningful. In the absence of standardisation of conduct and reporting of mixed treatment comparisons, we will follow the good research practices detailed in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force guidance.[81 82]

We will use methods developed and illustrated in NICE Technical Support Document 2,[83] which details the generalized linear modelling framework for network meta-analyses of randomized controlled trials. Estimates of treatment effects will be calculated using a Bayesian approach (using freely available software: WinBUGS), taking into account the correlation between multi-arm trials where appropriate. Direct and indirect treatment effects will be estimated, along with credible intervals and prediction intervals. The network meta-analysis method enables the comparison of indirect effects, treatment comparisons not addressed within the primary trials. Such network analysis can only be applied to connected networks of trials. We will evaluate model diagnostics and assumptions of similarity and consistency in the evidence network. As it is common to simultaneously consider the effects of an intervention whilst also considering for example acceptability, we will present the relative ranking for these two outcomes simultaneously.

Where sufficient studies allow, we will explore the possibility of estimation and adjustment of bias using the risk of bias domains random sequence generation, allocation concealment, and blinding (as per the meta-analysis synthesis). To aid readability we will use graphical methods to illustrate the comparative effectiveness of the different interventions.[84]

There are risks and benefits of including non-randomized studies in network meta-analyses (NMAs). There is potentially greater risk of bias associated with non-randomized studies which may impact on the validity of the NMA findings. Conversely, inclusion of both randomized and non-randomized studies potentially offers more timely, comprehensive and generalizable findings that can inform future trials in an emerging evidence base.

We will assess the risks and benefits of including non-randomized studies in the network meta-analyses (NMA) taking into account current methodological guidance. [85] Firstly, we will be guided by state of the art risk of bias assessment methods for non-randomized studies. Studies with substantial risk of bias will not be included in the NMA to avoid perpetuating the bias of these studies in our findings. Secondly, if there are non-randomized studies of sufficient quality, and we judge the benefits of their inclusion outweighs the risks, we will conduct sensitivity analyses to examine the validity of different methods of integrating randomized and non-randomized studies in the NMA.

4.1.8.4. Qualitative synthesis

Our review will offer an integrative synthesis of quantitative and qualitative evidence about acceptability of interventions. An integrative review not only addresses questions about effectiveness but can identify barriers and facilitators to uptake of interventions and include summaries about how interventions are experienced by individuals, their families, and their carers. Synthesised qualitative and mixed-methods evidence reviews can thus offer policy makers a broader perspective on solutions and recommendations that are relevant to end users and stand a greater chance of being implemented.[86]

Drawing on guidance for qualitative syntheses to inform policy making and research prioritisation we will use a narrative synthesis approach.[87] This approach offers an efficient and practicable means to include a qualitative description and map of findings of included studies (presented in matrices across studies), interpretation and synthesis, and the identification of common and emergent themes. Narrative synthesis draws on the techniques of thematic analysis which we have used before to categorise emergent and recurring themes within and between transcripts.[88] Consistent with previous NIHR funded qualitative syntheses that we have conducted,[65] we will place greater emphasis on studies presenting 'thicker' data descriptions (i.e. those studies employing rigorous data collection/analysis techniques and providing in-depth examinations of user experience). Thinner data descriptions (i.e. those which lack this detail) will be used to augment and contextualise the findings. As outlined in section 4.1.8.2. the relative contribution of individual studies, the impact of methodological limitations, and certainty on the findings will be summarised narratively in line with the CerQual approach.

Once we have extracted and synthesised all available quantitative and qualitative data, we will seek, wherever possible, to integrate our findings. This will be achieved by exploring the extent to which our identified qualitative themes map onto the quantitative acceptability ratings about intervention uptake.

4.1.8.5. What are the priorities for future effectiveness trials for treating mental health in people with a history of complex traumatic events?

The main basis for research recommendations will be the evidence outlined in the quantitative and qualitative syntheses. Following methods used in previous EPPI-Centre reviews[89] we will develop a matrix, where the rows represent the core questions concerning population, intervention content, comparison and outcomes, and the columns represent the findings from the qualitative and quantitative synthesis. We will populate the matrix with these findings to identify what is known about psychological and pharmacological interventions and the utility of existing outcomes for and mental health and psychiatric and medical comorbidities and areas where significant uncertainty remains.

It is likely that the research evidence will be insufficient in scope and quality to definitively identify the most promising interventions for future evaluation. We will therefore run a consultation exercise for core stakeholders, including service users and their carers (see PPI in section 8 below), and health professionals with experience of mental health problems associated with complex traumatic events. This exercise will run as a one-off half-day workshop, facilitated by co-applicant Lovell. We will present the results of our syntheses, using focussed summaries[90] and highlight those areas where uncertainty remains, and conduct a facilitated discussion using Delphi techniques to fill in gaps in the matrix and develop a final list of research priorities for future trials. We have used these techniques successfully in previous work.[91]

5. Plan of investigation and timetable

We estimate that the proposed work will take 18 months. This estimate is based on scoping searches of MEDLINE, PsycINFO, CDSR/DARE, and PILOTS which identified 2176 unique records. Extrapolating from this result we estimate

a threefold hit rate from searches of all databases and grey literature which will take approximately 1.5 months to screen titles and full texts; 1.5 months to extract data from ≈50 studies; 4 months to conduct analyses; 2 months to complete critical appraisals. Significant efficiencies in searching and data extraction will be gained by working closely with collaborator Bisson who has led previous Cochrane reviews on psychological treatments for PTSD, and also with international contents expert Barbui who is an investigator on a review of treatments for PTSD in refugees and asylum seekers in HICs. This strategy will afford our team more time to devote to other elements of the evidence syntheses and research prioritisation exercise. Further detail about timings and workflow are given in **section 10: Justification of costs**.

Months 1-3: Set-up, protocol development and PROSPERO registration; Months 4-5: Literature searching and cross checking searches held by CCMD and first meeting of advisory group; Months 6-9: Eligibility and data extraction; Months 10-15: Second meeting of advisory group, narrative, statistical, and qualitative syntheses; Month 16: Research prioritisation exercise facilitated by Advisory Group and applicants Coventry, Churchill and Temple. Months 17-18: Third meeting of advisory group and completion of final analyses and report and wider dissemination.

6. Project management

6.1. Research team

Each applicant will be involved in the project and will contribute significant methodological (applicants Coventry, Churchill, Meader, Wright) and/or content expertise (applicants Barbui, Lovell, Gilbody, McMillan, Temple) to ensure the various components of this review are delivered to the highest standard and on time. The PI, Coventry will be responsible for overall project management; co-applicant Churchill will line manage the full time researcher in CRD. Applicant Wright will design and run the searches (assisted by a part-time project administrator); collaborator Bisson and applicants Churchill and Barbui will be chiefly responsible for linking our review with existing Cochrane reviews and liaising with CCMD. Applicants Coventry, Churchill, McMillan and Gilbody will lead on analyses of clinical effectiveness. Applicants Meader and Churchill will oversee the statistical elements of the quantitative evidence synthesis and lead on the network meta-analyses. Applicant Coventry will lead on the qualitative and cross-syntheses with input from applicant Temple who is a clinical specialist in delivery of complex trauma services. Applicants Lovell with Gilbody will lead on PPI training and delivery of our PPI strategy.

6.2. Advisory group

We have assembled and will convene a small project advisory group, consisting of health professionals with expertise and experience of delivering trauma focused therapies for people with complex trauma, members of CCMD with track record of delivering Cochrane reviews in PTSD, and patient and public representation (see below). The advisory group will act as an independent check on progress of our review against the protocol especially in relation to making adjudications about inclusion and exclusion, support recruitment of PPI representatives, and co-facilitate the research prioritisation exercise with applicants Coventry and Churchill.

7. Ethical considerations

As the bulk of this programme will involve secondary data analyses we do not anticipate the need for ethical approval to conduct the evidence syntheses. The research prioritisation exercise will employ stakeholders as equal partners with the research team and as such will not be treated as research involving participants in NHS settings, but treated as patient and public involvement.

8. Patient and public involvement

We recognise that PPI must be flexible to meet the needs of those who participate, and will therefore offer a range of PPI opportunities within the project.[92] However, the structure and content of this programme has been primarily driven by the

requirements of the HTA brief and our prior experience of delivering reviews in the area of mental health. We have identified three roles that service users can undertake to add value to the review process and make the results of the review more credible and relevant to end-users:

i. One member to sit on the Advisory Group during the project, to be consulted on the overall aims and design of the research and bring the perspective of "critical friends" to the process
ii. Two members to participate in a one-off stakeholder consultation exercise on the translation of findings into meaningful guidance for setting priorities for future primary research
iii. One member to contribute to dissemination activities by writing lay summaries and where feasible supporting the team in promoting the progress of the review and any findings via social media (e.g. using Twitter).

We will ensure that PPI activities are conducted in line with current guidance,[93 94] including clear discussion about roles, valuing different perspectives, clear budgeting for PPI, training for both researchers and PPI representatives, and reporting of the PPI contribution.

We will provide support to our PPI representatives to contribute to the research process and to contribute to specific research activities. Co-applicant Lovell has expertise in developing training to support PPI in primary and secondary research through an existing NIHR grant (Lovell RP-DF-1209-10020). Lovell and Gilbody will facilitate two half-day training events in York for our PPI representatives. The training will provide context for understanding the research content (including the prioritisation exercise) and the research process, and also contribute to capacity building amongst PPI partners. We will assess impact using the GRIPP checklist to ensure transparency and consistency of reporting.[95]

9. Expertise of review team

9.1. Research team

The team has an international track record in the delivery of evidence syntheses in mental health. The applicants have significant skills and experience in all aspects of evidence synthesis. They are skilled in information retrieval and data extraction (Wright), coding, risk of bias assessments and quantitative synthesis of complex, heterogeneous data sets, including meta-analysis, meta-regression, multilevel modelling and network meta-analyses (Coventry, Churchill, Meader, Gilbody, McMillan). Additionally we have experience in the delivery of qualitative syntheses to complement and cross tabulate with conventional quantitative reviews (Coventry, Meader) and expertise in mental health service user involvement in research (Lovell).

Our team includes subject experts in CBT for anxiety disorders (Lovell, McMillan), psychological medicine and health services research (Gilbody), international mental health and trauma disorders (Barbui), specialist personality disorder and trauma services (Temple), who bring national and international expertise in understanding the diagnosis and management of people with trauma disorders and mental health problems across multiple health settings.

Specifically, the expertise of the review team includes:

Dr Peter Coventry: is a Senior Lecturer in health services research and holds a joint appointment with the Mental Health & Addictions Research Group and Centre for Reviews and Dissemination at the University of York. He was a MRC Special Training Post-doctoral fellow between 2005-09 during which time he trained in systematic reviews at ScHARR, University of Sheffield. He has a very solid track record in leading quantitative systematic reviews of effectiveness of psychosocial interventions for common mental health problems in adults with long term conditions,[96] moderator analyses of treatment effects using meta-regression and individual participant data meta-analysis,[97] and has completed qualitative meta-syntheses of complex interventions in mental and physical multimorbidity.[98] He has contributed to Cochrane reviews and is an active collaborator with CCMD. He is the principal investigator for a NIHR School for Primary Care Research funded individual participant data meta-analysis of 10,962 participants to test if long term conditions moderate treatment effects of collaborative care for depressive symptoms.

Prof Rachel Churchill: is a Chair in Evidence Synthesis and Coordinating Editor of the Cochrane Common Mental Disorders group. She is a psychiatric epidemiologist with a long track record in undertaking and managing complex programmes of mental health systematic reviews and evidence syntheses, as well as in rapid reviews and network meta-analyses. She has authored a number of evidence syntheses in trauma related conditions, including PTSD and child abuse and neglect. Her work involves a variety of knowledge mobilisation and exchange activities and has been influential in both policy and practice.

Prof Simon Gilbody: is a leading health services researcher and psychiatrist/cognitive behaviour therapist by clinical background. He directs the Mental Health & Addictions Research Group (MHARG) at the University of York, and has a strong track record of delivering health technology assessments and systematic reviews on time and in budget. Gilbody trained in systematic reviews under the auspices of an MRC Fellowship (1996-2000) held at CRD. He is a long-time contributor to the Cochrane Collaboration (contributing editor to CCMD). His systematic reviews have influenced NHS policy and practice in the management of perinatal mental health, primary care mental health and screening polices for depression. Gilbody was an inaugural NIHR Senior Investigator and he has successfully used systematic reviews to prioritise and inform the design of some of the largest mental health trials ever funded by NIHR (CASPER, CASPER+, REEACT1 REEACT2, SCIMITAR).

Prof Karina Lovell: is Professor of Mental Health, CBT therapist and NIHR Senior Investigator with a track record of health services research including RCTs and systematic reviews. She has substantial clinical expertise in working with people with PTSD and has been involved in a number of large trials examining interventions for PTSD.

Dr Dean McMillan: is an experienced mental health services researcher and clinical psychologist by background with further specialist training and expertise in Cognitive Behaviour Therapy as applied to anxiety disorders. He has led or worked on a number of complex evidence synthesis, including those funded by the NIHR HTA.[99 100]

Prof Corrado Barbui: is a Full Professor of Psychiatry with a track record in leading quantitative systematic reviews of effectiveness of pharmacological and psychosocial interventions for mental health problems in adults with PTSD, depression and severe mental disorders.[101 102] He has completed network meta-analyses in mental health, and has been involved in the use of GRADE to produce evidence-based guidelines for the World Health Organization.[103 104] He is leading investigator of an individual patient data meta-analysis of psychological interventions for children exposed to humanitarian stressors in low- and middle-income countries.

Dr Nick Meader: is a research fellow in evidence synthesis. He has contributed to a number of systematic reviews on common mental health and other mental health disorders (for example, meta-analyses of pharmacological[105]and psychological[106] interventions for depression, network meta-analyses of pharmacological interventions for general anxiety disorder,[107] narrative synthesis of mental health crisis models).[108] In addition, he's been a guideline development group member for eight NICE mental health guidelines (e.g. borderline personality disorder and antisocial personality disorder).[109] He's experienced in using a range of evidence synthesis techniques of quantitative, qualitative and mixed methods data.

Dr Melanie Temple: is a consultant psychiatrist and psychotherapist, accredited EMDR Consultant Practitioner and Supervisor at the Retreat & Tuke Centre, York, where she specialises in treatment of all types of psychological trauma and its related difficulties with specific remit around complex trauma, dissociation, disassociative identity disorder and comorbid personality disorders especially emotionally unstable/borderline (EU-PD/BPD).

Ms Kath Wright: is the Information Service Manager at the Centre for Reviews and Dissemination, University of York and has 20 years' experience of designing and implementing search strategies for systematic reviews, health technology assessments, and other large scale research projects. Many of these are in mental health including for NIHR HTA.[110]

9.2. Advisory Group

Ms Stephanie Wetherill: Stephanie has an MSc in clinical psychology from Bangor University. Stephanie has been working for the last 19 months at the Kemp Unit at The Retreat, which is a specialist treatment unit for female patients

aged 18+ with severe and complex personality disorder with a focus on BPD. Stephanie has a particular interest in Compassion Focused Therapy and has experience in a support worker role and as an assistant psychologist.

(Chair) Prof Jonathon Bisson: is Director of Health and Care Research Wales, a Welsh Government funded, multi-faceted and nationally distributed organisation comprising an infrastructure that supports and increases capacity in R&D in Wales, runs a range of responsive funding schemes and manages resources to promote, support and deliver research. He is also a professor in psychiatry at Cardiff University and a consultant psychiatrist with the Cardiff and Vale Traumatic Stress Service. He developed an interest in traumatic stress during his time in the British Army and has conducted various studies including two widely cited randomised controlled trials of early psychological interventions following traumatic events and Cochrane systematic reviews in the traumatic stress field. He was co-chair of the Guideline Development Group for the UK's NICE guideline on the management of PTSD in primary and secondary care, is a past president of the European Society for Traumatic Stress Studies and chair of the Guidelines Committee of the International Society for Traumatic Stress Studies.

Ms Lizzy Ferguson: is the Involvement Lead for The Retreat, York, which is a specialist mental health care provider with services for Eating Disorders, Borderline Personality Disorder, Dissociative Disorder, CPTSD (especially for women). She has worked in the area of Involvement for the past eight years at The Retreat, and also at Garrow House, which was a step down service for women leaving secure services. Lizzy is an expert by experience and has used mental health services for all her adult life. Lizzy is interested in Appreciative Inquiry as a way to engage with people who use services.

PPI representative: To be recruited by Ms Ferguson from The Retreat if funded.

10. Justification of support required

We have budgeted for an 18 month project based on anticipated workloads following a scoping exercise that identified 2176 unique records. If we extrapolate from this we estimate a full search (including Cochrane searches) would yield approximately 60+ trials of relevance and a citation screening task in excess of 6500 titles.

Posts and salaries for the research team make up the largest part of the budget. Efficiencies will be gained by working with our Cochrane collaborators but we will still need to allocate resource to support the administration and running of the searches and review processes. This investment is reflected in the funding for an information specialist (Wright 10% FTE for 3 months) and a research administrator (20% FTE for 12 months) at CRD. To deliver the work in partnership with co-applicants we need 1 post-doctoral Research Fellow (1.0 FTE at York) priced at £58,253.

We have also costed in time for the lead applicant (Coventry) at 20% FTE to enable him to manage the overall programme, and time for co-applicants, commensurate with their contribution to the programme; Churchill and Meader will make significant contributions to data analysis and synthesis and are each costed for 10% FTE over the duration of the review. All other co-applicants are costed for 2.5% FTE for the duration of the project. The cost to the funder for 18 months for the lead and co-applicants is £67,587.

Our PPI activity will be reimbursed at INVOVLE[94] rates for contribution and travel at project meetings, the research prioritisation exercise, contributions to dissemination, and training days (£640). Co-applicant Barbui will attend up to two meetings at York in person, but all other scheduled and ad hoc meetings will be held via Skype to reduce travel and cost. The travel and subsistence budget for the research team supports attendance at project meetings for co-applicants Lovell (Manchester) and Barbui (Verona) and total £968; £516 has been allocated to travel for Advisory Group members. We have also allocated £566 for travel and registration at the Royal College of Psychiatry International Congress in 2017. Equipment costs cover purchase of 1 Dell desktop PC (£400). Inter-library loans will cost £640: we anticipate that 33% of full text papers will be retrieved as free downloads and the remainder as papers from the British Library @ £7 each. £1,920 has been allocated for Open Access publication charges; printing and Covidence fees are £112. Indirect costs (£87,806) are associated with Higher Education Costs for the research team and include estates costs.

Total requested from the funder at 80% FEC = £218,656

11. Dissemination, impact, and project outputs

11.1. Outputs

The proposed work will result in a number of valuable outputs:

i. Evidence of the effectiveness (including comparative effectiveness), safety, and acceptability of psychological and pharmacological interventions for mental health problems in people exposed to complex traumatic events will be synthesised and presented in formats for service users, health professionals and service providers, charities, policy makers (e.g. NICE), research and scientific community and the funder (NIHR HTA).
ii. An increased understanding of the relevance of international evidence to the NHS will be obtained.
iii. Future research priorities to be funded by NIHR HTA to support improvement of treatments and service delivery for underserved groups exposed to complex traumatic events.
iv. Collaborative partnership between experts in health services research, evidence synthesis, mental health, mental health service delivery, service users, and dissemination and knowledge mobilisation

11.2. Dissemination

The review will be reported according to PRISMA guidelines [66] and submitted in a final report to the NIHR HTA programme, for publication as a monograph in the NIHR Journals Library. A series of publications describing different aspects of the project (e.g. clinical effectiveness, acceptability) will be written and submitted to high impact academic and practice journals. In partnership with CCMD editor and applicant Churchill and collaborator Bisson we will identify existing Cochrane reviews that might be updated or identify opportunities for new Cochrane reviews to address additional unanswered questions about treating and measuring outcomes in people with complex trauma histories. Abstracts will be submitted to relevant major national and international conferences such as the Royal College of Psychiatrists International Congress. Presentations to professional, research, and service user audiences will also be made at key events organised by partner organisations such as NIHR CLAHRC Yorkshire and Humber which hosts a mental health and comorbidity theme directed by applicant Gilbody, and the Northern IAPT Practice Research Network which hosts two annual events to showcase research relevant to delivery of low and high intensity psychological services – applicant Coventry is speaking at the event in 2016 and is a colleague of the chairman of this IAPT network.

Dissemination will also be supported by a pro-active social media campaign to promote the programme among professional and public audiences, report on progress and highlight key achievements, and cite more broadly research and patient initiatives and trends in treating people with complex trauma histories. Applicants Coventry and Churchill will lead on social media communications and set up a bespoke Twitter account for INCiTE, and the programme will be more widely promoted among professionals, charities, services and service users and the research community via institutional Twitter accounts that are followed by more than 106K (@MHARG_york; @crd_york; @TheTukeCentre, @TheYorkMind; @HealthSciYork; @CLAHRCYH; @NIHR_DC; @OfficialNIHR; @cochranecollab; @Cochrane_CCMD)

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