



Efficacy of eye movement desensitization & reprocessing versus cognitive behavioral therapy in Post-Traumatic Stress and Depressive Symptoms: Study protocol for a Randomized Controlled Trial



Anwar Khan^{a,*}, Salim Khan^b, Syed Tahir Shah^b

^a Department of Social Sciences, Khushal Khan Khattak University, Karak, Pakistan

^b Department of Psychiatry, Ayub Medical College, Abbotabad, Pakistan

ARTICLE INFO

Keywords:

Post-traumatic stress disorder
Depressive symptoms
Comorbidity
Eye movement desensitization & reprocessing
Cognitive behavioral therapy

ABSTRACT

Post-Traumatic Stress Disorder (PTSD) develops after exposure to or witnessing traumatic events. PTSD is highly comorbid and individuals with PTSD usually report Depressive Symptoms (DS). Common treatment choices for PTSD and DS are either EMDR or CBT, however, little is known about their comparative efficacy, especially in Pakistan. Therefore, this Randomized Controlled Trial (RCT) aims at determining the comparative efficacy of EMDR vs CBT in Pakistan. This study will also examine the association between reduction in symptoms of PTSD and DS over course of treatment. In this regard, two arms Crossover Randomized Controlled Trial (RCT) with Repeated Measures Design will be selected. This study will be conducted at two rehabilitation centers and patients will be screened at Time:01, baseline; Time:02, during treatment; Time:03, post treatment and Time:04, 06 months follow-up. All analyses will be performed according to intention-to-treat principle. Variations in symptoms will be analysed by using descriptive statistics, χ^2 tests, t-tests, and one way ANOVA. To examine changes in PTSD and DS across time and to check efficacy of each treatment, a series of Linear Mixed Models will be run. Furthermore, a series of multi-level lagged mediation analysis will be performed to check bi-directional mediation between changes PTSD and DS over time. This protocol has outlined the rationale for determining efficacy of EMDR and CBT in Pakistan. It will help in answering a broad range of questions concerning efficacy of newly developed evidence-based treatments. Moreover, it may also guide future research on the treatment of PTSD and DS in the developing countries.

1. Introduction

1.1. Background

Post-Traumatic Stress Disorder (PTSD) develops after exposure to or witnessing traumatic events [1]. It is characterized by distressed recollection of the traumatic events and hyper-vigilance [2]. PTSD is highly comorbid and approximately half of the individuals with PTSD usually report comorbid depressive symptoms across various epidemiological samples [3]. PTSD is manageable either with the pharmacotherapeutic or psychotherapeutic treatments, however, practitioners sometimes prefer psychotherapy, especially if the pharmacotherapy is not effective [4]. Recent research indicates that Eye Movement Desensitization & Reprocessing (EMDR) and Cognitive Behavioral Therapy (CBT) are effective treatment choices for both PTSD and Depressive Symptoms [5].

1.2. Study rationale

Despite the efficacy of EMDR and CBT for both post-traumatic and depressive symptoms, little is known about their comparative effectiveness. Similarly, less is understood about the association between reduction in these two symptoms over the course of treatment. As both are comorbid, so it is expected that changes in the post-traumatic symptoms may cause changes in the depressive symptoms, either in a reciprocal or non-reciprocal way. It means that either PTSD or DS might become the mediator of therapeutic changes for EMDR and CBT or both. Therefore, examining such mediators of therapeutic changes can clarify how and why a particular treatment is effective [6]. However, there is paucity of research on the said topic, mostly because EMDR is relatively a recent psychotherapy technique and few researchers have examined it. And to the best of our knowledge, only one study, i.e., Lenferink, et al. [7], has developed a study protocol for knowing the

* Corresponding author.

E-mail addresses: anwar.khan@kku.edu.pk (A. Khan), drmarwat@gmail.com (S. Khan), drtahirshah123@gmail.com (S.T. Shah).

<https://doi.org/10.1016/j.conctc.2019.100439>

Received 8 April 2019; Received in revised form 23 July 2019; Accepted 21 August 2019

Available online 22 August 2019

2451-8654/ © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

efficacy of EMDR and CBT, while examining changes in PTSD due to changes in DS, which indicating a serious research gap.

Pakistan has about 50 million mentally sick patients [8]. Such rise in the mental illnesses is due to increasing domestic violence, coupled by poverty and cultural constraints. Moreover, Pakistan is continually suffering from the war on terrorism [9]. These conditions have created breeding grounds for PTSD in Pakistan. Therefore, requiring not only an urgent uplift in health care facilities but also an overhaul in mental health policies [10]. Unfortunately, mental health is the neglected areas in Pakistan with 500 psychiatrists and only five government owned mental health hospitals [11]. Due to lack of health care facilities, patients either visit general physicians or traditional faith healers [12]. In such situation, it is imperative to find a mechanism for controlling mental illnesses in Pakistan. It also motivates the researchers to test the newly developed treatment, e.g., EMDR in Pakistan.

1.3. Aims of study

This Randomized Controlled Trial(RCT) has three aims

1. To compare EMDR vs CBT in the treatment of PTSD and comorbid Depressive Symptoms in Pakistan by determining whether EMDR will be non-inferior to CBT?
2. To find whether PTSD and comorbid Depressive Symptoms gradually decrease from high at pre-treatment stage (1st week) to lower at post-treatment stage (30th week) and follow up stage (6th month).
3. To examine whether a reduction in the PTSD symptoms helps in reducing the Depressive Symptoms.

2. Brief literature review and hypotheses development

The modern history of PTSD can be traced back to the early 20th century, when it was termed as Shell Shock [13]. During Korean and Vietnam wars, similar symptoms were called Combat Exhaustion [14]. During 1970s Ann Wolbert Burgess and Lynda Lytle Holmstrom formed a term "Rape Trauma Syndrome" [15]. During late 1980s, the PTSD was finally included in the Diagnostic and Statistical Manual of Mental Disorders-III [16]. PTSD is characterized by the symptoms of distressed recollection or flash back memory of the traumatic events, hyper-vigilance, nightmares, startle responses, problems in concentration, and avoiding of traumatic cues [2,17]. PTSD is also accompanied by certain comorbid symptoms like, e.g., Depression and Generalized Anxiety [18].

Following assessment, the common psychotherapeutic techniques include Eye Movement Desensitization & Reprocessing [19] and the Cognitive Behavioral Therapy [20]. The selection and efficacy of treatment interventions are dependent on factors, e.g., the type of mental illness, severity and duration of illness, etc [21] and each of these treatments have its own qualities. For this reason it is recommended that patients should be comparatively treated with both CBT and EMDR, so that their efficacy could be established [22]. In this way we may know whether EMDR is equivalent or superior to the CBT. The existing literature documents studies, e.g. Refs. [23,24], which reported EMDR as non-inferior to CBT. In the current study while comparing the two therapies in Pakistan, it has been hypothesized that EMDR will be non-inferior to CBT in the treatment of PTSD and comorbid depression (Hypothesis: 01).

Both the EMDR and CBT have certain steps. EMDR therapy has eight distinct steps [19], whereas CBT has six phases [25]. EMDR is based on the Francine [26] Adaptive Information Processing model, therefore it is a gradual treatment process, and the adaptive emotions are gradually added into the person neural network through bilateral stimulation [27]. For this reason, EMDR treatment range from 06 to 14 sessions, normally one to two times per week. CBT combines cognitive and behavioral aspects and targets emotions by changing painful thoughts and negative behaviors [28]. However, scientists believe that EMDR is

significantly more efficient as compared to CBT [29]. There are certain other causes of prolonged treatment, e.g., Treatment Resistance (i.e., even after receiving at least six month treatment, with 12 sessions of first-line treatment show less than 30% symptoms reduction [30]. In a normal situation reduction in the symptoms is usually experienced after the first or second session and as the patient moves towards final sessions, then a complete reduction in the symptoms is achieved [31]. Therefore, in the present study it has been hypothesized (Hypothesis: 02) that PTSD and comorbid depressive symptoms will gradually decrease from high at pre-treatment stage (1st week) to lower at post-treatment stage (30th week) and follow up stage (6th month).

PTSD is highly comorbid, especially among the individual who had experienced multiple traumas [32]. In this regard the comorbidity of PTSD and depressive-anxiety disorders is of particular interest because they are sequelae of exposure to traumatic events. Likewise, the previous history of depressive disorder can act as a risk factor for the development of PTSD [33]. Understanding such linkages PTSD and comorbid depressive symptoms can help in devising proper treatment sequence. Due to overlapping nature of PTSD comorbidities, it is believed that reduction in the symptoms of PTSD can help in relieving the comorbid depressive symptoms [34]. Hence, in the present study it has been hypothesized (Hypothesis: 03) that reduction in the PTSD symptoms will help in reducing the comorbid depressive symptoms.

3. Materials and methods

3.1. Study design

The current study will be a two arms cross over Randomized Controlled Trial (RCT) with Repeated Measures. Such design has certain advantages like e.g., it is helpful in minimizing the selection bias, participants can be allocated randomly [35], doesn't require large pool of participants and it allows the participants' exposure to a variety of treatments, with pre-treatment and post-treatment measurements [36]. Moreover, the Consolidated Standards of Reporting Trials (CONSORT) group flow diagram and SPIRIT Checklist will be followed to carry out and report this study. Fig. 1 shows the CONSORT flow diagram.

3.2. Participants

This study will be conducted at two rehabilitation centers, i.e., Paraplegic Centre¹ and Dost Foundation,² both of which are situated in the district Peshawar, Pakistan. According to official statistics, the Paraplegic Centre has a capacity of accommodating up to 60 indoor patients, whereas more than 80 patients are weekly examined in the outdoor patients department. Similarly, Dost Foundation has a capacity of accommodating up to 40 indoor patients and more than 60 indoor patients. The Paraplegic Centre deal patients with spinal injuries and physical disabilities, which are caused by traumatic events, e.g., vehicle accidents, falls, and violent acts such as stabs or gunshot wounds. Existing research shows that such patients experience severe PTSD symptoms [37]. On the other side, Dost Foundation provides rehabilitation services to the patients suffering from drug addiction, major depression and associated psychiatric illnesses.

Participants will be selected by a consecutive sampling technique with a rolling recruitment strategy. The consecutive sampling technique can help in selecting every consecutive patient that meet the inclusion criteria, until the required sample size is obtained [38]. All the consecutive outdoor patients who will visit the selected centers for treatment (during first three months of the study period) and pass exclusion criteria (criteria given in Table 1) and also screen positive for the symptoms of PTSD with or without Depressive Symptoms will be

¹ <https://paraplegiccenter.org/index.php>.

² <https://www.dostfoundation.org>.

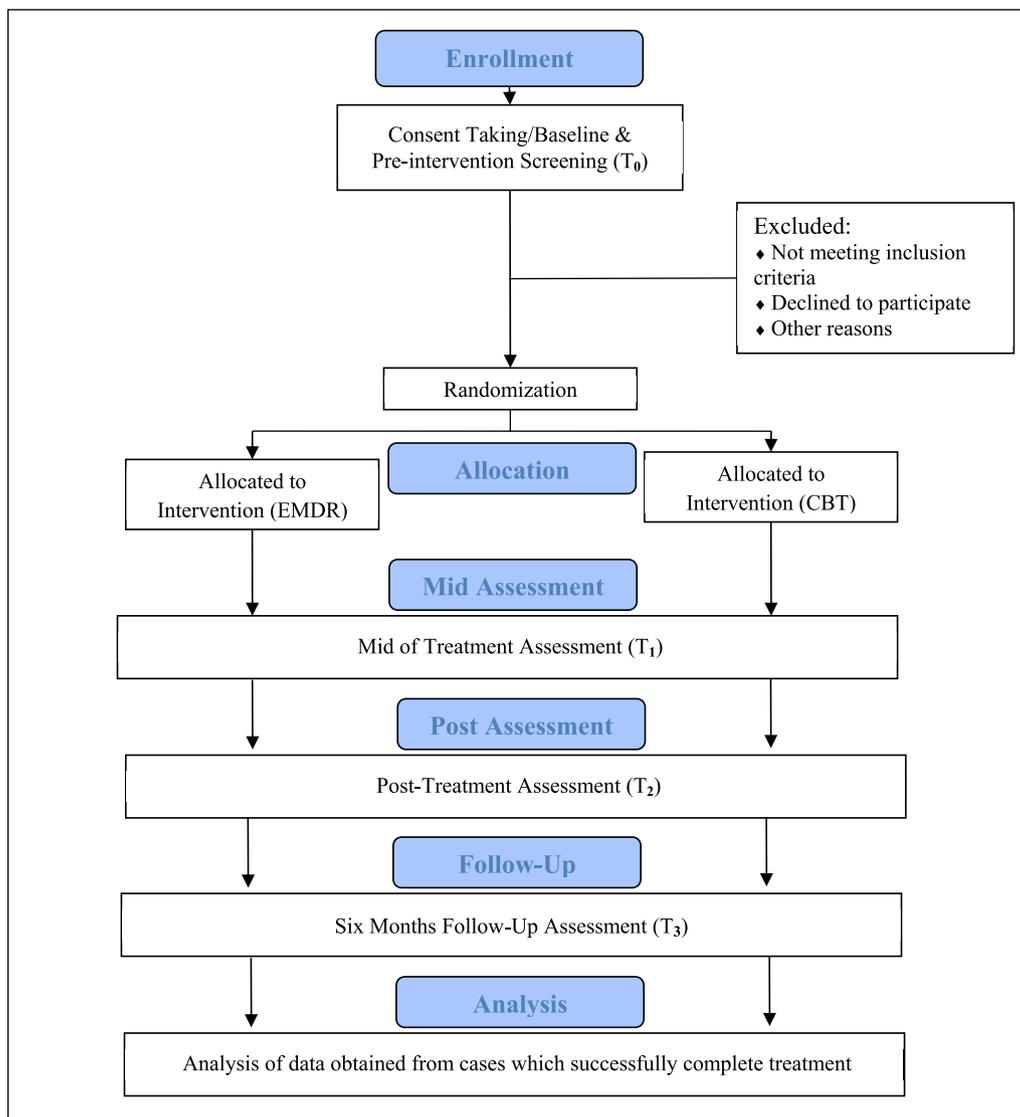


Fig. 1. CONSORT flow diagram for the study.

Table 1
Exclusion criteria.

- The following patients will be excluded:
1. Patients below the age of 18 years and above 60 years as this study is not on the children or older patients;
 2. Patients who can't move their hands and eyes/or can't perform basic movements;
 3. Patients who are unconscious for longer periods and unable to recover consciousness;
 4. Patients that are not diagnosed with symptoms of PTSD or PTSD is not the main problem;
 5. Patients having Depressive Symptoms that are not experienced after the development of PTSD;
 6. Patients with severe intellectual impairments, since such patients are difficult to communicate.

recruited for this study. Moreover, the already admitted indoor patients will also be recruited, after they pass exclusion criteria and screen positive for the symptoms of PTSD with or without Depressive Symptoms. For the patient to be screened positive for the symptoms of PTSD, the patient should at least score 03 in each six criterions of the CAPS-V. For symptoms of depression, a cutoff score 50 on BDI-II will be applied. The rolling recruitment will be continued till a sample size of n = 120 is achieved. The participants will be stratified according to gender, age, symptom types, symptom severity and any previous history of trauma.

The participants will be randomly allocated either to EMDR or CBT with an allocation ratio of 1:1.

3.3. Data collection and screening tools

The selected patients will be initially screened (baseline/pre-treatment screening, T-1) for the symptoms of PTSD with or without comorbid DS (please refer to Table 2 for the list of screening tools). The suitable patients will be those who will be positive screened for symptoms of PTSD with or without comorbid DS. The suitable patients will be given treatment and will be assessed in the mid of treatment, normally after six weeks (during treatment screening, T-2). Once the treatment is completed, then patients will be once again assessed after 12 weeks (post-treatment assessment, T-3). Finally, the patients will be assessed after six months (follow up assessment, T-4). The patients will be assessed through blinded multi-informant assessment by taking information from the family members, therapists and even patients themselves. The family members will be asked to provide information about past family history of any psychiatric illness, moreover, they will be asked for family acceptance for treatment. The patients will be asked to provide socioeconomic and demographic information and information about perceived psychiatric symptoms. Finally, the therapist will be asked to provide information about treatment time, treatment

Table 2
List of assessment tools.

Psychiatric/Mental Health Symptoms	Assessment Tools and Sources	Time Point
Primary Outcomes		
Symptoms of PTSD	Clinician-Administered PTSD Scale-5 [39] PTSD Checklist for DSM-5 (civilian) [40]	T-1,T-2, T-3, T-4 T-1, T-2, T-3, T-4
Secondary Outcomes		
Symptoms of Depression	Beck Depression Inventory-II [41,42]	T-1,T-2, T-3, T-4
Other Measures	Socio-demographic characteristics of the patients EMDR Fidelity Rating Scale [43]	Start of treatment Each session

procedure, treatment response and any complications that might have occurred during the treatment process.

3.4. Treatment and interventions

Psychotherapeutic treatment will be provided by two to three psychotherapists (Clinical Psychologists), which will be either recruited from the selected centers or outsourced. These Clinical Psychologists will be licensed psychotherapists and will be specialized in EMDR and CBT psychotherapies. The psychotherapy sessions will depend on the severity of the symptoms and will range from minimum 06 sessions to maximum 14 sessions (normally one time per week). This range of sessions has been decided on the basis of existing practice adopted in previous studies like, e.g., Refs. [23,44]. The EMDR protocol include Standard EMDR Protocol for PTSD [45] and Trauma-focused Cognitive Behavioral Therapy [46]. As it is not known either CBT or EMDR is efficacious in Pakistan, therefore, non-inferiority and equivalence tests will be performed according to the guidelines provided by Refs. [47–49]. Moreover intention-to-treat analysis will be performed to avoid any misleading artifacts, e.g., dropouts or non-compliance [50] and per-protocol analysis will be performed on those patients who patients who complete all treatment sessions [51].

3.5. Ethics

Formal permission has been taken from the two rehabilitation centers to conduct this study. Moreover, written consent will be obtained from each participant at the start of treatment. The initial protocol was approved by the Institutional Review Board, under the Office of Research, Innovation and Commercialization of the Khushal Khan Khattak University, Karak, Pakistan on 31st January 2019, Letter No: 230/ORIC/Research/KKKUK/19.

3.6. Statistical analysis

Data will be analysed by SPSS-20. Missing data analysis will be performed and Little's test for missing completely at random will be run [52]. Variations in the symptoms with regard to demographic/baseline characteristics will be analysed by using descriptive statistics, χ^2 tests for categorical variables, t-tests, and one way ANOVA for continuous variables. Means and standard deviations of outcome variables will be used to compute effect sizes (Cohen's d) for the pre, during treatment, post treatment and 6 months follow up. Pearson Correlation Coefficients will be calculated to know the bivariate relationship between outcome variables. To check that data is free from reliability and validity issues, Cronbach's Alpha Coefficients will be calculated and detailed Factor Analysis (Exploratory Factor Analyses) will be also run.

To test hypothesis 01, i.e., compare the efficacy of the each treatment group, a series of General Linear Models with repeated measures MANOVA [53] will be run on the scores of outcomes variables during T-1, T-2, T-3 and T-4 for comparing EMDR with CBT across time. Furthermore, the non-inferiority tests will be performed according to the guidelines provided by Refs. [47–49] to compare the efficacy of each treatment group.

To test hypothesis 02, i.e., PTSD and comorbid symptoms will gradually decrease from high at pre-treatment stage (1st week) to lower at post-treatment stage (30th week) and follow up stage (6th month). A series of Linear Mixed Models (H [54]. will be run. The dependent variable will be outcome variables (e.g., PTSD at T2, T3 or T4), whereas the categorical variables, e.g., age, gender, time and treatment will be entered as factors, moreover variables, e.g., baseline scores of PTSD that are without any sort of coding will be entered as covariates. Time will be coded 0 for the baseline (week 1) and as 2, 3 and so on, representing weeks. On the other side, treatment will be coded as 0 for EMDR and 1 for CBT. Both fixed and random effects will be checked for knowing the main effects of treatment, the effects of time and the interaction effects of treatment*time on the outcome variables. An advantage of Linear Mixed Models is that they can help in testing whether time trajectory during pre, post and follow up treatment is different or same?

Finally, to test hypothesis 03, i.e., reduction in the PTSD symptoms will help in reducing comorbid depressive symptoms, a series of multi-level lagged mediation analysis along with moderated mediation analysis [55,56] will be performed to check the bi-directional mediation between changes PTSD (as mediator) and changes in outcome variables (depressive symptoms) over time. In other words, the PTSD (as mediator) and outcome variables (depressive symptoms) at each time point (baseline, mid-treatment, and post-treatment) will predict both PTSD (as mediator) and outcome variables (depressive symptoms) at the next time point (mid-treatment, post-treatment, and 06months follow-up). Lagged mediation will test following possibilities, which are consistent with the conditions set by Ref. [57] and applied to meditation framework by Ref. [58]; **a)** time directly predicts outcome variables, i.e., depressive symptoms, path = c; **b)** time predicts PTSD (mediator) path = a; **c)** PTSD (mediator) predicts outcome variables, i.e., depressive symptoms, path = b; **d)** both time and PTSD simultaneously predicts outcome variables, i.e., depressive symptoms, path = ab in such a way that reduction in PTSD symptoms over time will reduce the depressive symptoms. Time will be modeled as measurement number, beginning at 0.0 from baseline assessment and increasing by one for the subsequent assessments. The PTSD symptoms and depressive symptoms will be lagged so that particular symptoms at time_t (previous time T-1) will predict the other symptoms at Time t+1 (future time). This selected analytic approach will investigate mediation of change and not mediation of treatment, therefore, the predictor in mediation model will be time, whereas the treatment groups, i.e., EMDR or CBT will be used as moderators to know whether the treatment conditions moderate the relationship between predictors and outcome variables. Before running analysis, the model fit will be determined by statistical criteria, e.g., Akaike Information Criterion [59] and both linear and non-linear models will be compared and the best fit model will be selected. Analysis will be done by Hierarchical Linear or Non-Linear Modeling data analytic softwares, e.g., STATA-15 [60].

3.7. Duration of study

The duration of this study will range from ten to fifteen months. The duration will also depend on the post-treatment assessment of the patients. In case if the patients take longer time for giving response to the

psychotherapy, then this project will be extended to twenty months.

4. Discussion and conclusion

PTSD is caused by traumatic events and it is characterized by distressed recollection of the traumatic events [2]. PTSD often exists with comorbid Depressive Symptoms across various epidemiological samples [33]. Pakistan is continually suffering from the war on terrorism [9]. Such circumstances have created breeding grounds for PTSD in Pakistan. Therefore, there is a dire need of research on the management of PTSD in Pakistan. Recent research indicates that EMDR and CBT are effective treatment choices for both PTSD and Depressive Symptoms [5]. However, there is a paucity of research on the EMDR, mostly because it is relatively a recent intervention and few researchers have examined it. Therefore, this RCT sought to evaluate the efficacy of EMDR by comparing it with the CBT in the treatment of PTSD and comorbid Depressive Symptoms in Pakistan. This study will help to know whether EMDR will be non-inferior to CBT. Moreover, it will also help in knowing gradual changes in PTSD and Depressive Symptoms during and after treatment and the relationship between both symptoms.

The strengths of this RCT include 1) broader sample and multicenter study, which will provide a diverse group of participants for testing the efficacy of the newly developed EMDR therapy. In this way results of the current study can be subsequently generalized successfully. The involvement of a diverse sample will also give the potentials for a broader range of clinical judgments regarding the value of EMDR in comparison with CBT. This will be an important contribution since it will allow the researchers and clinicians to consider the EMDR therapy as an appropriate treatment, particularly in PTSD with or without Depressive Symptoms 2) manualized EMDR and CBT treatments with independent fidelity checks, which will help the therapists to adhere to the therapy's standard procedure; 3) six months follow-up assessment that can help in tracing any unresolved or recurring episodes of PTSD or Depressive Symptoms; 4) blinded and multi-informant diagnostic assessment will enable to collect information about the patients from therapists, family members of patients and even patients themselves. Such assessment will be helpful to determine the true etiology of PTSD and Depressive Symptoms; 5) multiple assessments, i.e., baselines, during treatment, post treatment and follow-up will give the true picture of changes in the level of PTSD and Depressive Symptoms, moreover, it will also help to know relationship of changes in the level of PTSD and Depressive Symptoms overtime.

Research on the evidence-based treatments for addressing PTSD and Depressive Symptoms comorbidity is critically important. We are expecting that the results obtained from this study will be a valuable addition to the existing literature, e.g., see Refs. [24,61] on the treatment of PTSD and Depressive Symptoms. Moreover, it will be an empirical contribution to the existing clinical practice. In this way the understanding about the efficacy of EMDR and CBT could be improved. The results obtained from this study are also expected to be relevant to the future research on the effectiveness of EMDR and CBT in the treatment of PTSD and Depressive Symptoms, especially in developing countries. To achieve such ends, the current study will be carried out through the collaborative efforts of a team of Clinical Psychologists with expertise in psychotherapeutic interventions; Psychometricians who can handle the analysis of multi-stage data; consent & cooperation of the patients; and most importantly the administrative support of the participating organizations.

Despite the major strengths of the current study, there are certain limitations, which need to be considered. As earlier mentioned, a formal sample size cannot be calculated at this protocol development stage because the exact number of PTSD patients located in the selected area is not known. Therefore, this study will initially rely on the figures provided by the participating organizations about the indoor and outdoor patients. The number of treatment sessions for both EMDR and

CBT will range from 06 minimum to 14 sessions maximum, although EMDR is considered to be a shorter treatment procedure as compared to CBT [22]. Such difference in treatment sessions may affect the our understanding about the efficacy of both treatments, especially in case of Treatment Resistant Patients, i.e., even after receiving at least six month treatment, show less than 30% symptoms reduction [30]. Another limitation is the baseline assessment will be done at one time point that may lead to the overestimation of the treatment effects because of the regression to the mean of extreme scores of PTSD or Depressive Symptoms. Problems may also arise due to language differences (since all of screening and assessment tools are in English), especially among the patients with low English language proficiency.

To conclude, the current study protocol has outlined the rationale for determining the efficacy of EMDR and CBT in the treatment of PTSD and comorbid Depressive Symptoms in a developing country. This RTC is innovative in the sense that its results will be helpful in answering a broad range of questions concerning the efficacy of newly developed evidence-based treatments. Such results may contribute to the refinement of such treatments, especially by tailoring it according to the local needs. Moreover, it may also guide the future research on the treatment of PTSD and comorbid Depressive Symptoms in the developing countries.

References

- [1] B. Bandelow, M. Koch, P. Zimmermann, K.-H. Biesold, D. Wedekind, P. Falkai, Posttraumatic stress disorder (PTSD) in the German Armed Forces: a retrospective study in inpatients of a German army hospital, *Eur. Arch. Psychiatry Clin. Neurosci.* 262 (6) (2012) 459–467.
- [2] A. Rasmussen, H. Smith, A.S. Keller, Factor structure of PTSD symptoms among west and central African refugees, *J. Trauma. Stress: Off. Publ. Int. Soc. Trauma. Stress Stud.* 20 (3) (2007) 271–280.
- [3] L.A. Brown, A. Jerud, A. Asnaani, J. Petersen, Y. Zang, E.B. Foa, Changes in post-traumatic stress disorder (PTSD) and depressive symptoms over the course of prolonged exposure, *J. Consult. Clin. Psychol.* 86 (5) (2018) 452–463 <https://doi.org/10.1037/ccp000292>.
- [4] D.J. Lee, C.W. Schnitzlein, J.P. Wolf, M. Vythilingam, A.M. Rasmusson, C.W. Hoge, Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systematic review and meta-analyses to determine first-line treatments, *Depress. Anxiety* 33 (9) (2016) 792–806.
- [5] A.M. Khan, S. Dar, R. Ahmed, R. Bachu, M. Adnan, V.P. Kotapati, Cognitive behavioral therapy versus eye movement desensitization and reprocessing in patients with post-traumatic stress disorder: systematic review and meta-analysis of randomized clinical trials, *Cureus* 10 (9) (2018) e3250–e3250 <https://doi.org/10.7759/cureus.3250>.
- [6] A.E. Kazdin, Mediators and mechanisms of change in psychotherapy research, *Annu. Rev. Clin. Psychol.* 3 (2007) 1–27.
- [7] L.I.M. Lenferink, E. Piersma, J. de Keijser, G.E. Smid, P.A. Boelen, Cognitive therapy and eye movement desensitization and reprocessing for reducing psychopathology among disaster-bereaved individuals: study protocol for a randomized controlled trial, *Eur. J. Psychotraumatol.* 8 (1) (2017) 1388710.
- [8] Mian, 50m Pakistanis Suffering from Mental Disorders, (2016) Retrieved from <https://www.dawn.com/news/1288880>.
- [9] T.M. Ali, S. Gul, Community mental health services in Pakistan: review study from muslim world 2000-2015, *Psychol. Community Health* 7 (1) (2018) 57–71.
- [10] M.T. Khalily, Mental health problems in Pakistani society as a consequence of violence and trauma: a case for better integration of care, *Int. J. Integr. Care* 11 (2011).
- [11] A. Bashir, The state of mental health care in Pakistan, *The Lancet Psychiatr.* 5 (6) (2018) 471 [https://doi.org/10.1016/S2215-0366\(18\)30191-3](https://doi.org/10.1016/S2215-0366(18)30191-3).
- [12] B.T. Shaikh, J. Hatcher, Complementary and alternative medicine in Pakistan: prospects and limitations, *Evid. Based Complement Altern. Med.* 2 (2) (2005) 139–142.
- [13] P. Leese, Shell Shock: Traumatic Neurosis and the British Soldiers of the First World War, Palgrave Macmillan UK, 2002 Retrieved from <https://books.google.com.pk/books?id=DfOSoAEACAj>.
- [14] E. Jones, S. Wessely, Shell Shock to PTSD: Military Psychiatry from 1900 to the Gulf War, Taylor & Francis, 2005 Retrieved from <https://books.google.com.pk/books?id=5xt5AgAAQBAJ>.
- [15] A.W. Burgess, L.L. Holmstrom, Rape trauma syndrome, *Am. J. Psychiatry* 131 (9) (1974) 981–986.
- [16] D.A. Regier, E.A. Kuhl, D.J. Kupfer, The DSM-5: classification and criteria changes, *World Psychiatry: Off. J. World Psychiatr. Assoc. (WPA)* 12 (2) (2013) 92–98 <https://doi.org/10.1002/wps.20050>.
- [17] I. Jarero, L. Artigas, S. Uribe, A. Miranda, EMDR therapy humanitarian trauma recovery interventions in Latin America and the Caribbean, *J. EMDR Pract. Res.* 8 (4) (2014) 260–268.
- [18] M. Price, K. van Stolk-Cooke, Examination of the interrelations between the factors

- of PTSD, major depression, and generalized anxiety disorder in a heterogeneous trauma-exposed sample using DSM 5 criteria, *J. Affect. Disord.* 186 (2015) 149–155.
- [19] F. Shapiro, M.S. Forrest, *EMDR: the Breakthrough Therapy for Overcoming Anxiety, Stress, and Trauma*, Basic Books, 2016 Retrieved from <https://books.google.com.pk/books?id=5-83DgAAQBAJ>.
- [20] J.S. Beck, J. Carlson, *Cognitive Therapy*, American Psychological Association, 2006.
- [21] J. Hunsley, K. Elliott, Z. Therrien, The efficacy and effectiveness of psychological treatments for mood, anxiety, and related disorders, *Can. Psychol./Psychol. Can.* 55 (3) (2014) 161.
- [22] C. de Roos, R. Greenwald, M. den Hollander-Gijsman, E. Noorthoorn, S. van Buuren, A. De Jongh, A randomised comparison of cognitive behavioural therapy (CBT) and eye movement desensitisation and reprocessing (EMDR) in disaster-exposed children, *Eur. J. Psychotraumatol.* 2 (1) (2011) 5694.
- [23] F. Horst, B. Den Oudsten, W. Zijlstra, A. de Jongh, J. Lobbstaal, J. De Vries, Cognitive behavioral therapy vs. Eye movement desensitization and reprocessing for treating panic disorder: a randomized controlled trial, *Frontiers in Psychology*, (2017) Retrieved from <https://www.frontiersin.org/article/10.3389/fpsyg.2017.01409>.
- [24] L. Ostacoli, S. Carletto, M. Cavallo, P. Baldomir-Gago, G. Di Lorenzo, I. Fernandez, Comparison of eye movement desensitization reprocessing and cognitive behavioral therapy as adjunctive treatments for recurrent depression: the european depression EMDR network (EDEN) randomized controlled trial, *Front. Psychol.* (2018).
- [25] Turk, Meichenbaum, A cognitive-behavioral approach to pain management, *The Evolution of Cognitive Behavior Therapy: A Personal and Professional Journey with Don Meichenbaum*, Taylor & Francis, 2017, pp. 132–154.
- [26] Francine Shapiro, EMDR, adaptive information processing, and case conceptualization, *J. EMDR Pract. Res.* 1 (2) (2007) 68–87.
- [27] M. Hase, U.M. Balmaceda, L. Ostacoli, P. Liebermann, A. Hofmann, The AIP model of EMDR therapy and pathogenic memories, *Front. Psychol.* 8 (2017) 1578 <https://doi.org/10.3389/fpsyg.2017.01578>.
- [28] J.A. Cully, A.L. Teten, A Therapist's Guide to Brief Cognitive Behavioral Therapy, Department of Veterans Affairs South Central MIRECC, Houston, 2008.
- [29] N. Jaberghaderi, R. Greenwald, A. Rubin, S.O. Zand, S. Dolatabadi, A comparison of CBT and EMDR for sexually-abused Iranian girls, *Clin. Psychol. Psychother.*: *Int. J. Theory Pract.* 11 (5) (2004) 358–368.
- [30] M. Zepeda Méndez, M.J. Nijdam, F.J.J. ter Heide, N. van der Aa, M. Olf, A five-day inpatient EMDR treatment programme for PTSD: pilot study, *Eur. J. Psychotraumatol.* 9 (1) (2018) 1425575.
- [31] P. Gauvreau, S. Bouchard, Preliminary evidence for the efficacy of EMDR in treating generalized anxiety disorder, *J. EMDR Pract. Res.* 2 (1) (2008) 26–40.
- [32] J. Sareen, Posttraumatic stress disorder in adults: impact, comorbidity, risk factors, and treatment. *Canadian Journal of Psychiatry*, *Rev. Canad. Psychiatr.* 59 (9) (2014) 460–467 <https://doi.org/10.1177/070674371405900902>.
- [33] J.D. Flory, R. Yehuda, Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations, *Dialogues Clin. Neurosci.* 17 (2) (2015) 141–150 Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/26246789>.
- [34] C.P. McLean, Y.-J. Su, J.K. Carpenter, E.B. Foa, Changes in PTSD and depression during prolonged exposure and client-centered therapy for PTSD in adolescents, *J. Clin. Child Adolesc. Psychol.: Off. J. Soc. Clin. Child Adolesc Psychol, Am. Psychol. Assoc., Div. 46* (4) (2017) 500–510 53 <https://doi.org/10.1080/15374416.2015.1012722>.
- [35] A.R. Jadad, M.W. Enkin, *Randomized Controlled Trials: Questions, Answers and Musings*, Wiley, 2008 Retrieved from <https://books.google.com.pk/books?id=6cmAur1f6MYC>.
- [36] D. Raghavarao, L. Padgett, *Repeated Measurements and Cross-Over Designs*, Wiley, 2014 Retrieved from <https://books.google.com.pk/books?id=t58yAwAAQBAJ>.
- [37] N. Moodley, B.J. Pillay, Post-traumatic stress disorder in patients with spinal-cord injuries, *S. Afr. J. Psychol.* 43 (2) (2013) 182–197.
- [38] K. Mathieson, Making sense of biostatistics: probability versus non-probability sampling, *J. Clin. Res. Best Pract.* 10 (8) (2014) 1–2.
- [39] Weathers, D.D. Blake, P.P. Schnurr, D.G. Kaloupek, B.P. Marx, T.M. Keane, The clinician-administered PTSD scale for DSM-5 (CAPS-5), Interview Available from the National Center for PTSD at www.Pttd.va.gov. Retrieved from, 2013. <http://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp>.
- [40] Weathers, B.T. Litz, T.M. Keane, P.A. Palmieri, B.P. Marx, P.P. Schnurr, The ptsd checklist for dsm-5 (pcl-5), Scale Available from the National Center for PTSD at, 2013. www.Pttd.va.gov.
- [41] R.A. Steer, R. Ball, W.F. Ranieri, A.T. Beck, Dimensions of the beck depression inventory-II in clinically depressed outpatients, *J. Clin. Psychol.* 55 (1) (1999) 117–128.
- [42] Ward Beck, Mock Mendelson, Erbaugh, An Inventory for Measuring Depression, *Archives of General Psychiatry*, 1961, <https://doi.org/10.1001/archpsyc.1961.01710120031004>.
- [43] D.L. Korn, L. Maxfield, R. Stickgold, N.J. Smyth, EMDR fidelity rating scale, Retrieved from, 2019. <https://emdrresearchfoundation.org/research-grants/emdr-fidelity-rating-scale/>.
- [44] C. Kullack, J. Laugharne, Standard EMDR protocol for alcohol and substance dependence comorbid with posttraumatic stress disorder: four cases with 12-month follow-up, *J. EMDR Pract. Res.* 10 (1) (2016) 33–46.
- [45] A.M. Leeds, Standard protocol for PTSD with the standard procedural steps for EMDR reprocessing, *A Guide to the Standard EMDR Therapy Protocols for Clinicians, Supervisors, and Consultants*, Springer Publishing Company, 2016, pp. 141–211.
- [46] S. Dorsey, E.C. Briggs, B.A. Woods, Cognitive-behavioral treatment for posttraumatic stress disorder in children and adolescents, *Child Adolesc. Psychiatr. Clin. North Am.* 20 (2) (2011) 255–269 <https://doi.org/10.1016/j.chc.2011.01.006>.
- [47] G. Piaggio, D.R. Elbourne, S.J. Pocock, S.J.W. Evans, D.G. Altman, C. Group, Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement, *Jama* 308 (24) (2012) 2594–2604.
- [48] E. Lesaffre, Superiority, equivalence, and non-inferiority trials, *Bull. Hosp. Joint Dis.* 66 (2) (2008) 150–154.
- [49] A.C. Leon, Comparative effectiveness clinical trials in psychiatry: superiority, non-inferiority and the role of active comparators, *J. Clin. Psychiatry* 72 (3) (2011) 331.
- [50] S.K. Gupta, Intention-to-treat concept: a review, *Perspect. Clin. Res.* 2 (3) (2011) 109–112 <https://doi.org/10.4103/2229-3485.83221>.
- [51] M. Suchmacher, M. Geller, *Practical Biostatistics: A Friendly Step-by-step Approach for Evidence-Based Medicine*, Elsevier Science, 2012 Retrieved from <https://books.google.com.pk/books?id=jYQ1Sk2aLgQC>.
- [52] R.J.A. Little, A test of missing completely at random for multivariate data with missing values, *J. Am. Stat. Assoc.* 83 (404) (1988) 1198–1202.
- [53] A. Rutherford, ANOVA and ANCOVA: a GLM Approach, John Wiley & Sons, 2011.
- [54] H. Brown, R. Prescott, *Applied Mixed Models in Medicine*, John Wiley & Sons, 2014.
- [55] D.J. Bauer, K.J. Preacher, K.M. Gil, Conceptualizing and testing random indirect effects and moderated mediation in multilevel models: new procedures and recommendations, *Psychol. Methods* 11 (2) (2006) 142.
- [56] D. MacKinnon, L.W. Cheong, A.G. Pirlott, Statistical mediation analysis, in: Cooper (Ed.), *APA Handbook of Research Methods in Psychology*, American Psychological Association, 2012.
- [57] R.M. Baron, D.A. Kenny, The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations, *J. Personal. Soc. Psychol.* 51 (6) (1986) 1173.
- [58] D.A. Kenny, J.D. Korchmaros, N. Bolger, Lower level mediation in multilevel models, *Psychol. Methods* 8 (2) (2003) 115.
- [59] H. Akaike, Factor analysis and AIC, *Selected Papers of Hirotugu Akaike*, Springer, 1987, pp. 371–386.
- [60] A. Stata, *STATA Structural Equation Modeling Reference Manual Release 15*, Citeseer, Texas, 2017 Retrieved from <https://www.stata.com/manuals/sem.pdf>.
- [61] C. de Roos, S. van der Oord, B. Zijlstra, S. Lucassen, S. Perrin, P. Emmelkamp, A. de Jongh, Comparison of eye movement desensitization and reprocessing therapy, cognitive behavioral writing therapy, and wait-list in pediatric posttraumatic stress disorder following single-incident trauma: a multicenter randomized clinical trial, *JCPP (J. Child Psychol. Psychiatry)* 58 (11) (2017) 1219–1228.