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### To prepare or not?

*Phase-based treatment versus direct trauma-focused treatment in patients with posttraumatic stress disorder related to childhood abuse*

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Noortje Inez van Vliet

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The studies presented in this thesis were conducted at Dimence Mental Health. During the last years Noortje van Vliet was also supported by GGZ Oost-Brabant in completing the work presented here.

Van Vliet, N. I.

To prepare or not? Phase-based treatment versus direct trauma-focused treatment in patients with posttraumatic stress disorder related to childhood abuse.

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ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

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# General Introduction

## 1. General Introduction

### *1.1 Introduction*

In 2012 the International Society for Traumatic Stress Studies (ISTSS) published expert consensus treatment guidelines for the treatment of patients with Complex Posttraumatic Stress Disorder (Complex PTSD; Cloitre et al., 2012). These guidelines were an addition to the PTSD guidelines from 2008 (Foa, Keane, Friedman & Cohen, 2009) and acknowledged that patients who were exposed to prolonged and repeated traumas might not fit in these regular PTSD guidelines because of the severity of symptoms they may display. Although Complex PTSD was not yet recognized as a separate classification at that time, the guidelines were an attempt to make recommendations for the treatment of this patient group, based on research and expert consensus.

In these ISTSS guidelines (2012) Complex PTSD was defined as a diagnosis that included the regular PTSD symptoms (reliving the trauma, avoidance, and hyper-arousal), with the addition of emotion regulation difficulties, disturbances in relational capacities, alterations in attention and consciousness (e.g., dissociation), adversely affected belief systems, and somatic distress or disorganization. This classification was seen as the result of exposure to repeated or prolonged interpersonal trauma, often occurring under circumstances difficult to escape from (Herman, 1992), like childhood abuse. The guidelines prescribed to treat these patients differently than patients with regular PTSD.

The guidelines proposed to treat patients with Complex PTSD using a phase-based treatment, instead of a direct trauma-focused treatment approach as prescribed for “regular” PTSD. A phase-based treatment exists of three phases in which the first phase is a preparation phase that focuses on ensuring the individual’s safety, reducing symptoms, and increasing important emotional, social and psychological competencies. The second phase is meant to

process unresolved traumatic experiences by a trauma-focused treatment. The third phase involves consolidation of treatment gains and using the learned skills in daily life.

Although the guidelines were based on study results and expert consensus, a lot of criticism raised after the publication of them (De Jongh et al., 2016) from experts not involved in the committee. They criticized the validity of the Complex PTSD construct, the selection procedure of the used studies, and the evidence of the used studies for using a phase-based approach instead of a trauma-focused approach. One of the raised questions in this debate was whether a phase-based approach really results in better treatment outcomes than a direct trauma-focused treatment in this patient group, as there had never been a head-to-head comparison. This question was a starting point for the present study.

### *1.2 The development of the Complex PTSD construct over time*

Although Complex PTSD was not yet an official classification at the start of the present study, the term Complex PTSD was already launched in 1992 by Judith Herman (1992) and was assumed to develop following the experience of severe, prolonged, and/or repeated interpersonal trauma. Herman pleaded for a separate diagnosis with symptoms like changes in affect regulation, consciousness, identity, perception of the perpetrator, and systems of meaning. These symptoms formed the basis for the diagnosis DES-NOS (Disorders of Extreme Stress Not Otherwise Specified; Van der Kolk et al., 2005), the former Complex PTSD diagnosis that involved the following symptoms; changes in affect regulation and impulses, changes in consciousness or attention, changes in self-esteem of identity, changes in relations with other persons, somatization and system of meaning. From that time the conceptualization of the concept Complex PTSD varied and has been named in various ways (ISTSS, 2012). The task force of the ISTSS guidelines tried to come to a single definition, and proposed that in addition to the symptoms of a posttraumatic stress disorder (reexperiencing,

avoidance/numbing, and hyper arousal), patients should exhibit in symptoms of five clusters: Emotion regulation difficulties, disturbances in relational capacities, alterations in attention and consciousness (e.g., dissociation), adversely affected belief systems, and somatic distress or disorganization (ISTSS, 2012). Although the DSM-5 never included a separate Complex PTSD classification, but added some symptoms to that of PTSD and distinguished the dissociative subtype (APA, 2013), the ICD-11 eventually included Complex PTSD that differed from the former suggested classification in the ISTSS guidelines of 2012 (ISTSS, 2012; WHO, 2018). To fulfil the diagnostic criteria of Complex PTSD a person would need to display, in addition to PTSD criteria, disturbances in three domains of self-organization (DSO): Affect dysregulation, negative core beliefs, and interpersonal problems.

The ISTSS Guidelines (2012) also assert, like Herman (1992) already did, that childhood abuse is one of the trauma types that increases the risk to develop Complex PTSD. In the past decades proof increased that the survival of childhood abuse is indeed related to more and more severe symptoms than the survival of a single trauma (Cloitre, Miranda, Stovall-McClough, & Han, 2005; Gekker et al., 2018; Messman-Moore & Bhuptani, 2017) and that the survival of childhood abuse is more common among patients with Complex PTSD than patients with regular PTSD (Rink & Lipinska, 2020) .

### *1.3 Development of PTSD treatment for patients with a history of childhood abuse*

There is considerable evidence that EMDR and trauma-focused Cognitive Behavioral Therapy are effective for the treatment of PTSD (Mavranouzouli et al., 2020). But there is some evidence that childhood onset traumas may lead to poorer PTSD treatment outcomes than adulthood trauma (Karatzias et al., 2019). These outcomes confirm the idea of the ISTSS Complex PTSD guidelines of 2012, that this patient group is at risk for less profitable PTSD treatment outcomes. It was argued that patients with Complex PTSD might have problems to

regulate their emotions and tolerate the distress of a trauma-focused treatment (Cloitre et al., 2002) and that they might need a skills training to improve their skills of self-organization, such as emotion regulation and interpersonal skills, in order to decrease the distress and to better tolerate the trauma-focused treatment (Cloitre et al., 2002). Opponents of this approach argue that evidence that a phase-based approach is more effective than a trauma-focused approach and that a trauma-focused approach is not safe, is lacking (De Jongh et al., 2016). They argue that the use of a phase-based approach is an unnecessary delay of an evidence-based PTSD treatment for this patient group.

In 2018 the ISTSS published a Guideline Position Paper on Complex PTSD in Adults (ISTSS, 2018). These guidelines were an adaptation to the former guidelines, explaining the status of Complex PTSD classification to enable evidence based treatments and giving future recommendations. By that time Complex PTSD was already established within the ICD-11 (WHO, 2018), although the DSM-5 did not develop a Complex PTSD classification (APA, 2017). The committee argues that this may not necessarily lead to differences in treatment recommendation, but instead pleads for personalized treatment. This approach suggests the identification of clinically significant symptoms in the individual patient and the adjustment of interventions towards the needs of the individual patients (ISTSS, 2018). Their future research recommendations are to study whether added interventions to established treatments may lead to better treatment outcomes. Another implication of a personalized treatment is that predictors for worse treatment outcomes or dropout and moderators between treatment interventions and treatment gain should be studied.

#### *1.4 Research questions and outline of this thesis*

From the paragraphs above it can be concluded that there is a clear need for more knowledge about the treatment of patients with a PTSD resulting from repeated childhood abuse. One of

the questions is whether a phase-based treatment is more effective than a trauma-focused treatment in this patient group. In addition, it is unclear whether specific patient characteristics do predict worse PTSD treatment outcomes in this patient group, and whether some characteristic moderate between treatment condition and PTSD gain scores. Furthermore, it is unknown what patient characteristics do predict dropout from PTSD treatment. Finally, the question raises whether a phase-based treatment is more cost-effective than a trauma-focused treatment only. These research questions will be addressed in the chapters 2 to 7.

Chapter 2 describes the theoretical basis for this study and the study protocol. It describes where the study was based on and what choices were made in designing the study. Chapter 3 answers the main study question whether a phase-based treatment is more effective than a trauma-focused treatment concerning PTSD symptoms, symptoms of Complex PTSD, dissociation and general psychopathology. Chapter 4 answers the question whether some baseline characteristics do predict PTSD treatment gain or do moderate between condition and PTSD treatment gain. The predictor and moderators are chosen based on literature and theoretical constructs and clear hypotheses are formulated to test whether they are confirmed or not, in order to answer some important questions in the field of Complex PTSD treatment. In the fifth chapter a PAI analysis is performed. Moderators and predictors were selected by machine learning, without theory-based hypotheses, in order to include all the baseline characteristics of participants in this study. Once the moderators and predictors were selected the PAI clarified whether patients receiving their PAI indicated treatment did have significantly higher treatment gain than patients receiving their non-PAI indicated treatment. In chapter 6 predictors for dropout are selected by machine learning, with the inclusion of all the pre-treatment characteristics. In chapter 7 a cost-effectiveness analysis is described, comparing a phase-based treatment with a trauma-focused treatment, answering the question

whether a phase-based treatment or a direct trauma-focused treatment is more cost-effective compared to the other treatment choice. In chapter 8 the findings of the chapters 2 to 7 will be discussed. Chapter 8 gives a summary of the complete dissertation.



## References

- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, DSM-5*.
- American Psychiatric Association (2017). *Diagnostic and statistical manual of mental disorders* (5th ed.).
- Cloitre, M., Courtois, C. A., Charuvastra, A., Carapezza, R., Stolbach, B. C., & Green, B. L. (2011). Treatment of complex PTSD: results of the ISTSS expert clinician survey on best practices. *Journal of Traumatic Stress, 24*(6), 615–627.  
<https://doi.org/10.1002/jts.20697>
- Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., Herman, J. L., Lanius, R., Stolbach, B. C., Spinazolla, J., Van der Kolk, B. A., & Van der Hart, O. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in adults*.  
<https://terrorvictimresponse.ca/wp-content/uploads/ISTSS-Expert-Concesnsus-Guidelines-for-Complex-PTSD-Updated-060315.pdf>
- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han, H. (2002). Skills training in affective and interpersonal regulation followed by exposure: A phase-based treatment for PTSD related to childhood abuse. *Journal of Consulting and Clinical Psychology, 70*(5), 1067–1074. <https://doi.org/10.1037//0022-006x.70.5.1067>
- Cloitre, M., Miranda, R., Chase Stovall-McClough, K., & Han, H. (2005). Beyond PTSD: Emotion regulation and interpersonal problems as predictors of functional impairment in survivors of childhood abuse. *Behavior Therapy 36*(2), 119-124.  
[https://doi.org/10.1016/S0005-7894\(05\)80060-7](https://doi.org/10.1016/S0005-7894(05)80060-7)
- De Jongh, A., Resick, P. A., Zoellner, L. A., van Minnen, A., Lee, C. W., Monson, C. M., Foa, E. B., Wheeler, K., Broeke, E. T., Feeny, N., Rauch, S. A., Chard, K. M., Mueser, K. T., Sloan, D. M., van der Gaag, M., Rothbaum, B. O., Neuner, F., de Roos, C.,

- Hehenkamp, L. M., Rosner, R., ... Bicanic, I. A. (2016). Critical analysis of the current guidelines for Complex PTSD in adults. *Depression and Anxiety, 33*(5), 359–369. <https://doi.org/10.1002/da.22469>
- Foa, E. B., Keane, T. M., Friedman, M. J., & Cohen, J. A. (2009). *Effective treatments for PTSD: Practice guidelines from the International Society for Traumatic Stress Studies* (2nd ed.). The Guilford Press.
- Gekker, M., Coutinho, E. S. F., Berger, W., Luz, M. P. D., Araújo, A. X. G., Pagotto, L. F. A. D. C., Marques-Portella, C., Figueira, I., & Mendlowicz, M. V. (2018). Early scars are forever: Childhood abuse in patients with adult-onset PTSD is associated with increased prevalence and severity of psychiatric comorbidity. *Psychiatry Research, 267*, 1–6. <https://doi.org/10.1016/j.psychres.2018.05.042>
- Herman, J. L. (1992). Complex PTSD: A syndrome of survivors of prolonged and repeated trauma. *Journal of Traumatic Stress, 5*, 377-391.
- Karatzias, T., Murphy P., Cloitre, M., Bisson, J., Roberts, N., Shevlin, M., Hyland, P., Maercker, A., Ben-Ezra, M., Coventry, P., Mason-Roberts, S., Bradley, A., & Hutton, P. (2019). Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. *Psychological Medicine, 49*(11), 1761-1775. <https://doi.org/10.1017/s0033291719000436>
- Kolk, B. A. van der, Roth, S., Pelcovitz, D., Sunday, S., & Spinazzola, J. (2005). Disorders of extreme stress: the empirical foundation of a complex adaptation to trauma. *Journal of Traumatic Stress, 18*(5), 389-399. <https://doi.org/10.1002/jts.20047>
- Mavranouzouli, I., Megnin-Viggars, O., Daly, C., Dias, S., Welton, N.J., Stockton, S., Bhutani, G., Grey, N., Leach, J., Greenberg, N., Katona, C., El-Leithy, S., & Pilling, S. (2020). Psychological treatments for post-traumatic stress disorder in adults: a network meta-

analysis. *Psychological Medicine*, 50(4), 542-555.

<https://doi.org/10.1017/s0033291720000070>

Messman-Moore, T. L., & Bhuptani, P. H. (2017). A review of the long-term impact of child maltreatment on posttraumatic stress disorder and its comorbidities: An emotion dysregulation perspective. *Clinical Psychology: Science and practice*, 24(2), 154–169. <https://doi.org/10.1111/cpsp.12193>

Rink, J., & Lipinska, G. (2020). Evidence of distinct profiles of ICD-11 post-traumatic stress disorder (PTSD) and complex PTSD in a South African sample. *European Journal of Psychotraumatology*, 11(1), Article 1818965.

<https://doi.org/10.1080/20008198.2020.1818965>

World Health Organization (2018). *The ICD-11 for mortality and morbidity statistics*. WHO, Retrieved from: <https://icd.who.int/browse11/l-m/en>

**Phase-Based Treatment versus Immediate Trauma-Focused Treatment in Patients with Childhood Trauma-Related Posttraumatic Stress Disorder: Study Protocol for a randomized controlled trial**

Noortje van Vliet  
Rafaele Huntjens  
Maarten van Dijk  
Ad de Jongh

**Abstract***Background*

The treatment of posttraumatic stress disorder (PTSD) related to a history of sexual and/or physical abuse in childhood is the subject of international debate, with some favoring a phase-based approach as their preferred treatment, while others argue for an immediate trauma-focused treatment. A history of (chronic) traumatisation during childhood has been linked to the development of distinct symptoms, that are often labelled as symptoms of Complex PTSD. Many therapists associate the presence of symptoms of Complex PTSD with a less favourable treatment prognosis. The purpose of this study is to determine whether a phase-based approach is more effective than a stand-alone trauma-focused therapy in individuals with PTSD and possible symptoms of Complex PTSD resulting from a history of repeated sexual and/or physical abuse in childhood. An additional aim is to investigate moderators, predictors of treatment (non) response and drop-out.

*Method*

The sample consists of patients between 18 and 65 years with a diagnosis of PTSD who report a history of repeated sexual and/or physical abuse in childhood ( $N = 122$ ). Patients will be blindly allocated to either 16 sessions eye movement desensitization and reprocessing (EMDR) therapy preceded by a stabilization phase (eight sessions Skills Training in Affect and Interpersonal Regulation, STAIR) or only 16 sessions of EMDR therapy. Assessments are carried out at pre-treatment, after every eighth session, post-treatment, and at three and six months follow-up. The main parameter will be the severity of PTSD symptoms (PTSD Symptoms Scale-Self Report). Secondary outcome variables are the presence of a PTSD diagnosis (Clinician-Administered PTSD Scale for DSM-5), severity of Complex PTSD symptoms (Structured Interview for Disorders of Extreme Stress-Revised and symptoms specific questionnaires), changes in symptoms of general psychopathology (Brief Symptom

Inventory), and quality of life (EQ5D). Health care consumption and productivity loss in patients will also be indexed.

### *Discussion*

The study results may help to inform the ongoing debate whether a phase-based approach has added value over immediate trauma-focused therapy for patients suffering from PTSD due to childhood abuse. Furthermore, the results will contribute to the knowledge about safety, efficacy, and cost-effectiveness of treatments for this target group.

Keywords: PTSD, Complex PTSD, trauma-focused therapy, treatment, STAIR, EMDR

## Background

For posttraumatic stress disorder (PTSD), international expert consensus guidelines recommend the use of evidence-based, trauma-focused psychological treatments, particularly cognitive behavioral therapy (i.e., prolonged exposure) and Eye Movement Desensitization and Reprocessing (EMDR) therapy (National Collaborating Centre for Mental Health, 2005; WHO, 2013). For PTSD following childhood abuse, the application of trauma-focused treatments is generally associated with reductions in PTSD symptom severity and comorbid symptoms of depression, anxiety, and dissociation (Ehring et al., 2014; Foa et al., 2013; Mueser et al., 2008; Resick et al., 2002; Resick et al., 2003).

Childhood physical and/or sexual abuse is considered to be one of the traumatic stressors associated with the development of Complex PTSD (Cloitre et al., 2012). The term Complex PTSD was first launched by Herman (1992) and is assumed to develop following the experience of severe, prolonged, and/or repeated interpersonal trauma. Complex PTSD is diagnosed when, in addition to meeting criteria for PTSD, trauma survivors exhibit disturbances in three domains of self-organization: affect regulation, self-concept, and interpersonal functioning (Cloitre et al., 2013), and is currently being considered for inclusion as a separate diagnostic entity in International Classification of Diseases (ICD-11) (Maercker et al., 2013).

It has been argued that individuals with a history of childhood abuse who suffer from symptoms of Complex PTSD may be insufficiently stable to tolerate an evidence-based immediate trauma-focused treatment (Cloitre et al., 2012; Cloitre et al., 2010). In 2011 the International Society for Traumatic Stress Studies (ISTSS) Complex Trauma Task Force published the results of a survey meant to obtain expert opinions about the treatment of patients with symptoms of Complex PTSD (Cloitre et al., 2011) showing that 85% of the experts reported that they would use a phase-based approach as their first line of treatment.

Based upon these results, a phase-based treatment has been recommended for these patients (Cloitre et al., 2012), in which trauma-focused treatment (phase II) is preceded by a stabilization phase (phase I) aimed at ensuring the individual's safety, reducing self-regulatory problems, and improving emotional, social, and other psychological skills. This phase-based approach is then completed with a reintegration phase (phase III), aimed at consolidating treatment gains and helping the person to adapt to his or her present life circumstances (Cloitre et al., 2012). In clinical practice, the phase I treatment for PTSD with symptoms of Complex PTSD varies from 8 weekly sessions (i.e., the program STAIR, Skills Training in Affective and Interpersonal Regulation; Cloitre et al., 2002) up to programs with a much longer duration (Dorrepaal et al, 2008; Zlotnick et al., 1997). In the guidelines of the International Society for Traumatic Stress Studies (ISTSS) the majority of the experts considered 6 months as a reasonable length for phase I (Cloitre et al., 2012).

Until now, the safety and efficacy of the phase-based treatment approach for treating Complex PTSD has been addressed in two studies (Cloitre et al., 2002; Cloitre et al., 2010). The first study used a randomized controlled trial (RCT) to compare the efficacy of STAIR (a phase I treatment) followed by prolonged exposure versus a waiting-list condition in a sample of female patients that suffer from PTSD as a result of childhood physical and/or sexual abuse (Cloitre et al., 2002). Significant symptom reductions were found in the STAIR/Exposure condition (i.e., PTSD severity, depression, general anxiety, dissociation), including mood and anger regulation skills improvement. Depression, anxiety, anger expression, and negative mood regulation improved significantly in the STAIR phase. No improvements were found in PTSD symptoms, dissociation, and alexithymia. PTSD symptoms, dissociation and alexithymia were reduced in the prolonged exposure (PE) phase, just as depression and anxiety. Negative mood regulation and in anger expression did not improve in the PE phase. The findings of this study indicate that the combination of STAIR/Exposure is feasible and



results in a reduction of PTSD as well as a variety of symptoms associated with Complex PTSD. One limitation of this study, however, was the relatively high drop-out rate in the STAIR/exposure condition (29% against 11% in the waiting list control group). Also, effect sizes pointed to the phase of exposure treatment conferring the bulk of the therapeutic benefits. Hence, although this study supports the effectiveness of a STAIR/exposure combination, the results do not provide univocal support for the contention that a phase-based treatment is superior to immediate trauma-focused treatment for individuals suffering from severe PTSD and symptoms of Complex PTSD (see also Cahill et al., 2004). Clearly, there was a need for a direct comparison between a phase-based and an immediate trauma-focused treatment condition. Accordingly, in a second study, Cloitre and colleagues evaluated the efficacy of a phase-based treatment approach (STAIR/exposure) in comparison to two other interventions: Supportive counselling followed by prolonged exposure (Support/ Exposure) and STAIR followed by supportive counselling (STAIR/support) (Cloitre et al., 2010). Women with PTSD related to childhood sexual and/or physical abuse were assigned to one of the three treatment conditions. The application of STAIR/exposure demonstrated superior outcomes compared to the support/exposure condition in terms of self-reported reduction in PTSD symptom severity, interpersonal problems, and emotion regulation, but only at follow-up (both 3 and 6 months). Immediately post-treatment, all three experimental treatment conditions led to a significant proportion of patients being PTSD negative, while no notable differences among the three conditions were observed. However, the absence of a treatment condition wherein patients were directly confronted with their traumatic memories prevents making definitive conclusions about the comparative advantages of a phase-based treatment strategy versus an immediate trauma-focused approach for individuals suffering from PTSD related to childhood abuse (see De Jongh et al., 2016). In other words, the core question is still whether the addition of a stabilization phase is a necessary condition for, and/or has added

value over, immediate trauma-focused treatment. And if so, it is important to know which of the two treatment approaches works best for whom. The present study aims to address these questions.

## **Methods/design**

### *Aim*

The purpose of the current study “ToPrepareOrNot” (TOPRON), is to determine whether a phase-based approach is more effective than an immediate trauma-focused treatment in individuals with PTSD related to repeated childhood abuse, and possible symptoms of Complex PTSD. For the trauma-focused condition we used eye movement and desensitization and reprocessing (EMDR) therapy, because it is one of the guideline treatments for PTSD (WHO., 2013) with an efficacy similar to PE. Our first hypotheses is based upon the current guidelines for the treatment of Complex PTSD (Cloitre et al., 2012), and expert consensus about the treatment of this target population (Cloitre et al., 2011); that is, that the phase-based treatment condition (i.e., STAIR/EMDR) is significantly more effective in PTSD (severity of PTSD symptoms and proportion of diagnoses lost) than the immediate trauma-focused condition (i.e., EMDR/EMDR). Our second hypothesis is that the phase-based treatment approach leads to a significantly better outcome in terms of reduced symptoms of Complex PTSD and comorbid symptoms, drop-out rate, quality of life, and health care consumption than the immediate trauma-focused condition. An additional aim is to investigate potential moderators and predictors of drop-out or treatment (non) response. To this end, we hypothesized that signs of affect dysregulation and having interpersonal problems at the start of therapy would be related to worse outcome in the trauma-focused condition (Cloitre et al., 2016; Dorrepaal et al., 2014). We also expect patients with a comorbid personality disorder

(Cloitre et al., 2014) and high level of dissociation at the start of therapy (Bae et al., 2016) to be more at risk for deterioration and drop-out in both conditions.

### *Study design*

The TOPRON study entails a randomized controlled trial with two arms: A phase-based treatment approach (STAIR-EMDR) versus a trauma-focused treatment condition (EMDR therapy only). In the STAIR-EMDR condition, patients will receive eight sessions of stabilization treatment (STAIR), followed by 16 sessions of EMDR therapy, adding up to a total number of 24 treatment sessions. In the trauma-focused condition, patients will receive 16 sessions of EMDR therapy. All sessions last 90 minutes. The two groups will be compared on a number of variables before treatment, after every eighth session, post-treatment and at follow-up, that is three months and six months after the post-treatment session (see Figure 1 and 2). By assessing every eight sessions it will be possible to determine the added value of a stabilization phase examining the results after an equal amount of sessions. For this study, we chose to use a fixed number of sessions. All patients in the STAIR-EMDR condition will receive eight sessions STAIR while in both conditions patients will receive a maximum of 16 sessions EMDR. When all targets are processed to a SUD (Subjective Unit of Distress) score of 0 and a VoC (Validity of Cognition) score of 7, the patient will be assessed to determine whether he or she no longer meets the criteria of PTSD. In case of early completion, the remaining sessions are cancelled. Because STAIR is meant as a first-phase treatment prior to the start of trauma-focused treatment (i.e., EMDR therapy) following STAIR, all patients will receive EMDR Therapy. That is the reason that early completion during STAIR is not possible.

### *Research setting*

Patients will be recruited from various departments of Dimence, a large mental health organization in the east of the Netherlands. Dimence specialises in treating patients with severe mental illnesses.

### *Participants*

The inclusion criteria are a) age between 18 and 65 years, b) diagnosis of PTSD according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5; APA, 2013), and c) victim of repeated sexual and/or physical abuse before the age of 18 by a carer or a person in a position of authority (i.e., with repeated abuse defined as more than one incident by the same or different perpetrator[s]). The exclusion criteria are a) insufficient proficiency in the Dutch language, b) high risk of suicidality assessed by the Beck Depression Inventory (BDI)-II (Beck et al., 1996), c) treatment for PTSD in the past year with at least eight sessions (EMDR, prolonged exposure or any well evaluated stabilization program) d) alcohol or drug dependence or abuse according to DSM-IV-TR (APA, 2000) e) mental retardation, and f) victim of ongoing physical and/or sexual abuse.

### *Interventions*

STAIR (Cloitre et al., 2002) will be applied in the first treatment phase (phase I, stabilization). The goals of this treatment are (a) addressing problems in affect and interpersonal regulation and (b) preparing the individual for the effective and successful use of the trauma-focused treatment (Cloitre et al., 2002). The program consists of eight sessions with different topics (introduction, emotional awareness, emotion regulation, emotionally engaged living, understanding relationship patterns, changing relationship patterns, agency in relationships, and flexibility in relationships). All STAIR sessions have more or less an identical format and structure: psycho-education about the rationale and goals of the interventions, skills acquisition, skills application, and practice. The therapeutic techniques employed include for

example identifying and exploring cognitive schemes, role-playing, behavioral exercises at home, and respiration exercises.

The trauma-focused element in therapy will be EMDR therapy which is a protocolized evidence-based trauma treatment, aimed at resolving symptoms as a result from disturbing or unprocessed life experiences (Shapiro, 2001). The treatment starts with recalling the traumatic memory and selecting the most distressing part of this memory with associated dysfunctional thoughts and feelings about oneself. Whilst concentrating on the traumatic memory, the patient is asked to follow the therapists' fingers with his/her eyes, while being encouraged to follow every association that comes up in the patient's mind. Repeatedly the patient is asked to report the experiences that come up, which may be cognitive, emotional, somatic, or imaginary. After some sets of eye movements, the patient is asked to report a SUD (Subjective Unit of Disturbances) between 0 and 10, until the disturbance related to the memory reaches a SUD of zero and positive beliefs about oneself related to the trauma are rated as feeling true on a VoC scale of 1-7. Like previous studies (Van den Berg et al., 2015), we removed stabilization elements (e.g., establishing a 'safe place') from the EMDR Standard protocol to avoid interference with the stabilization condition to assure an absolute distinction between the two conditions. Like STAIR, EMDR therapy will be offered twice a week in this study.

All participating therapists hold a post-Master's psychology degree, have completed a STAIR training and advanced training in EMDR therapy, and will provide therapy in both treatment conditions. They will be supervised by experienced trainers who were trained by the originators of both treatment protocols (i.e., Shapiro and Cloitre). Adherence to treatment will be encouraged in several ways. Prior to the start of treatment, a supervised case-conceptualisation will be made in order to plan the treatment sessions. Furthermore, the therapists will be asked to fill out protocol-specific checklists and to explicitly report and

explain deviations from the treatment protocol after each session. In addition, all treatment sessions will be recorded on video and a random selection of these recordings will be evaluated during monthly group supervision meetings (one hour for EMDR therapy and one hour for STAIR). Additional supervision will be provided via e-mail and telephone upon request from the therapist. Ultimately, a random selection of individual therapy sessions (33%) will be rated for adherence by two trained psychology graduates using both EMDR and STAIR specific fidelity checklists.

### *Procedures*

During the regular intake procedure conducted by a clinician not involved in this study and without influence on assignment to the conditions, patients with PTSD due to repeated sexual and/or physical abuse during childhood will be asked to participate in the study. After their approval by signing an informed consent form, they will be assessed on the inclusion and exclusion criteria.

After assessment for eligibility (T0) and baseline assessment (T1; see Figure 1), the patients will be randomly assigned to one of the two conditions. The randomization will be executed by a computerized randomization program (Sealed Envelope, 2016), creating a list of randomized assignment per location (strata). Randomization blocks of six or eight will be employed (divided over four strata based on treatment location) and generated by a study-independent collaborator. The assignments will be put into envelopes per location and will be picked for each patient in order from top to bottom as listed by the computerized randomization. Within each randomly assigned condition, the participants will be assigned to one of the therapists, based on availability. During treatment, assessments will take place after every eight sessions, post-treatment, and at three and six months follow-up.

Due to the nature of the trial, participants and clinicians in the study cannot be blinded to treatment assignment. The research assistants (students studying for Master's degree in

psychology), who will carry out the assessments, will attend an intensive training concerning the interviews and do not have any interest in the outcomes of this study.

### *Assessments*

**Assessment of eligibility for inclusion.** Eligibility for inclusion of patients will be assessed by using the Clinician-Administered PTSD scale for DSM-5 (CAPS-5) (Weathers et al., 2013; Boeschoten et al., 2014). A symptom is considered present only if the corresponding severity score is rated two or higher (on a 0 to 4 scale) (Weathers et al., 2013). When a patient scores positive on all the symptoms belonging to PTSD, the diagnosis is established. As part of the CAPS-5, the Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013), will be used to screen and identify repeated or multiple sexual and/or physical abuse before the age of 18 by a carer or other person in a position of authority. In order to exclude patients with high risk of suicidality, those with a score of 3 on item 9 of the Beck Depression Inventory (BDI-II; Beck et al., 1996; Van der Does, 2002) will be excluded.

**Main outcome variable.** The main study parameter will be the severity of PTSD symptoms, assessed by the PTSD Symptoms Scale-Self Report (Foa et al., 1993; Arntz, 1993). This is a 17-item self-report scale developed as a brief measure of PTSD symptom frequency in trauma victims. Items are scored on a four-point scale from 0 ('not at all/only one time') to 3 ('almost always/five or more times a week'). The English version (Foa et al., 1993) and Dutch version (Arntz, 1993) showed good psychometric properties

**Secondary outcome variables.** As a secondary outcome variable, the presence of a PTSD diagnosis will be assessed with the CAPS-5 (Weathers et al., 2013; Boeschoten et al., 2014). The questions in the CAPS-5 about trauma clusters (the sexual and / or physical abuse) will be asked instead of traumatic events, as all the participants were exposed to multiple or repeated trauma. The CAPS-5 will also be used for deciding whether a patient is an early completer or not.

At the moment, a validated interview or questionnaire adhering to the ICD-11 criteria for Complex PTSD is not available. We will therefore use the Structured Interview for Disorders of Extreme Stress-Revised (SIDES-R) (Scobordia et al., 2008), more specifically the 37-item version developed by Ford et al. (2006), as the best available instrument to assess the severity of Complex PTSD symptoms. In addition, validated questionnaires measuring the different Complex PTSD symptoms will be used. More specifically, to index trauma-related thoughts and beliefs, the Posttraumatic Cognitions Inventory (PTCI) (Foa et al., 1999) will be used. Patients have to score on a likert-scale from 1 (I totally disagree) to 7 (I totally agree). Psychometric properties for the English and Dutch (Foa et al., 1999; Van Emmerik et al., 2007) version were found to be good. Trait dissociation will be measured using the Dissociative Experiences Scale (DES-II; Carlson & Putman, 1993). The DES-II is a 28-item self-report questionnaire with scores ranging from 0 to 100. Scores above 20 or more conservatively, above 30 suggest pathological dissociation. The DES has been used in well over 200 published studies and its psychometric properties are well-attested (Van IJzendoorn et al., 1996). To index interpersonal difficulties, the Inventory of Interpersonal Problems (IIP) will be used (Horowitz et al., 2000; Vanheule et al., 2006). Each of the 32 items of the IIP can be scored on a five-point scale from 0 (not at all) to 4 (very strongly). The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004), (Neumann A, Koot H. Nederlandse vertaling van de Difficulties in Emotion Regulation Scale, unpublished) will be used to measure difficulties in emotion regulation. Each item is rated on a 5-point scale and has been validated for clinical (Fox et al., 2006; Gratz et al., 2008) and nonclinical populations (Gratz & Roemer, 2004; Johnson et al., 2008).

The brief Symptom Inventory (Derogatis, 1975; De Beurs, 2006) will be used to measure symptoms of general psychopathology. This is a self-report instrument measuring severity of complaints. Each item can be rated on a 5-point scale from 0 (not at all) to 4 (a



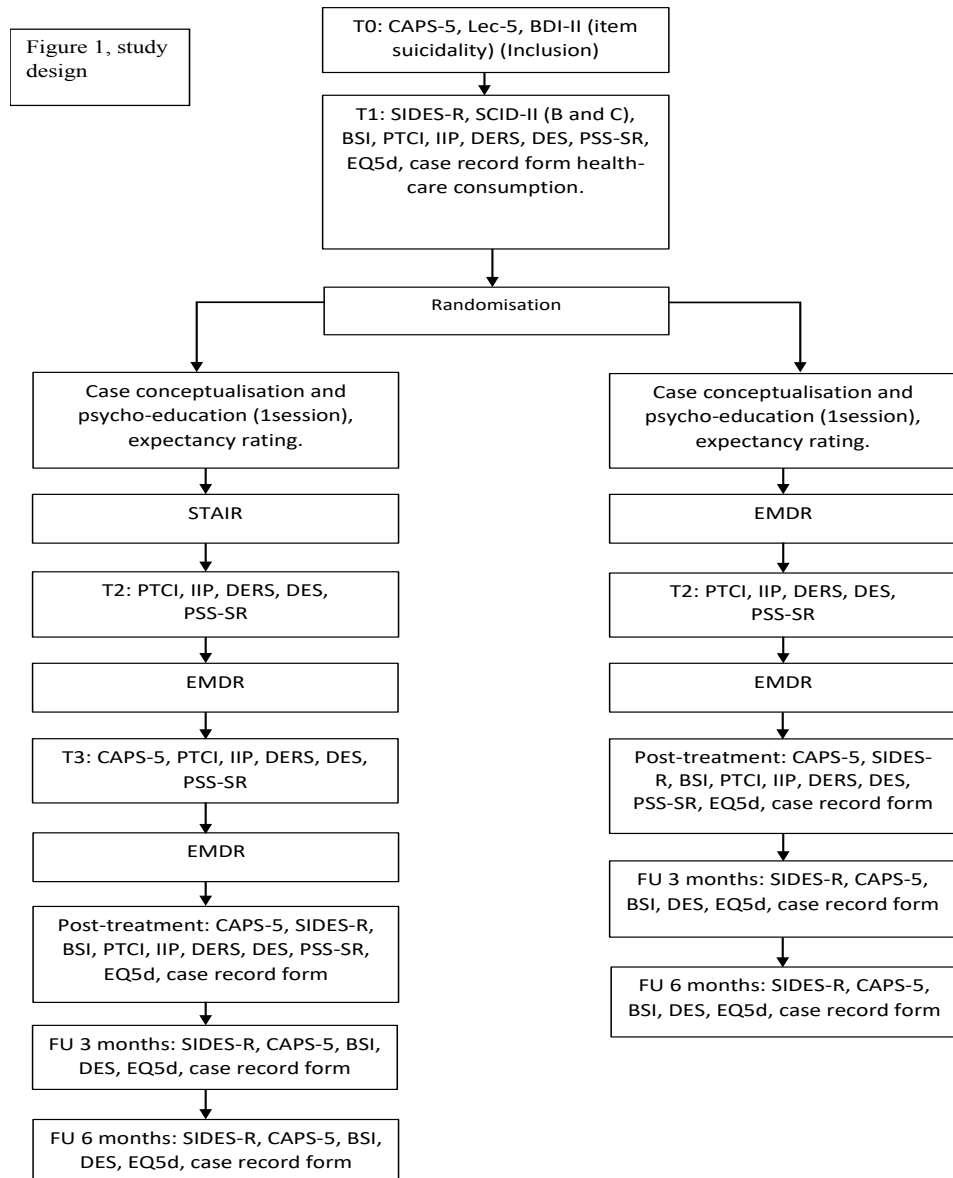
lot). The reliability, validity, and utility of the BSI have been tested in more than 400 research studies (Derogatis et al., 1983; De Beurs et al., 2006).

The Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID-II; First et al., 1997) will be used to determine the presence of a personality disorder (cluster B and C). This interview is considered as the gold standard in semi-structured assessment instruments for personality disorders. The Dutch translation and adaptation was developed by Weertman et al., (2000) and validated by Weertman et al., (2003).

The EQ-5D will be used to index health-related quality of life (EuroQol, 1990). This is a questionnaire consisting of five dimensions with three levels each (from having no problems until being unable to execute an activity). The questionnaire has been validated for different groups and in different countries (EuroQol Group).

Health care consumption and productivity loss in patients will be indexed to measure the cost-effectiveness of both treatments, using a case record form based on a form in other studies (Stant et al., 2007; Van der Gaag et al., 2011; Van Apeldoorn et al., 2014).

Other variables that will be included in the study are age and gender of the participating patients, as well as socio-economic status, psychotropic medication use at baseline and during treatment, and level of education. After the first session in which psycho-education is given and a case-conceptualization is made, the expectancy rating of the therapist and the patient will be measured by asking to what extent they expect that the patient will profit from the treatment that he or she is allocated to using a VAS-scale from 0 (not at all) to 100 (totally). Drop-out rate and deterioration of the patient will be registered (i.e., the number of extra face-to-face contacts with a health care professional, including additional medication consultations, to avoid crises). Patients who drop-out from the study will engage in assessments at every timepoint as far as possible.



Study design, showing treatment conditions and measurements. BDI-II, Beck Depression Inventory; BSI, Brief Symptom Inventory; CAPS, Clinician-Administered PTSD Scale for DSM-5; DERS, Difficulties in Emotion Regulation Scale; DES-II, Dissociative Experiences Scale; EMDR, Eye Movement Desensitization and Reprocessing; EQ-5D, Euroqol-5D; IIP, Inventory of Interpersonal Problems; LEC-5, Life Events Checklist for DSM-5; PSS-SR, PTSD Symptoms Scale-Self Report; PTCI, Posttraumatic Cognitions Inventory; SCID-II, Structured Clinical Interview for DSM-IV Axis II; SIDES-R, Structured Interview for Disorders of Extreme Stress-Revised; STAIR, Skills Training in Affect and Interpersonal regulation; T, time point; FU, follow up

*Power and sample size calculation*

To our knowledge, methods for power calculation in the context of linear mixed models are unavailable. A power calculation based on a repeated measures ANOVA was therefore used as a conservative approximation, with treatment condition as the between-subjects factor and time as the within subjects factor. For a 2 between (treatment condition) x 5 within (pre-treatment, after every eight sessions, post-treatment, 3 month follow-up and 6 month follow-up) repeated measures ANOVA (alpha of .05, power of .80, correlation between measures .5, and small effect-size  $f$  of .10), a total sample size of  $N = 122$  will be required (G power; Faul et al., 2007).

**Data analysis**

Descriptive analyses will be used to evaluate demographic, clinical and baseline characteristics of both treatment arms. Analyses will be performed on the intent-to-treat and the completers sample: The data of all randomized participants will be analyzed using both groups as defined at randomization. On the continuous outcome measures, the groups will be compared using linear mixed models. Baseline scores will be included as covariates, time as a categorical variable, and treatment condition as a fixed effect.

**Discussion**

There is debate about the treatment of PTSD related to physical and/or sexual abuse during childhood. A history of (chronic) traumatization during childhood has been linked to the development of distinct symptoms, such as problems in affect regulation, negative self-concept, and interpersonal problems, symptoms that are categorized under the name of Complex PTSD (Cloitre et al., 2013).

Many experts in the trauma field consider a phase-based approach as the preferred treatment for individuals suffering from the consequences of (repeated) early childhood interpersonal trauma, with symptoms of Complex PTSD (Cloitre et al., 2012; Cloitre et al., 2010; McFretridge et al., 2017). Proponents of such a treatment trajectory argue that with the addition of a stabilization phase prior to a trauma-focused treatment, these individuals are more likely to profit from, and less likely to drop out of, treatment. Stated differently: “*without stabilization, operating at least at an implicit relational level, no trauma-focused intervention can have a durably positive outcome in the treatment of Complex PTSD*” (Liotti, 2017). Conversely, proponents of the application of immediate evidence-based treatments for this target population argue that a stabilization phase could delay or restrict access to trauma-focused treatments, thereby preventing immediate benefit from those treatments (De Jongh et al., 2016). Because of this controversy, the results of the present study may deliver a pivotal contribution to the field, and the worldwide debate about the treatment of individuals suffering from PTSD due to prolonged or repeated childhood abuse which may lead to the development of more effective, tailor-made treatments for this group of patients.

An improvement in study design relative to previous studies is that the present study specifically focuses on the added value of stabilization. Assessing the two groups after the same amount of treatment sessions (after eight or 16 sessions) may provide answers to the question as to which of the two conditions works best and in what phase of treatment. Comparing the two conditions post-treatment makes it possible to answer the question whether STAIR has an added value over EMDR only. As some previous studies found that treatment gains emerged only months after treatment has ended (Cloitre et al., 2010), the follow-up assessments are pivotal. To ensure that patients engaging in this study represent a group with severe psychopathology, our in- and exclusion criteria state that patients must *repeatedly* be exposed to sexual and/or physical abuse during childhood (i.e., Complex

trauma). Further, psychotic symptoms and bipolar disorders are not excluded with the only exception of those displaying *acute* suicidality at T0. Finally, to increase the generalizability of the results of the present study, we will also include male patients.

There are some potential limitations of the present study that need to be noted. First, instead of exposure therapy as the trauma-focused components, EMDR will be used, rendering a direct comparison more difficult with previous studies that employed PE as the trauma-focused therapy. However, same as PE, EMDR is one of the first-choice trauma-focussed treatment for PTSD (NCCMH, 2005; WHO, 2013). An advantage of using EMDR therapy rather than imaginal exposure is that most therapists in the research setting are already well educated in using EMDR therapy, as EMDR maybe more widely used as a trauma-focused therapy than other trauma-focused therapies, at least in Europe (Becker et al., 2004; Jaycox & Foa, 1996; Van Minnen et al., 2010).

Furthermore, the quality of assessment of symptoms of Complex PTSD is not ideal. While in clinical practice, the term Complex PTSD is widely used, definitions of Complex PTSD have changed over time and validated diagnostic interviews are not yet available for the current construct of CPTSD as proposed for ICD-11 (Maercker et al., 2013). Therefore, in this study, the SIDES is used to index severity of Complex PTSD and additionally, a variety of psychometrically sound questionnaires to measure the different symptoms associated with Complex PTSD separately (e.g. interpersonal functioning, emotion regulation, dissociation).

Most importantly, the results of this study might help to ameliorate treatment for patients suffering from PTSD due to repeated sexual and/or physical abuse during childhood thereby providing important insights on how to improve tailor-made guideline recommendations for this target group.

## References

- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*. 5th ed. American Psychiatric Publishing.
- American Psychiatric Association (2002). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev). American Psychiatric Publishing.
- Arntz A. (1993). *Dutch translation of the PSS-SR*. Universiteit Maastricht.
- Bae, H., Kim, D., & Park, Y. C. (2016). Dissociation predicts treatment response in eye-movement desensitization and reprocessing for posttraumatic stress disorder. *Journal of Trauma & Dissociation: The official journal of the International Society for the Study of Dissociation (ISSD)*, *17*(1), 112–130.  
<https://doi.org/10.1080/15299732.2015.1037039>
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory II*. Psychological corporation.
- Becker, C. B., Zayfert, C., & Anderson, E. (2004). A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. *Behaviour Research and Therapy*, *42*(3), 277–292. [https://doi.org/10.1016/S0005-7967\(03\)00138-4](https://doi.org/10.1016/S0005-7967(03)00138-4)
- Boeschoten, M. A., Bakker, A., Jongedijk, R. A., Van Minnen, A., Elzinga, B. M., Rademaker, A. R., & Olf, M. (2014). *Clinician Administered PTSD Scale for DSM-5 – Nederlandstalige versie*. Arq Psychotrauma Expert Groep.
- Cahill, S. P., Zoellner, L. A., Feeny, N. C., & Riggs, D. S. (2004). Sequential treatment for child abuse-related posttraumatic stress disorder: methodological comment on Cloitre, Koenen, Cohen, & Han (2002). *Journal of Consulting and Clinical Psychology*, *72*(3), 543–551. <https://doi.org/10.1037/0022-006X.72.3.543>
- Carlson, E. B., & Putnam, F. W. (1993). An update on the Dissociative Experiences Scale. *Dissociation*, *6*(1), 16-27.

- Cloitre, M., Courtois, C. A., Charuvastra, A., Carapezza, R., Stolbach, B. C., & Green, B. L. (2011). Treatment of complex PTSD: results of the ISTSS expert clinician survey on best practices. *Journal of Traumatic Stress, 24*(6), 615–627.  
<https://doi.org/10.1002/jts.20697>
- Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander P, Briere J, Herman, J. L., Lanius, R., Stolbach, B. C., Spinazzola, J., Van der Kolk, B. A., Van der Hart, O. (2012). *The ISTSS Expert Consensus Treatment Guidelines for Complex PTSD in adults*. [https://istss.org/ISTSS\\_Main/media/Documents/ISTSS-Expert-Concesnsus-Guidelines-for-Complex-PTSD-Updated-060315.pdf](https://istss.org/ISTSS_Main/media/Documents/ISTSS-Expert-Concesnsus-Guidelines-for-Complex-PTSD-Updated-060315.pdf)
- Cloitre, M., Garvert, D. W., Brewin, C. R., Bryant, R. A., & Maercker, A. (2013). Evidence For proposed ICD-11 PTSD and complex PTSD: A latent profile analysis. *European Journal of Psychotraumatology, 4*. <https://doi.org/10.3402%2Fejpt.v4i0.20706>
- Cloitre, M., Garvert, D. W., Weiss, B., Carlson, E. B., & Bryant, R. A. (2014). Distinguishing PTSD, complex PTSD, and borderline personality disorder: A latent class analysis. *European Journal of Psychotraumatology, 5*, 25097.  
<https://doi.org/10.3402%2Fejpt.v5.25097>
- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han, H. (2002). Skills training in affective and interpersonal regulation followed by exposure: a phase-based treatment for PTSD related to childhood abuse. *Journal of Consulting and Clinical Psychology, 70*(5), 1067–1074. <https://doi.org/10.1037//0022-006x.70.5.1067>
- Cloitre, M., Petkova, E., Su, Z., & Weiss, B. (2016). Patient characteristics as a moderator of post-traumatic stress disorder treatment outcome: combining symptom burden and strengths. *BJPsych open, 2*(2), 101–106. <https://doi.org/10.1192/bjpo.bp.115.000745>
- Cloitre, M., Stovall-McClough, K. C., Noonan, K., Zorbas, P., Cherry, S., Jackson, C. L.,

- Gan, W., & Petkova, E. (2010). Treatment for PTSD related to childhood abuse: a randomized controlled trial. *The American Journal of Psychiatry*, *167*(8), 915–924. <https://doi.org/10.1176/appi.ajp.2010.09081247>
- De Beurs, E. (2006). *Brief Symptom Inventory. Handleiding*. PITS.
- De Beurs, E., & Zitman, F. G. (2006). De Brief Symptom Inventory (BSI). De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL- 90. *Maandblad Geestelijke Volksgezondheid [monthly magazine of mental health care]*, *61*, 120-141.
- De Jongh, A., Resick, P. A., Zoellner, L. A., van Minnen, A., Lee, C. W., Monson, C. M., Foa, E. B., Wheeler, K., Broeke, E. T., Feeny, N., Rauch, S. A., Chard, K. M., Mueser, K. T., Sloan, D. M., van der Gaag, M., Rothbaum, B. O., Neuner, F., de Roos, C., Hehenkamp, L. M., Rosner, R., ... Bicanic, I. A. (2016). Critical analysis of the current guidelines for Complex PTSD in adults. *Depression and Anxiety*, *33*(5), 359-369. <https://doi.org/10.1002/da.22469>
- Derogatis, L. R. (1975). *Brief Symptom Inventory (BSI)*. Clinical Psychometric Research.
- Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory: an introductory report. *Psychological Medicine*, *13*(3), 595–605. <https://psycnet.apa.org/doi/10.1017/S0033291700048017>
- Dorrepaal, E., Thomaes, K., & Draijer, N. (2008). *Vroeger en verder, stabilisatiecursus na misbruik of mishandeling (Past and beyond, stabilization course after sexual and physical abuse)*. Pearson.
- Dorrepaal, E., Thomaes, K., Hoogendoorn, A. W., Veltman, D. J., Draijer, N., & Van Balkom, J. L. M. (2014). Evidence-based treatment for adult women with child abuse-related Complex PTSD: a quantitative review. *European Journal of Psychotraumatology*, *5*, 23613. <https://doi.org/10.3402%2Ffejpt.v5.23613>



- Ehring, T., Welboren, R., Morina, N., Wicherts, J. M., Freitag, J., & Emmelkamp, P. M. G. (2014). Meta-analysis of psychological treatments for posttraumatic stress disorder in adult survivors of childhood abuse. *Clinical Psychology Review, 34*(8), 645-657. <https://doi.org/10.1016/j.cpr.2014.10.004>
- Engelhard, I. M., Arntz, A., & Van den Hout, M. A. (2007). Low specificity of symptoms on the post-traumatic stress disorder (PTSD) symptom scale: A comparison of individuals with PTSD, individuals with other anxiety disorders and individuals without psychopathology. *The British Journal of Clinical Psychology, 46*(4), 449-456. <https://doi.org/10.1348/014466507X206883>
- EuroQol Group (1990). EuroQol: A new facility for the measurement of health-related quality of life. *Health Policy, 16*, 199-208. [https://doi.org/10.1016/0168-8510\(90\)90421-9](https://doi.org/10.1016/0168-8510(90)90421-9)
- EuroQol Group. *The EQ-5D*. <http://www.euroqol.org/eq-5d-publications/search.html>.
- Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G\*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behaviour Research Methods, 39*, 175-191. <https://doi.org/10.3758/BF03193146>
- Foa, E. B., McLean, C. P., Capaldi, S., & Rosenfield, D. (2013). Prolonged exposure versus supportive counselling for abuse-related PTSD in adolescent girls, a randomized clinical trial. *JAMA, 310*(2), 1-8. <https://doi.org/10.1001/jama.2013.282829>
- Foa, E. B., Riggs, D. S., Dancu, C. V., & Rothbaum, B. O. (1993). Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. *Journal of Traumatic Stress, 6*(4), 459-473. <https://doi.org/10.1002/jts.2490060405>
- Foa, E. B., Tolin, D. F., Ehlers, A., Clark, D. M., & Orsillo, S. M. (1999). The Posttraumatic Cognitions Inventory (PTCI). Development and validation. *Psychological Assessment, 11*(3), 303-314. <http://doi.org/10.1037/1040-3590.11.3.303>

- Ford, J. D., Stockton, P., Kaltman, S., & Green, B. L. (2006). Disorders of extreme stress (DESNOS) symptoms are associated with type and severity of interpersonal trauma exposure in a sample of healthy young women. *Journal of Interpersonal Violence, 21*(11), 1399–1416. <https://doi.org/10.1177/0886260506292992>
- Fox, H. C., Axelrod, S. R., Paliwal, P., Sleeper, J., & Sinha, R. (2007). Difficulties in emotion regulation and impulse control during cocaine abstinence. *Drug and Alcohol Dependence, 89*(2-3), 298–301. <https://doi.org/10.1016/j.drugalcdep.2006.12.026>
- First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B. W., & Benjamin, L. S. (1997). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. American Psychiatric Press.
- Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. *Journal of Psychopathology and Behavioral Assessment 26*, 41–54. <https://doi.org/10.1023/B:JOBA.0000007455.08539.94>
- Gratz, K. L., Tull, M. T., Baruch, D. E., Bornovalova, M. A., & Lejuez, C. W. (2008). Factors associated with co-occurring borderline personality disorder among inner-city substance users: the roles of childhood maltreatment, negative affect intensity/reactivity, and emotion dysregulation. *Comprehensive Psychiatry, 49*(6), 603–615. <https://doi.org/10.1016/j.comppsy.2008.04.005>
- Herman, J. L. (1992). Complex PTSD: A syndrome of survivors of prolonged and repeated trauma. *Journal of Traumatic Stress, 5*(3), 377-391. <https://psycnet.apa.org/doi/10.1002/jts.2490050305>
- Horowitz, L. M., Alden, L. E., Wiggins, J. S., & Pincus, A. L. (2000). *Inventory of Interpersonal Problems*. Psychological Corporation.
- Jaycox, L. H. J., & Foa, E. B. (1996). Obstacles in implementing exposure therapy for PTSD:

Case discussions and practical solutions. *Clinical Psychology and Psychotherapy*, 3, 176-184. [https://doi.org/10.1002/\(SICI\)1099-0879\(199609\)3:3%3C176::AID-CPP100%3E3.0.CO;2-1](https://doi.org/10.1002/(SICI)1099-0879(199609)3:3%3C176::AID-CPP100%3E3.0.CO;2-1)

Johnson, K. A., Zvolensky, M. J., Marshall, E. C., Gonzalez, A., Abrams, K., & Vujanovic, A. A. (2008). Linkages between cigarette smoking outcome expectancies and negative emotional vulnerability. *Addictive Behaviours*, 33, 1416-1424. <https://doi.org/10.1016%2Fj.addbeh.2008.05.001>

Liotti, G. (2017). Notes on the concept of stabilization in the treatment of complex PTSD. *ESTD Newsletter*, 6, 5-7.

Maercker, A., Brewin, C. R., Bryant, R. A., Cloitre, M., Reed, G. M., van Ommeren, M., Humayun, A., Jones, L. M., Kagee, A., Llosa, A. E., Rousseau, C., Somasundaram, D. J., Souza, R., Suzuki, Y., Weissbecker, I., Wessely, S. C., First, M. B., & Saxena, S. (2013). Proposals for mental disorders specifically associated with stress in the International Classification of Diseases-11. *Lancet*, 381(9878), 1683–1685. [https://doi.org/10.1016/S0140-6736\(12\)62191-6](https://doi.org/10.1016/S0140-6736(12)62191-6)

McFetridge, M., Hauenstein-Swan, A., Heke, S., Karatzias, T., Greenberg, N., Kitchiner N, & Morley, R. (2017). *Guideline for the treatment and planning of services for complex post-traumatic stress disorder in adults*. UK Psychological Trauma Society. <http://dx.doi.org/10.13140/RG.2.2.14906.39365>

Mueser, K. T., Rosenberg, S. D., Xie, H., Jankowski, M. K., Bolton, E. E., Lu, W., Hamblen, J. L., Rosenberg, H. J., McHugo, G. J., & Wolfe, R. (2008). A randomized controlled trial of cognitive-behavioral treatment for posttraumatic stress disorder in severe mental illness. *Journal of Consulting and Clinical Psychology*, 76(2), 259–271. <https://doi.org/10.1037/0022-006X.76.2.259>

National Collaborating Centre for Mental Health (2005). *Post-traumatic stress disorder: The*

*management of PTSD in adults and children in primary and secondary care. Clinical guideline 26.* National Institute for Clinical Excellence.

- Resick, P. A., Nishith, P., & Griffin, M. G. (2003). How well does cognitive-behavioral therapy treat symptoms of complex PTSD? An examination of child sexual abuse survivors within a clinical trial. *CNS Spectrums*, *8*(5), 340-55.  
<https://doi.org/10.1017%2Fs1092852900018605>
- Resick, P. A., Nishith, P., Weaver, T. L., Astin, M. C., & Feuer, C. A. (2002). A comparison of cognitive processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. *Journal of Consulting and Clinical Psychology*, *70*(4), 867-879.  
<https://psycnet.apa.org/doi/10.1037/0022-006X.70.4.867>
- Scoboria, A., Ford, J., Lin, H., & Frisman, L. (2008). Revision of the Structured Interview for Disorders of Extreme Stress (SIDES): An exploratory and confirmatory factor analytic approach. *Assessment*, *15*, 404-425. <https://doi.org/10.1177/1073191108319005>
- Sealed Envelope Ltd. (2016). *Create a blocked randomisation list*. Available from:  
<https://www.sealedenvelope.com/simple-randomiser/v1/lists>. Accessed 29 Aug 2016].
- Shapiro, F. (2001). *Eye movement desensitization and reprocessing: Basic Principles, protocols and procedures* (2nd ed.). Guilford Press.
- Stant, A. D., TenVergert, E. M., Wunderink, A., Nienhuis, F. J., & Wiersma, D. (2007). Economic consequences of alternative medication strategies in first episode non-affective psychosis. *European Psychiatry*, *22*, 347-353.  
<https://doi.org/10.1016/j.eurpsy.2007.02.003>.
- Van Apeldoorn, F. J., Stant, A. D., van Hout, W. J., Mersch, P. P., & den Boer, J. A. (2014).

Cost-effectiveness of CBT, SSRI, and CBT+SSRI in the treatment for panic disorder. *Acta Psychiatrica Scandinavica*, 129(4), 286–295.

<https://doi.org/10.1111/acps.12169>

Van den Berg, D. P., De Bont, P. A., Van der Vleugel, B. M., De Roos, C., De Jongh, A., Van Minnen, A., & Van der Gaag, M. (2015). Prolonged exposure vs eye movement desensitization and reprocessing vs waiting list for posttraumatic stress disorder in patients with a psychotic disorder: a randomized clinical trial. *JAMA Psychiatry*, 72(3), 259–267. <https://doi.org/10.1001/jamapsychiatry.2014.2637>

Van der Does, A. J. W. (2002). *Handleiding. De Nederlandse versie van de Beck Depression Inventory* (2nd ed.). Harcourt Test Publishers.

Van der Gaag, M., Stant, A. D., Wolters, K. J., Buskens, E., & Wiersma, D. (2011). Cognitive-behavioural therapy for persistent and recurrent psychosis in people with schizophrenia-spectrum disorder: cost-effectiveness analysis. *The British Journal of Psychiatry: The journal of mental science*, 198(1), 59–1. <https://doi.org/10.1192/bjp.bp.109.071522>

Van Emmerik, A. A. P., Schoorl, M., Emmelkamp, P. M.G., & Kamphuis, J. H. (2007). Psychometrische kenmerken van de Nederlandstalige Posttraumatische Cognities Inventarisatielijst (PTCI). *Gedragstherapie [behavior therapy]*, 40, 269-284.

Vanheule, S., Desmet, M., & Rosseel, Y. (2006). The factorial structure of the Dutch translation of the inventory of interpersonal problems: a test of the long and short versions. *Psychological Assessment*, 18(1), 112–117. <https://doi.org/10.1037/1040-3590.18.1.112>

Van Minnen, A., Hendriks, L., & Olf, M. (2010). When do trauma experts choose exposure therapy for PTSD patients? A controlled study of therapist and patient

factors. *Behaviour Research and Therapy*, 48(4), 312–320.

<https://doi.org/10.1016/j.brat.2009.12.003>

Van IJzendoorn, M. H., & Schuengel, C. (1996). The measurement of dissociation in normal and clinical populations: Meta-analytic validation of the Dissociative Experiences Scale (DES). *Clinical Psychology Review*, 16, 365-382. [https://doi.org/10.1016/0272-7358\(96\)00006-2](https://doi.org/10.1016/0272-7358(96)00006-2)

Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G., Marx, B.P., & Keane, T.M. (2013). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. [Assessment] Available from [www.ptsd.va.gov](http://www.ptsd.va.gov).

Weathers, F.W., Blake, D.D., Schnurr, P.P., Kaloupek, D.G., Marx, B.P., & Keane, T.M. (2013). *The Life Events Checklist for DSM-5 (LEC-5)*. Instrument available from the National Center for PTSD at [www.ptsd.va.gov](http://www.ptsd.va.gov)

Weertman, A., Arntz, A., Dreessen, L., van Velzen, C., & Vertommen, S. (2003). Short-interval test-retest interrater reliability of the Dutch version of the Structured Clinical Interview for DSM-IV personality disorders (SCID-II). *Journal of Personality Disorders*, 17(6), 562–567. <https://doi.org/10.1521/pedi.17.6.562.25359>

Weertman, A., Arntz, A., & Kerkhofs, M. (2000). *Handleiding Gestructureerd Klinisch Interview voor DSM-IV As-II Persoonlijkheidsstoornissen*. Swets test publishers.

World Health Organization (2013). *Guidelines for the management of conditions specifically related to stress*. World Health Organization.

Zlotnick, C., Shea, T. M., Rosen, K., Simpson, E., Mulrenin, K., Begin, A., & Pearlstein, T. (1997). An affect-management group for women with posttraumatic stress disorder and histories of childhood sexual abuse. *Journal of Traumatic Stress*, 10(3), 425–436. <https://doi.org/10.1023/a:1024841321156>

Figure 2

Enrolment, treatment and assessments over time. BDI-II, Beck Depression Inventory; BSI, Brief Symptom Inventory; CAPS, Clinician-Administered PTSD Scale for DSM-5; DERS, Difficulties in Emotion Regulation Scale; DES-II, Dissociative Experiences Scale; EMDR, Eye Movement Desensitization and Reprocessing; EQ-5D, Euroqol-5D; IIP, Inventory of Interpersonal Problems; LEC-5, Life Events Checklist for DSM-5; PSS-SR, PTSD Symptoms Scale-Self Report; PTCI, Posttraumatic Cognitions Inventory; SCID-II, Structured Clinical Interview for DSM-IV Axis II; SIDES-R, Structured Interview for Disorders of Extreme Stress-Revised; STAIR, Skills Training in Affect and Interpersonal regulation; *t*, time point; FU, follow up

	Enrolment	Post-allocation					
TIMEPOINT	<i>t</i> <sub>0</sub>	<i>t</i> <sub>1</sub>	<i>t</i> <sub>2</sub>	<i>t</i> <sub>3</sub>	Post treatment	FU 3 months	FU 6 months
<b>ENROLMENT:</b>							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
<b>INTERVENTIONS:</b>							
STAIR/EMDR or EMDR alone							
EMDR alone condition							
<b>ASSESSMENTS:</b>							
LEC-5, BDI-II (item suicidality)	X						
PSS-SR		X	X	X	X	X	X
CAPS-5,	X	X		X	X	X	X
SIDES-R		X			X	X	X
DES-II, BSI		X	X	X	X	X	X
PTCI, IIP, DERS		X	X	X	X		
SCID-II		X					
EQ5-D, case record form		X			X	X	X

**Phase-Based Treatment versus Immediate Trauma-Focused Treatment in Patients with PTSD due to childhood abuse: A randomized clinical trial.**

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**Abstract***Background*

It is unclear whether people with post-traumatic stress disorder (PTSD) and symptoms of complex PTSD due to childhood abuse need a treatment approach different from approaches in the PTSD treatment guidelines.

*Aims*

To determine whether a phase-based approach is more effective than a direct trauma-focused approach in people with childhood-trauma related PTSD.

*Methods*

Adults with PTSD following childhood abuse were randomly assigned to either a phase-based treatment condition (8 sessions of Skills Training in Affect and Interpersonal Regulation (STAIR), followed by 16 sessions of eye-movement desensitization and reprocessing (EMDR) therapy;  $n = 57$ ) or an immediately trauma-focused treatment condition (16 sessions of EMDR therapy;  $n = 64$ ). Participants were assessed for symptoms of PTSD and complex PTSD, and other forms of psychopathology before, during and after treatment and at 3- and 6-month follow-ups.

*Results*

Data were analysed with linear mixed models. No significant differences between the two treatments on any variable at post-treatment or follow-up were found. Post-treatment, 68.8% no longer met PTSD diagnostic criteria. Self-reported PTSD symptoms significantly decreased for both STAIR-EMDR therapy ( $d = .93$ ) and EMDR therapy ( $d = 1.54$ ) from pre- to post-treatment assessment, without difference between the two conditions (Est. -2.84, SE 2.18, 95% CI -7.15, 1.47). No differences in drop-out rates between the conditions were found (STAIR-EMDR 22.8% versus EMDR 17.2%). No study-related adverse events occurred.

*Conclusions*

The current study provides compelling support for the use of EMDR therapy alone for the treatment of PTSD due to childhood abuse as opposed to needing any preparatory intervention.

## **Introduction**

### *Complex PTSD*

Repeated trauma in childhood has been found to be a risk factor for developing complex post-traumatic stress disorder (PTSD) (ISTSS, 2018). Complex PTSD was officially introduced in ICD-11 as part of the “Disorders specifically associated with stress” category (WHO, 2021). To fulfil the diagnostic criteria a person needs to display, in addition to PTSD criteria, disturbances in three domains of self-organisation (i.e., affect dysregulation, negative core beliefs, and interpersonal problems). Eye-movement desensitisation and reprocessing (EMDR) therapy and prolonged exposure therapies are effective trauma-focused treatments for PTSD (ISTSS, 2018), but it is still unclear whether people who meet criteria of complex PTSD need a different treatment approach than those based on existing international treatment guidelines for PTSD (De Jongh et al., 2016).

### *Phase-based treatment approach*

One of the treatment approaches for Complex PTSD suggested, even before complex PTSD was included in the ICD-11, is a phase-based treatment (Cloitre et al., 2012). In the first phase - cognitive behavioural therapy- patients experiment with emotion regulation and interpersonal skills. The second phase is trauma-focused treatment in which the traumatic memories are processed. The third and final phase focuses on the consolidation of treatment gains and the resumption of daily activities (Cloitre et al., 2012). The purpose of the first phase is also to establish a therapeutic relationship and increase safety and flexibility in skills (Cloitre et al., 2002).

### *Evidence for the phase-based approach*

The value of using a phase-based approach was supported by the results of a three-armed randomised controlled clinical trial conducted by Cloitre et al. (2010). This study evaluated the effectiveness of phased-based treatment approach by comparing three treatment

conditions: a) eight sessions of Skills Training in Affect and Interpersonal Regulation (STAIR; Cloitre et al., 2002), followed by eight sessions of prolonged exposure therapy; b) supportive counseling followed by a comparable number of sessions of exposure therapy; and c) STAIR followed by supportive counselling (n = 104). Because the outcomes of both conditions differed at follow-up for some variables (PTSD symptoms, interpersonal problems and several scales for affect-regulation) in favor of the STAIR/Exposure condition, the researchers concluded that the results of their study suggested that a phase-based approach is superior to a trauma-focused approach. However, the fact that a pure exposure condition was lacking makes it difficult to draw conclusions about the relative benefits of a phased-treatment approach over conventional trauma-focused PTSD treatment (De Jongh et al., 2016).

#### *Comparison of the phased-based approach with the trauma-focused treatment*

The most recent version of the treatment guidelines for complex PTSD of the International Society of Traumatic Stress Studies (ISTSS) proposes a "personalised medicine" approach aimed at identifying symptoms that are clinically significant to a particular patient and tailoring interventions or series of interventions to address these (ISTSS, 2018). The guideline committee acknowledged that the research supporting this guideline is lacking and that only a head-to-head comparison of a phase-based treatment with a direct trauma-focused treatment using a randomised controlled design can answer this important question. Recently Oprel and her colleagues conducted a randomised controlled trial (RCT) in which prolonged exposure therapy was directly compared with a phase-based treatment (prolonged exposure therapy preceded by STAIR) among 149 individuals with PTSD due to childhood abuse (Oprel et al., 2020). The hypothesis that the phase-based treatment would be associated with larger PTSD symptom reductions compared with the direct prolonged exposure therapy was not supported by their data. A comparable study with EMDR therapy as the trauma-focused treatment has not been performed.

*Aim of the present study*

The purpose of the present study was to help find an answer to the question as to whether a phase-based treatment approach is more effective than an immediate trauma-focused treatment in ameliorating the treatment outcomes in individuals with PTSD due to repeated sexual and/or physical childhood abuse. To make a direct comparison between both treatment options, two types of therapies were applied: EMDR therapy preceded by STAIR (Cloitre et al., 2002), and immediate EMDR therapy not preceded by STAIR. Because STAIR was developed especially for individuals with PTSD and symptoms of Complex PTSD to ameliorate treatment outcomes, we hypothesized that, compared to the EMDR therapy only condition, the phase-based treatment condition would be significantly more effective in reducing symptoms of PTSD, symptoms of complex PTSD and other forms of psychopathology, and would also lead to significantly less drop-out than the stand-alone trauma-focused condition.

**Method***Design*

The study is a single-blind RCT with two arms (EMDR therapy versus EMDR therapy preceded by STAIR) with measurements at pre-treatment, every eight sessions, post-treatment and at 3- and 6-month follow-up. The design paper of this trial (Van Vliet et al., 2018) is available at <https://doi.org/10.1186/s13063-018-2508-8>. This also includes a CONSORT checklist. The study design was registered in NTR5991 and approved by the medical ethics committee Twente NL 56641.044.16 CCMO.

### *Participants*

Participants were recruited from two out-patient mental health organisations in the Netherlands (Dimence and GGZ Oost-Brabant) from 5 September 2016, and the last measurement was on 8 August 2020. Patients were included if aged between 18 and 65 years and diagnosed with PTSD as measured by the Clinician-Administered PTSD scale for DSM-5 (CAPS-5; Weathers et al., 2013). Furthermore, they had to be a victim of repeated sexual and/or physical abuse before the age of 18 by a caretaker or a person in a position of authority, as identified by the LEC-5 (Weathers et al., 2013).

### *Exclusion criteria*

Patients were excluded if they displayed insufficient Dutch language proficiency or an acute risk of suicidality for which direct crisis intervention was needed, as assessed by item 9 of the Beck Depression Inventory – II (BDI-II; Beck et al., 1996). Also, they were excluded if they had received treatment for PTSD in the past year with at least eight sessions (any well-evaluated program), reported being a victim of ongoing physical and/or sexual abuse, reported alcohol or drug dependence or misuse according to DSM-5 criteria during screening for eligibility (American Psychiatric Association, 2013), or if they had an intellectual disability at registration at the institution.

### *Procedure*

Patients eligible for inclusion received oral and written information about the study. If they agreed to participate and signed the informed consent form, they were examined for inclusion (N=151). After inclusion, patients were randomly assigned to one of the two treatment conditions (the exact randomization procedure was described in the design paper, Van Vliet et al., 2018).

*Measurements*

The self-reported severity of PTSD symptoms was the primary outcome and was assessed by the PTSD Symptoms Scale-Self Report (Foa et al., 1993) at pre-treatment, after eight sessions and at post-treatment. The internal reliability at baseline was high (Cronbach's  $\alpha = .83$ ).

Several secondary outcome measures were included. The presence and severity of PTSD diagnoses were assessed using the CAPS-5 (Weathers et al., 2013) at pre-treatment, post-treatment and at both follow-ups.

The presence and severity of symptoms of Complex PTSD were measured using the Structured Interview for Disorders of Extreme Stress (SIDES; Scobordia et al., 2008), more specifically the 38-item version developed by Ford et al. (Ford et al., 2006).

We investigated distinct symptoms of complex PTSD pre-treatment, after eight sessions and post-treatment as follows. In addition to the PTSD symptoms as indexed by the CAPS (Weathers et al., 2013), symptoms of complex PTSD were measured based on the symptom clusters of the ICD-11 complex PTSD classification (WHO, 2021), that is, by using the Inventory of Interpersonal Problems (IIP; Horowitz et al., 2000) to measure interpersonal difficulties (Cronbach's  $\alpha = .85$  at baseline of the current study), the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004) to assess difficulties in emotion regulation (Cronbach's  $\alpha = .92$  at baseline of the current study) and the Post-traumatic Cognitions Inventory (PTCI; Foa et al., 1999) to index trauma related thoughts and beliefs (Cronbach's  $\alpha = .96$  at baseline of the current study).

Trait dissociation was measured using the Dissociative Experiences Scale (DES-II; Carlson & Putman, 1993; Cronbach's  $\alpha = .93$  at baseline of the current study) at pre-treatment, post-treatment, and both follow-ups.

The Brief Symptom Inventory (Derogatis, 1975; Cronbach's  $\alpha = .95$  at baseline of the current study) was used to index symptoms of general psychopathology at every measurement point.

### *Treatment*

In both treatment conditions, participants first received one 90 minutes session, consisting of psychoeducation and determining a hierarchy of relevant traumatic experiences. Both the STAIR and EMDR therapy were thereafter delivered twice a week for 90 minutes and sessions were video recorded. STAIR was conducted according to the program described by Cloitre and her colleagues (Cloitre et al., 2002). EMDR therapy was conducted according to the protocol by Shapiro using the Dutch translation of the treatment protocol (De Jongh & Ten Broeke, 2013). After treatment (8 sessions of STAIR followed by 16 sessions of EMDR therapy, or 16 sessions of EMDR therapy only), participants were not allowed to receive psychological therapy for 6 months. Psychiatric consultation or support by a nurse were allowed to prevent deterioration during treatment and follow-up, but this had to be reported. Participants were considered to have dropped out of the study if they left any time after the first session. Patients were considered as early completers if all their trauma targets were processed and they did not meet the criteria for PTSD anymore before the maximum amount of treatment sessions. Those who dropped out as well as early completers were assessed at the planned time points. Regular monitoring of participant safety was conducted by therapists and researchers, and serious adverse events were recorded and reported to the main researcher, who reported these to the medical ethics committee.

### *Therapists*

All 27 participating therapists were experienced psychologists and already trained (at advanced level) in EMDR therapy prior to the trial. In addition, they received two days of training in STAIR by an experienced STAIR protocol trainer (MM), and a half-day training



on how to make a hierarchy of relevant traumatic experiences with the patient from another of the authors (AdJ). Within each condition, the participants were assigned to a therapist based on availability.

#### *Supervision and treatment fidelity*

Supervisions took place every 2 months for both EMDR therapy (provided by an EMDR Europe accredited trainer, AdJ) and STAIR (provided by an experienced STAIR protocol trainer, MM). All therapists received individual feedback about the first set of video recorded sessions at the start of a treatment. For the rating of the treatment fidelity, 15% of the sessions were randomly selected and rated by the researchers for treatment adherence. A perfectly executed STAIR protocol was rated as 100% (the percentage of well performed interventions per session), and the mean percentage over the rated sessions was 98.01% ( $SD = 6.04$ ). For EMDR therapy sessions the maximum number of rated points was 15 (one point for every observed step of the protocol), and the mean amount over the rated sessions was 14.45 ( $SD = 0.69$ ). For each treatment condition, six recorded sessions were rated by a second independent rater, in order to compute the level of agreement between the researchers and the rater. The agreement between the researcher and the independent rater was 92.5% in the STAIR-EMDR condition, and 96.7% in the EMDR condition and inconsistencies were discussed.

#### *Statistical analysis*

Analyses were conducted using SPSS 27 for Windows (IBM, 2020). Possible demographic baseline differences were analysed using  $\chi^2$  - tests. Analyses were performed on an intention-to-treat basis. For dichotomous outcomes, a  $\chi^2$  - test was used to test differences in outcome between the treatment conditions. For continuous variables, we used a linear mixed models (LMM) analysis, with treatment conditions and time (i.e., measurements at different time points) as categorical variables, using a covariance pattern model (Liu et al., 2012).

Compound symmetry was used as the covariance type and the standard Restricted Maximum

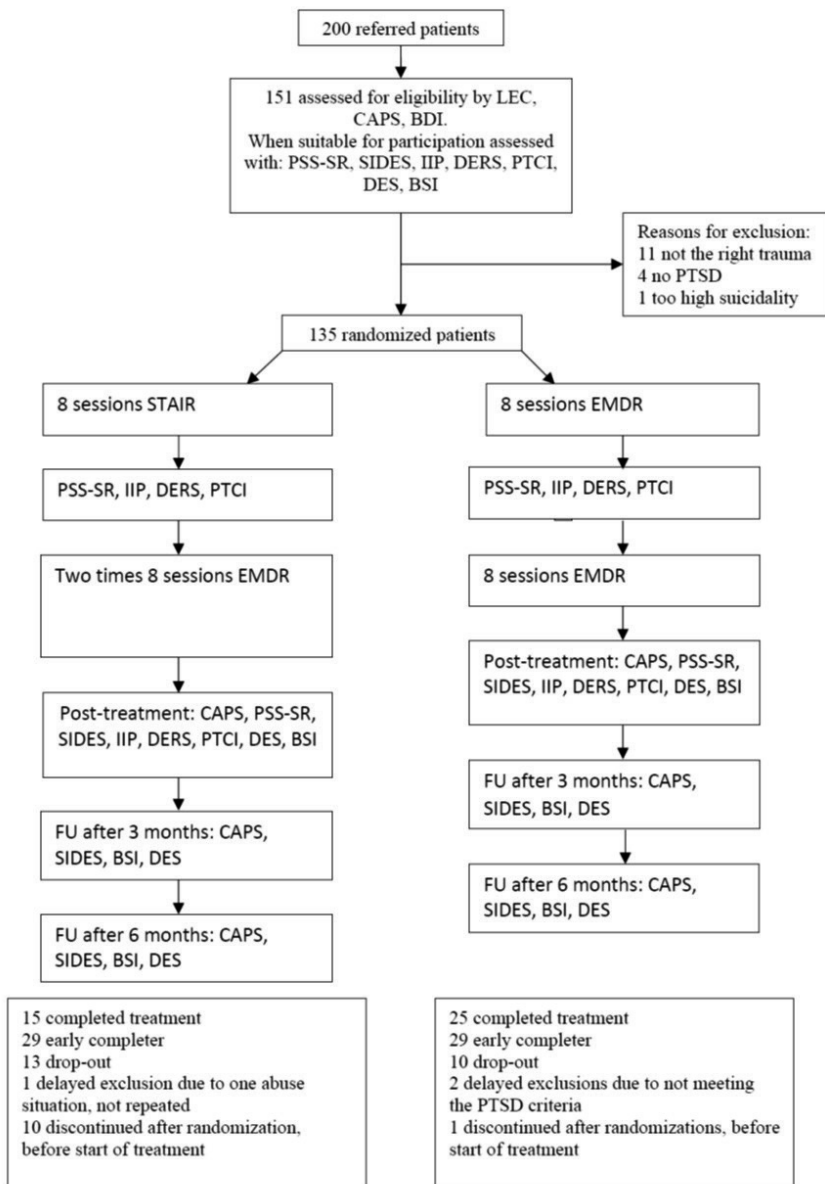
Likelihood (REML) as the estimation method. The STAIR-EMDR condition was the reference category. The analyses were conducted both with and without pre-measurement of the respective outcome variable as a covariate. As the mixed linear model analyses without a covariate provides a better overview for complete changes over time, these are represented in the main text. The results for the LMM analyses with the pre-treatment as a covariate are presented (Supplementary Tables 3a and 3b). To determine whether patients experienced symptom improvement beyond what could be attributed to measurement error, the reliable change index (RCI) for the CAPS was calculated (Lancaster et al., 2020) in combination with test–retest reliability information based on previous research (Weathers et al., 2017).

## Results

### *Patient flow and sample characteristics*

Figure 1 shows the flow chart of participants through the trial. Ten individuals in the STAIR-EMDR group and one in the EMDR group discontinued the trial before the start of treatment. The psychopathological and demographic characteristics of participants and those who discontinued did not differ at baseline, except for a significantly lower score on the self-report on the PTSD symptom scale in the group of patients who did not participate ( $t(118) = 2.20, p = 0.03$ ). The demographic characteristics at baseline are presented in a supplementary Table 1, with no demographic differences between the treatment groups, except for living situation (with relatively more cohabitating participants in the EMDR condition, and more patients living alone in the STAIR-EMDR condition). Given the RCT design we did not correct for pre-treatment differences (De Boer et al., 2015).

Figure 1: Flow of study participants



*Overall pre- to post treatment effects*

In both treatment groups, participants showed significant pre- to post treatment reductions (i.e., a significant effect of time) on all variables (i.e., symptoms of PTSD, symptoms of complex PTSD symptoms and other forms of psychopathology; Supplementary Tables 2a and 2b). The within-group effect sizes pertaining to these differences were medium to large in both conditions for the different variables ( $d = 0.50$  to  $1.70$ ; Table 1). Based on the CAPS, 68.8 % of all participants across treatment conditions did not fulfil the diagnostic criteria of PTSD at post-treatment. Based on the SIDES, only 3.3% of the participants still met the criteria of Complex PTSD at post-treatment (compared to 28.9% prior to treatment).

*Treatment effectiveness of phase-based versus immediate trauma-focused treatment*

None of the variables showed a significant effect of treatment condition or a significant treatment x time interaction effect from pre- to post-treatment (Supplemental Table 2a and Table 2b).

For three variables, we did find a differential course of symptom decrease between pre-and post-treatment (i.e., although the levels were comparable at post-treatment; Supplemental Table 2a). This was the case for self-report of PTSD symptoms (PSS-SR;  $F(2, 164.26) = 3.90, p = .022$ ), interpersonal problems (IIP;  $F(2, 155.17) = 4.86, p = .009$ ) and posttraumatic cognitions (PTCI;  $F(2, 158.22) = 4.17, p = .017$ ). As shown in Figure 2, a comparable pattern was present for these three variables, as symptom decrease in the STAIR-EMDR group only began in the EMDR part (i.e., from eight sessions to post-treatment) and not in the STAIR part (i.e., first eight sessions). In contrast, in the EMDR condition the decline in symptoms was gradual across the sessions from pre- to post treatment.

The dichotomous CAPS outcome did not show a significant difference in the proportions who no longer met PTSD diagnostic criteria between the two treatment groups at post-treatment (66.7% in the EMDR group and 68.9 % in the STAIR-EMDR group,  $\chi^2(2, n =$

96) = 0.05,  $p = .816$ ). The proportion of participants who no longer met complex PTSD diagnostic criteria was 28.8% in the EMDR group and 22.2% in the STAIR-EMDR (pre-treatment 32.8% fulfilled the complex PTSD diagnosis in the EMDR group and 24.6% in the STAIR-EMDR group). No significant differences between the proportion of individuals with a reliable change on the CAPS were found (RCI = 21.4; 53.3% in the STAIR-EMDR group and 45.1% in the EMDR group;  $\chi^2(1, n=96) = 0.36, p = 0.55$ )

#### *Long term treatment results*

For the variables measured at follow-up (see Supplemental Table 2b), no significant treatment effect, time effect, or treatment x time interaction, was found between post-treatment measurement and the 3 month follow-up. Also, no significant changes across to time were found between 3- and 6-months follow-up for scores on the CAPS ( $t(268.42) = .238, p = .812$ ), SIDES ( $t(251.12) = .90, p = .367$ ), DES ( $t(233.63) = 1.21, p = .226$ ) and BSI ( $t(244.00) = .821, p = .413$ ).

#### *Early completion, serious adverse events, and drop-out*

The percentage of early completers (STAIR-EMDR group: 50.9%; EMDR group: 45.3%), participants who dropped out (STAIR-EMDR group: 22.8%; EMDR group: 17.2%) and participants who completed all sessions (STAIR-EMDR group: 26.3%; EMDR group: 37.5%) did not differ significantly between the two treatment groups at post treatment ( $\chi^2(2, n=121) = 1.85, p = .40$ ). We did not find clinical or demographic characteristics related to drop-out. In the STAIR-EMDR group one serious non-study-related (as assessed by the medical ethics committee) adverse event was reported, which included short hospital admission after a suicide attempt. In the EMDR group two non-study-related adverse events were reported (one due to increased suicidal ideation during the follow-up, and one due to increased psychotic experiences following changes in medication).

## Discussion

In contrast to our hypothesis, that phase-based treatment would lead to better treatment outcomes than stand-alone trauma-focused treatment, no differences were found between the two treatment conditions on any variable indexing PTSD, complex PTSD or other forms of psychopathology. The only differences between the groups consisted of faster recovery (i.e., within eight sessions) in the EMDR therapy group on self-reported PTSD symptoms, interpersonal problems, and post-traumatic cognitions, but this advantage did not last, as the results between groups were found comparable at later time intervals. Because the drop-out rates between both treatment groups did not differ significantly, the hypothesis that a phase-based treatment would lead to significantly less attrition than an immediate trauma-focused treatment could also not be supported. These results suggest that a stabilisation phase is not a necessary condition for applying a trauma-focused treatment in a sample of individuals with PTSD due to repeated sexual and/or physical childhood abuse. The results confirm the findings of other studies indicating that both phase-based and immediate trauma-focused therapies are safe and effective treatments (e.g., Boterhoven et al., 2020; Voorendonk et al., 2020; Wagenmans et al., 2018).

This was the third RCT that has been conducted so far comparing a phase-based treatment with a trauma-focused treatment in people with PTSD due to childhood abuse (Cloitre et al., 2010; Oprel et al., 2020), but the first using EMDR therapy. The results of this study are in line with both previous studies in that no differences were found between the treatment groups at post-treatment in favor of a phase-based treatment approach. In other words, both prolonged exposure therapy and EMDR therapy are likely to be safe and effective treatments for individuals suffering from symptoms of complex PTSD due to childhood abuse, whereas a stabilisation phase does not additionally improve treatment results. On the

contrary according to our results, for some symptoms (i.e., interpersonal problems, post-traumatic cognitions), a phase-based treatment approach may even delay the recovery process.

The present study also found no support for the hypothesis that EMDR therapy preceded by STAIR would lead to less drop-out than an EMDR only. To this end, the results are in line with the results of Oprel et al. (2020), but in contrast with the study of Cloitre et al. (2010) which showed that significantly fewer people dropped out of the STAIR/exposure group compared with the support/exposure group. However, a closer look at this study reveals that the higher drop-out rate in the support/exposure group was largest during the supportive counselling phase, not during the trauma-focused part.

The present study has several strengths. Most important, the treatments were performed in two regular psychiatric out-patient settings. This increases the generalisability of these research findings. Another strength is that therapists received individual feedback on their treatment sessions, which may have led to treatment efficiency and high levels of treatment integrity. Conversely, a limitation of the present study is that the two treatment groups were not compared with an inactive control group controlling for effects resulting from the mere passage of time. A second critical note refers to the fact that STAIR was offered twice a week, instead of once a week; this may have led to less time to practise new skills in between sessions.

Despite the compelling support for the use of an EMDR therapy alone for the treatment of Complex PTSD as opposed to needing any preparatory intervention it remains important to investigate in future studies whether specific symptoms of complex PTSD, and maybe also other relevant patient characteristics, might moderate treatment outcome in that some patients might profit more from an immediate trauma-focused treatment whereas others may profit more using a phase-based approach. More specifically, because not everyone fully benefited from the EMDR therapy alone (25% still fulfilled the diagnostic criteria of PTSD),

in future research it seems sensible and important to explore which variables determine an adequate or less adequate treatment response, and whether there may still be patients who benefit from some form of emotion regulation or other skills training. In addition, future studies should investigate the long-term effects of different trauma treatments, as the course of separate symptoms during follow-up on the long term may differ between the different treatments.

Our findings, and those of other recent studies on the treatment of symptoms of complex PTSD in relation to the phase-based approach, fit into a new vision that is emerging on this topic; that is, that a phase-based treatment for symptoms of complex PTSD is effective, but not necessary. As the duration of therapy is much longer and needs more resources in the phase-based condition, this suggests that time and finances for commitment to treatment of patients as well as training and supervision of therapists may be better spent when focusing on single trauma focused interventions.



## References

- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders*. <https://doi.org/10.1176/appi.books.9780890425596>
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory–II*. Psychological Corporation.
- Boterhoven de Haan, K. L., Lee, C. W., Fassbinder, E., van Es, S. M., Menninga, S., Meewisse, M. L., Rijkeboer, M., Kousemaker, M., & Arntz, A. (2020). Imagery rescripting and eye movement desensitisation and reprocessing as treatment for adults with post-traumatic stress disorder from childhood trauma: randomised clinical trial. *The British Journal of Psychiatry: The journal of mental science*, *217*(5), 609–615. <https://doi.org/10.1192/bjp.2020.158>
- Carlson, E. B., & Putnam, F. W. (1993). An update on the Dissociative Experiences Scale. *Dissociation: Progress in the dissociative disorders*, *6*(1), 16–27.
- Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., Herman, J. L., Lanius, R., Stolbach, B. C., Spinazolla, J., Van der Kolk, B. A., & Van der Hart, O. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in adults*. <https://terrorvictimresponse.ca/wp-content/uploads/ISTSS-Expert-Concesnsus-Guidelines-for-Complex-PTSD-Updated-060315.pdf>
- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han, H. (2002). Skills training in affective and interpersonal regulation followed by exposure: A phase-based treatment for PTSD related to childhood abuse. *Journal of Consulting and Clinical Psychology*, *70*(5), 1067–1074. <https://doi.org/10.1037/0022-006X.70.5.1067>
- Cloitre, M., Stovall-McClough, K. C., Noonan, K., Zorbas, P., Cherry, S., Jackson, C. L., Gan, W., & Petkova, E. (2010). Treatment for PTSD related to childhood abuse: a randomized controlled trial. *The American Journal of Psychiatry*, *167*(8), 915–924.

<https://doi.org/10.1176/appi.ajp.2010.09081247>

- De Boer, M. R., Waterlander, W. E., Kuijper, L. D., Steenhuis, I. H., & Twisk, J. W. (2015). Testing for baseline differences in randomized controlled trials: an unhealthy research behavior that is hard to eradicate. *The International Journal of Behavioral Nutrition and Physical Activity*, *12*, 4. <https://doi.org/10.1186/s12966-015-0162-z>
- De Jongh, A., Resick, P. A., Zoellner, L. A., van Minnen, A., Lee, C. W., Monson, C. M., Foa, E. B., Wheeler, K., Ten Broeke, E., Feeny, N., Rauch, S. A. M., Chard, K. M., Mueser, K. T., Sloan, D. M., Van der Gaag, M., Rothbaum, B. A., Neuner, F., De Roos, C., Hehenkamp, L. M. J.,...Bicanic, I. A. (2016). Critical analysis of the current treatment guidelines for complex PTSD in adults. *Depression and Anxiety*, *33*(5), 359–69. <https://doi.org/10.1002/da.22469>
- De Jongh, A., & Ten Broeke, E. (2013). *Handboek EMDR, een geprotocolleerde behandelmethode voor de gevolgen van psychotrauma* [EMDR Manual: A protocolized treatment method for the consequences of psychotrauma] (6th ed.). Benelux Pearson Education BV.
- Derogatis, L. R. (1975). *Brief Symptom Inventory (BSI)*. Clinical Psychometric Research. <https://doi.org/10.1037/t00789-000>
- Foa, E. B., Ehlers, A., Clark, D. M., Tolin, D. F., & Orsillo, S. M. (1999). The Posttraumatic Cognitions Inventory (PTCI). Development and validation. *Psychological Assessment*, *11*(3), 303–314. <https://doi.org/10.1037/1040-3590.11.3.303>
- Foa, E. B., Riggs, D. S., Dancu, C. V., & Rothbaum, B. O. (1993). Reliability and validity of a brief instrument for assessing posttraumatic stress disorder. *Journal of Traumatic Stress*, *6*(4), 459–473. <https://doi.org/10.1007/BF00974317>
- Ford, J., Stockton, P., Kaltman, S., & Green, B. L. (2006). Disorders of extreme stress (DESNOS) symptoms are associated with type and severity of interpersonal trauma

- exposure in a sample of healthy young women. *Journal of Interpersonal Violence*, 21(11), 1399–1416. <https://doi.org/10.1177/0886260506292992>
- Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology Behavioral Assessment*, 26(1), 41–54. <https://doi.org/10.1023/B:JOBA.0000007455.08539.94>
- Horowitz, L. M., Alden, L. E., Wiggins, J. S., & Pincus, A. L. (2000). *Inventory of Interpersonal Problems*. Psychological Corporation.
- IBM Corp. Released (2020). *IBM SPSS Statistics for Windows*, Version 27.0. IBM Corp.
- ISTSS Guidelines Committee. Guidelines Position Paper on Complex PTSD in Adults. International Society of Traumatic Stress Studies, 2018. Retrieved from [https://istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-TreatmentGuidelines/ISTSS\\_CPTSD-Position-Paper-\(Adults\)\\_FNL.pdf](https://istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-TreatmentGuidelines/ISTSS_CPTSD-Position-Paper-(Adults)_FNL.pdf)
- Liu, S., Rovine, M. J., & Molenaar, P. C. M. (2012). Selecting a linear mixed model for longitudinal data: Repeated measures analysis of variance, covariance pattern model, and growth curve approaches. *Psychological Methods*, 17(1), 15–30. <https://doi.org/10.1037/a0026971>
- Lancaster, C. L., Gros, D. F., Mullarkey, M. C., Badour, C. L., Killeen, T. K., Brady, K. T., & Back, S. E. (2020). Does trauma-focused exposure therapy exacerbate symptoms among patients with comorbid PTSD and substance use disorders?. *Behavioural and Cognitive Psychotherapy*, 48(1), 38–53. <https://doi.org/10.1017/S1352465819000304>
- Oprel, D. A. C., Hoeboer, C. M., Schoorl, M., Kleine, R. A. D., Cloitre, M., Wigard, I. G., Van Minnen, A., & Van der Does, W. (2020). Effect of prolonged exposure, intensified prolonged exposure and STAIR+prolonged exposure in patients with PTSD related to childhood abuse: A randomized controlled trial. *European Journal of*

*Psychotraumatology*, 12(1), Article 1851511.

<https://doi.org/10.1080/20008198.2020.1851511>

Rosenthal, R. (1991). *Meta-analytic procedures for social research*. SAGE Publications.

Scoboria, A., Ford, J., Lin, H., & Frisman, L. (2008). Revision of the Structured Interview for Disorders of Extreme Stress (SIDES): An exploratory and confirmatory factor analytic approach. *Assessment*, 15(4), 404–425. <https://doi.org/10.1177/1073191108319005>

Van Vliet, N. I., Huntjens, R. J. C., Van Dijk, M. K., & de Jongh, A. (2018). Phase-based treatment versus immediate trauma-focused treatment in patients with childhood trauma-related posttraumatic stress disorder: Study protocol for a randomized controlled trial. *Trials*, 19(1), 1–10. <https://doi.org/10.1186/s13063-018-2508-8>

Voorendonk, E. M., De Jongh, A., Rozendaal, L., & Van Minnen, A. (2020). Trauma-focused treatment outcome for complex PTSD patients: results of an intensive treatment programme. *European Journal of Psychotraumatology*, 11(1), 1783955. <https://doi.org/10.1080/20008198.2020.1783955>

Wagenmans, A., Van Minnen, A., Sleijpen, M., & De Jongh, A. (2018). The impact of childhood sexual abuse on the outcome of intensive trauma-focused treatment for PTSD. *European Journal of Psychotraumatology*, 9(1). <https://doi.org/10.1080/20008198.2018.1430962>

Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013a). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. <https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp>

Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013b). *The Life Events Checklist For DSM-5 (LEC-5)*. <https://www.ptsd.va.gov/professional/assessment/te->

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G.,

Keane, T. M., & Marx, B. P. (2018). The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment, 30*(3), 383–395.

<https://doi.org/10.1037/pas0000486>

World Health Organization (2021). *The ICD-11 for mortality and morbidity statistics*.

(<https://icd.who.int/browse11/l-m/en>).

Table 1

Mean assessment scores and between-group effect sizes at posttreatment, 8 weeks follow up and 12 weeks follow up, and within-group effect sizes

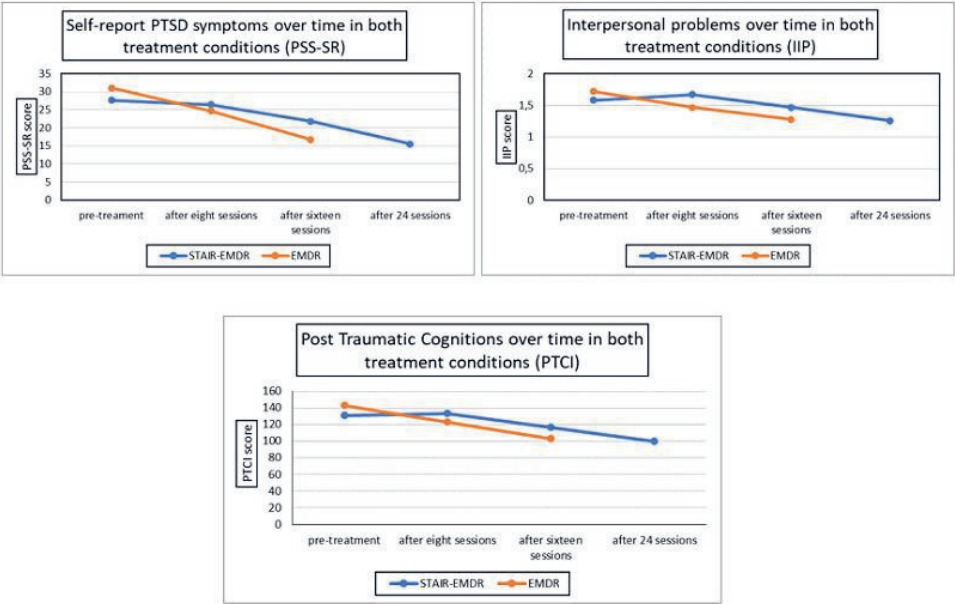
	pretreatment		Between groups effect size posttreatment		Between groups effect size 3-month's follow up		Between groups effect size 6-month's follow up		Within-group effect size between pre and post measurements			
	STAIR-EMDR	EMDR	STAIR-EMDR	EMDR	<i>d</i>	STAIR-EMDR	EMDR	<i>d</i>	STAIR-EMDR	EMDR		
<b>PSS-SR</b>	27.67 (8.23)	31.04 (9.11)	15.53 (11.71)	16.78 (11.75)	0.11	NA	NA	NA	0.93	1.54		
<b>CAPS</b>	37.61 (8.32)	39.34 (9.61)	17.44 (13.20)	19.04 (14.33)	0.12	14.50 (13.45)	16.02 (12.85)	14.24 (3.53)	16.20 (12.76)	0.15	1.66	
<b>SIDES-R</b>	30.77 (10.96)	31.90 (14.03)	19.95 (13.48)	18.10 (11.81)	0.15	17.69 (13.42)	14.05 (10.72)	16.56 (14.62)	15.55 (11.44)	0.08	1.04	
<b>IIP</b>	1.58 (0.54)	1.72 (0.61)	1.26 (0.74)	1.28 (0.73)	0.03	NA	NA	NA	NA	0.50	0.94	
<b>DERS</b>	110.47 (21.78)	118.08 (27.55)	94.00 (25.79)	96.81 (27.79)	0.10	NA	NA	NA	NA	0.78	0.74	
<b>PTCI</b>	130.76 (39.36)	142.89 (42.52)	99.70 (49.38)	102.71 (45.26)	0.06	NA	NA	NA	NA	0.87	0.85	
<b>DES</b>	21.42 (13.16)	28.30 (20.16)	12.36 (14.73)	16.02 (13.41)	0.26	12.91 (14.91)	13.25 (13.74)	11.20 (14.22)	11.48 (11.10)	0.02	0.71	0.77
<b>BSI</b>	1.72 (0.68)	2.03 (0.78)	1.16 (0.83)	1.72 (0.86)	0.14	1.06 (0.90)	1.10 (0.73)	0.97 (0.89)	1.05 (0.71)	0.10	0.82	0.95

PSS-SR = PTSD Symptoms Scale-self report, CAPS-5 = Clinician Administered PTSD Scale for DSM-5, SIDES = Structured Interview for Disorders of Extreme Stress-Revised, IIP = Inventory of Interpersonal Problems, DERS = Difficulties in Emotion Regulation Scale, PTCI = Posttraumatic Cognitions Inventory, BSI = Brief Symptom Inventory, DES = Dissociative Experiences Scale.

Note. NA = not available. Effect sizes are Cohen's *d*. Within-group effect size was calculated between pre-treatment and the posttreatment.

Figure 2

Mean scores at pre-treatment measurements, and the measurements after eight, sixteen and 24 sessions for the PTSD Severity Scale Self-Report, the Inventory of Interpersonal Problems, and the Post-traumatic Cognitions Inventory.



**Predictors and moderators of treatment outcomes in  
phase-based treatment and trauma-focused treatments in  
patients with childhood abuse-related post-traumatic  
stress disorder**

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## **Abstract**

### *Background*

Knowledge of treatment predictors and moderators is important for improving the effectiveness of treatment for PTSD due to childhood abuse.

### *Objectives*

The first aim of this study was to test the potential predictive value of variables commonly associated with PTSD resulting from a history of repeated childhood abuse, in relation to treatment outcomes. The second aim was to examine complex PTSD symptoms as potential moderators between treatment outcomes and conditions, by comparing phase-based treatment with direct trauma-focused treatment.

### *Method*

Data were obtained from a randomized controlled trial comparing a phase-based treatment (Skills Training in Affect and Interpersonal Regulation [STAIR] followed by Eye Movement Desensitization and Reprocessing [EMDR] therapy;  $n = 57$ ) with a direct trauma-focused treatment (EMDR therapy only;  $n = 64$ ) in people with PTSD due to childhood abuse. The possible predictive effects of the presence of borderline personality disorder, dissociative symptoms, and suicidal and self-injurious behaviors were examined. In addition, the possible moderating effects of emotion regulation difficulties, self-esteem, and interpersonal problems between the treatment condition and PTSD post-treatment, corrected for pre-treatment PTSD severity, were determined.

### *Results*

Pre-treatment PTSD severity proved to be a significant predictor of less profitable PTSD treatment outcomes. The same was true for the severity of dissociative symptoms, but only post-treatment, and not when corrected for false positives. Complex PTSD symptoms did not moderate the relationship between the treatment conditions and PTSD treatment outcomes.

*Conclusions*

The current findings suggest that regardless of the common comorbid symptoms studied, immediate trauma-focused treatment is a safe and effective option for individuals with childhood-related PTSD. However, individuals experiencing severe symptoms of PTSD or dissociative sequelae may benefit from additional treatment sessions or the addition of other evidence-based PTSD treatment approaches.

Keywords: PTSD, Childhood abuse, Predictors, Moderators, Treatment.

## Introduction

For long time, there has been a, sometimes heated, debate about the optimal treatment for individuals diagnosed with post-traumatic stress disorder (PTSD) stemming from childhood physical and sexual abuse (De Jongh et al., 2016). Childhood sexual and physical abuse are considered to be types of traumatic experiences associated with the development of Complex PTSD (ISTSS, 2012), a term that was initially launched by Herman (1992). She pleaded for a separate diagnosis with symptoms such as changes in affect regulation, consciousness, identity, perception of the perpetrator, and systems of meaning. These symptoms would form the basis for the diagnosis of DES-NOS (Disorders of Extreme Stress Not Otherwise Specified; Van der Kolk et al., 2005), the former Complex PTSD diagnosis. Recently Complex PTSD has been acknowledged as an official diagnosis according to the International Classification of Diseases 11th revision ICD-11 (ICD-11; World Health Organization, 2018), but involves fewer and different symptoms than the proposed DES-NOS diagnosis. Complex PTSD involves symptoms of “Disturbances in Self-Organization” (DSO; i.e., problems with affect regulation, negative self-concept, and interpersonal problems; World Health Organization, 2018), in addition to the full diagnostic criteria of PTSD. With the inclusion of Complex PTSD as a distinct classification within the ICD-11 discussions involving the diagnosis and treatment of patients with PTSD resulting from childhood abuse have become even more relevant. To this end, some studies have identified a clear distinction between diagnoses of PTSD and Complex PTSD (e.g., Rink & Lipinska, 2020), whereas others have not found much greater variability in clinical presentations among adult patients with PTSD (Achterhof et al., 2019). Nevertheless, there are indications that patients with a history of childhood abuse may exhibit more severe PTSD symptoms or display symptoms of Complex PTSD (Rink & Lipinska, 2020), which further fuels the debate on whether patients with

PTSD related to childhood abuse can benefit from evidence-based PTSD treatments to the same extent as individuals with other trauma histories.

Existing evidence-based trauma-focused therapies may lead to less favorable outcomes in patients with a history of early and repeated trauma, such as childhood abuse (Cloitre et al., 2002; Cloitre et al., 2012; Karatzias et al., 2019). One suggestion to improve the treatment outcomes in this patient group is to offer a phase-based treatment consisting of three phases (ISTSS; Cloitre et al., 2012). Phase one attempts to teach the patient skills for handling interpersonal problems and emotion regulation difficulties that could interfere with tolerating trauma-focused treatments in phase two (Cloitre et al., 2002). Phase three integrates the learned skills in daily life. Regarding the application of a phased approach to patients with a history of childhood abuse, the most studied protocolized first-phase program is STAIR (Skills Training in Affect and Interpersonal Regulation; Cloitre et al., 2002; Cloitre et al., 2010).

Recently, two randomized controlled studies have examined the effects of adding STAIR to a trauma-focused treatment compared to a trauma-focused treatment without the addition of STAIR in patients with PTSD related to childhood abuse (Raabe et al., 2022; Van Vliet et al., 2021). Van Vliet et al. (2021) found that among patients with PTSD related to repeated sexual and/or physical abuse before the age of 18 years ( $N = 121$ ), treatment with EMDR-only therapy and EMDR preceded by STAIR were equally effective with STAIR with regard to the primary outcome variable being PTSD severity (between conditions  $ES d = .12$ ). Additionally, for the secondary outcome measures (i.e., complex PTSD symptoms, dissociative symptoms and general psychopathology) no significant differences in change were found between the treatment conditions from pretreatment to posttreatment. Similarly, Raabe et al. (2022) found that for individuals with PTSD related to repeated sexual or physical abuse before the age of 15 years ( $N = 61$ ), Imagery Rescripting (ImRs) as a

standalone treatment and ImRs preceded by STAIR were equally effective regarding both primary (i.e., PTSD symptoms;  $d = .18$ ) and secondary outcomes (i.e., feelings of shame, guilt and anger, dissociative symptoms, depression, emotion regulation and interpersonal problems). These studies provide support for the effectiveness of trauma-focused treatments for patients with PTSD related to childhood abuse and, from a cost-effectiveness perspective, for the use of trauma-focused treatment as a standalone approach without the addition of a stabilizing treatment track. However, it remains unclear whether specific patient characteristics are associated with less favorable treatment outcomes, and whether moderation by patient characteristics differs between treatment conditions. Investigating patient characteristics that either predict or moderate treatment outcomes is important because it can aid the development of personalized treatment approaches for patients suffering from symptoms characteristic of Complex PTSD (ISTSS, 2018; Kraemer, 2013).

Key factors to consider when studying individuals with PTSD related to childhood abuse, to develop more personalized treatments, include the severity of dissociative symptoms, the presence of comorbid borderline personality disorder (BPD) and suicidal and self-injurious behavior. Dissociative symptoms are commonly found in PTSD diagnoses (Lyssenko et al., 2018) with the highest dissociation scores being observed in patients with a history of childhood abuse (Vonderlin et al., 2018). Clinicians are concerned about possible symptom exacerbation during trauma-focused treatments (van Minnen et al., 2012), and that dissociation could hinder fear activation, which is considered a key mechanism of successful PTSD treatment (Cooper et al., 2017; Little et al., 2017). Although there is evidence to suggest that dissociation is not predictive of the effectiveness of PTSD psychotherapy in patients with various trauma backgrounds (Hoeboer et al., 2020), questions about its impact on treatment outcomes, specifically in patients with PTSD related to a history of childhood abuse remain unanswered. The presence of borderline personality disorder (BPD) with

comorbid suicidal and self-injurious behaviors is frequently observed in patients with PTSD (Harned et al., 2010; Zlotnick et al., 2003) and has been found to be closely associated with the presence of Complex PTSD (Resick et al., 2012). A meta-analysis indicated that the effectiveness of psychotherapies for PTSD caused by diverse traumas is unlikely to be influenced by the presence of BPD (Slotema et al., 2020). However, in a particular patient group with a history of childhood abuse, BPD may partly explain the less profitable PTSD treatment outcomes. In addition, most studies among patients with PTSD related to childhood abuse excluded individuals with comorbid BPD and/or suicidal and self-injurious behavior or did not report treatment outcomes for this subgroup (Bohus et al., 2013; Van Minnen, et al., 2012). This knowledge gap makes it unclear whether these symptoms affect PTSD treatment outcomes. Separate DSO symptoms (i.e., emotion regulation difficulties, interpersonal problems, and negative self-esteem) are potentially relevant moderators between PTSD treatment outcomes, and are considered to particularly benefit from treatments such as STAIR. From this point of view, it has been reasoned that patients would benefit more from trauma-focused treatment preceded by STAIR than from a standalone trauma-focused treatment (Cloitre et al., 2002; Cloitre et al., 2010). Conversely, Hoeboer et al. (2021) found that the DSO symptoms cluster did not moderate between three forms of prolonged exposure (PE); that is, prolonged exposure as standalone treatment with weekly sessions (16 sessions), an intensified form of prolonged exposure with three sessions per week (14 sessions), and prolonged exposure (8 sessions) preceded by STAIR (8 sessions). However, they did not study whether or not STAIR, as an actual addition to trauma-focused treatment, would be associated with better treatment outcomes than trauma-focused treatment alone, which is a core question related to the discussion on the treatment of patients with PTSD related to childhood abuse (ISTSS, 2018).

Therefore, the first aim of the present study was to assess potential predictors of PTSD treatment outcomes in patients with PTSD stemming from repeated sexual and/or physical abuse before the age of 18, using EMDR therapy as a trauma-focused treatment. The second aim was to examine possible moderators influencing the relationship between treatment conditions and PTSD treatment outcomes, with direct trauma-focused treatment (EMDR therapy) and phase-based treatment (EMDR therapy preceded by STAIR) as treatment conditions. More specifically, we hypothesized that the presence of a borderline personality disorder or the severity of suicidality, self-injury, or dissociative experiences at pre-treatment would predict less favorable PTSD treatment effects. Furthermore, we hypothesized that disturbances in self-organization would moderate the relationship between treatment conditions and treatment outcomes and that, the presence of more DSO symptoms would be related to worse outcomes in the direct trauma-focused (EMDR only) condition than in the phase-based condition, as STAIR aims to address these disturbances (Cloitre et al., 2002).

## **Method**

### *2.1 Design*

The present study used data from the TOPRON study, a randomized controlled trial designed to determine whether a phase-based approach (STAIR followed by EMDR;  $n = 57$ ) would be more effective than an immediate trauma-focused approach (EMDR only;  $n = 64$ ) in people with childhood trauma-related PTSD (Vliet et al., 2021). The design paper of this study (Van Vliet et al., 2018) is available at <https://doi.org/10.1186/s13063-018-2508-8>. The study design was registered in NTR5991 and approved by the medical ethics committee Twente NL 56641.044.16 CCMO.

### *2.2 Participants*

From September 2016 until December 2019, participants were recruited in two outpatient mental health organizations in the Netherlands. After patients received information about the study and had time to read and overthink the information, patients were asked to sign an informed consent form when they were willing to participate. Patients were included when aged between 18 and 65 years and diagnosed with PTSD as verified with the CAPS-5 (Clinician-Administered PTSD scale for DSM-5 [Weathers et al., 2013]). Furthermore, they reported being victims of repeated sexual and/or physical abuse before the age of 18 by a caretaker or a person in a position of authority, as identified by the LEC-5 (Weathers et al., 2013). Patients were excluded if they had insufficient mastery of the Dutch language and in case of an acute risk of suicidality, for which direct crisis intervention was needed. In addition, they were excluded if they had received treatment for PTSD in the past year with at least eight sessions (of any evidence-based program), reported being a victim of ongoing physical and/or sexual abuse, reported alcohol or drug dependency according to DSM-5 criteria (American Psychiatric Association, 2013) or had intellectual disability.

### *2.3 Assessment schedule*

Patient characteristics and PTSD diagnosis and severity were assessed during the baseline assessment, at post-treatment (T4), and at three- and six-month follow-up. In addition to PTSD symptom change, which was the main outcome of this study, we investigated the severity of suicidality and self-injury, presence of a borderline personality disorder, and severity of dissociative experiences as potential predictors at baseline. Furthermore, we investigated DSO symptoms at baseline (i.e., interpersonal problems, emotion regulation problems, and problems in self-esteem) as possible moderators influencing the relationship between treatment conditions and PTSD treatment outcomes. For a detailed description of the instruments that were used to assess these symptoms, see paragraph *2.5 measurements*.

### *2.4 Treatment*



For a complete description of the two treatment conditions, see Van Vliet et al. (2018; 2021). Both STAIR and EMDR therapy were delivered twice a week in sessions lasting 90 minutes each. STAIR was conducted according to the treatment program described by Cloitre and her colleagues (Cloitre et al., 2002). The EMDR therapy was conducted according to the Dutch translation of the EMDR standard protocol (De Jongh & Ten Broeke, 2013). In both treatment arms, patients first received one 90 minutes session before the start of the actual treatment, consisting of psychoeducation and formulation of a hierarchy of relevant traumatic experiences with the most disturbing memory at the top. After the first session, patients started with STAIR sessions or EMDR therapy sessions, depending on the condition they were randomly assigned to. After treatment (eight sessions of STAIR followed by 16 sessions of EMDR therapy, or only 16 sessions of EMDR therapy), patients were not allowed to receive any psychological therapy during the six-month follow-up period.

## *2.5 Measurements*

### *Outcome measurements*

The presence and severity of PTSD were assessed using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013) at pre-treatment, post-treatment, and both follow-up measurement points. The pre-treatment score was used as a covariate for the post-treatment scores to determine whether the severity of pre-treatment scores would directly affect the post-treatment scores. Since the CAPS is the gold standard for classifying PTSD and its severity, we included only the total scores in the calculations. All the more since the internal consistency in validation of the Dutch CAPS-5 has turned out to be high ( $\alpha = .90$ ; Boeschoten et al., 2018). To ensure that our trained independent professionals scored the CAPS correctly we calculated the inter-rater reliability using the intra-class correlation coefficient (ICC) after the independent rating of the same patient by four trained

professionals. With an ICC of .999, the inter-rater reliability was excellent for this outcome measure in the present study.

Although the study protocol described the PSS-SR (Foa et al., 1993) as the primary outcome variable (Van Vliet et al., 2018), the CAPS-5 total scores were used in the present study because they contained fewer missing values in the dataset.

### *Predictors*

The presence of a borderline personality disorder was determined using the Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID-II interview; First et al., 1997), with items 97 and 98 determining the severity of self-injury (score 1 for absent, 2 for doubtful, and 3 for present; for statistical analyses, the scores were recoded as 0 for absent, 1 for doubtful, and 2 for present). The Dutch translation and adaptation have been evaluated well (mean Interrater reliability .84 [Lobbestael et al., 2011]; test-retest reliability .63 [Weertman et al., 2005]). The dichotomous outcomes of the SCID-II were used, (i.e., whether the patient fulfilled the diagnostic criteria for a personality disorder) therefore, we were unable to calculate the Cronbach's alpha for this measure.

The severity of suicidality was determined using Item 9 of the Beck Depression Inventory (BDI; Beck et al., 1996), a self-report questionnaire with a scale from 0 to 3 (with a score of 0 indicating the absence of suicidal thoughts, a score of 1 indicating suicidal thoughts, but no intention to carry them out, and a score of 2 indicating a clear intention to commit suicide). If a score of 3 indicated that a patient was acutely suicidal and in need of direct crisis interventions, the patient was permanently excluded for participation and received the needed crisis interventions. Since this measure was categorical, we were unable to calculate Cronbach's alpha.

Severity of dissociative symptoms was measured using the Dutch translation of Dissociative Experiences Scale (DES-II; Carlson & Putnam, 1993; Van IJzendoorn & Schuengel, 1996;

Cronbach's  $\alpha = .93$  in the present study at baseline). It is a 28-item self-report questionnaire, with scores ranging from 0 to 100.

### *Moderators*

The severity of interpersonal difficulties was indexed by the Dutch translation of the Inventory of Interpersonal Problems (IIP; Horowitz et al., 2000; Cronbach's  $\alpha = .85$  at baseline of the current study). Each of the 32 IIP items was scored on a 5-point scale from 0 (not at all) to 4 (very strongly). The psychometric properties of the IIP are satisfactory (Barkham & Hardy, 1996).

The severity of difficulties in emotion regulation was indexed using the Dutch version of the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004). The reliability of this study at baseline was high (Cronbach's  $\alpha = .92$ ). It consists of 36 items, each rated on a 5-point scale and the instrument has been validated with good results (Gratz & Roemer, 2004). To assess the severity of DSO symptom self-esteem the subscale for negative cognitions about self from the Dutch version of the Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999) was used consisting of 21 items, which has high reliability at baseline in this study (Cronbach's  $\alpha = .94$ ). Patients have to score on a Likert scale from 1 ("I totally disagree") to 7 ("I totally agree"). The Dutch PTCI had good psychometric properties (Van Emmerik et al., 2007).

### **Statistical analysis**

Analyses were conducted using SPSS version 25 (2017). The power calculation was based on a repeated-measures ANOVA, with treatment condition (phase-based treatment [EMDR preceded by STAIR] versus direct trauma-focused treatment [EMDR only]) as the between-subjects factor and time (pre-treatment, post-treatment/six month follow-up) as the within-subjects factor (Van Vliet et al., 2018). Inspection of the Mahalanobis distances of all the

variables in the original dataset indicated two cases as statistical outliers. Little's Missing Completely At Random test was used to examine the missing data, which showed an insignificant result ( $\chi^2(81) = 76.17, p = 0.63$ ), indicating that there were no systematically missing data in the current dataset. Missing data were handled by multiple imputations using the mice package in R (van Buuren, 2012). Continuous variables were imputed using predictive mean matching, and categorical variables were imputed using logistic regression (binary or ordinal, depending on the number of categories). The interactions were not imputed but were calculated from the imputed variables during the imputation process and were not used to impute the other variables (see van Buuren, 2012, for details about these procedures). As the maximum percentage of missing data for the variables was 33.9%, at least 34 imputations were deemed necessary, and we generated 50 imputed datasets as recommended by Graham (2009, 2012). The imputation methods (predictive mean matching and logistic regression) ensured that all imputed values were within the possible range of the observed values, and only the imputed values of the categorical variables were rounded (default method for logistic regression). As SPSS does not provide pooled outcomes for all statistics and tests, we calculated the pooled outcomes using functions in R for the following results: standard deviations of separate variables, multiple correlations, R-squared values (adjusted and unadjusted) and corresponding F-tests, R-squared change values and corresponding F-tests, standardized regression coefficient beta, and Variance Inflation Factor (VIF) scores. Before the regression analyses, preliminary analyses were conducted to check for violations of assumptions of normality, linearity, multicollinearity, and homoscedasticity. The results indicated no violation of these assumptions. Analyses performed with and without outliers did not lead to different conclusions; therefore, only the results with outliers are presented herein. Outcomes without outliers are available upon request.

To examine possible predictors of PTSD treatment outcomes and moderators between treatment outcome and condition, two hierarchical regression analyses were performed, with the pretreatment PTSD score as a covariate (to exclude the potential conclusion that DSO symptoms are just expressions of severe PTSD) and the scores at post-treatment and at the six-month follow-up as outcome variables. In the analyses, the severity of suicidality and self-injury, the presence of borderline personality disorder, and the severity of dissociative experiences were included as predictors, and emotion regulation problems, interpersonal problems, and self-esteem problems were included as predictors and moderators. To examine moderators influencing the relation between condition and treatment outcome, the interaction terms between condition and the three separate DSO symptoms (Frazier et al., 2004; Warner, 2013) were performed. Variables were entered into four blocks: 1) PTSD severity at pre-treatment, 2) treatment condition (i.e., phase-based treatment versus direct trauma-focused treatment), 3) various psychopathology symptoms at pre-treatment, and 4) interaction terms between treatment form and DSO variables.

## Results

Possible baseline differences between the two treatment groups were analyzed using chi-squared tests and t-tests. Categorical variables did not differ significantly between the two conditions (presence of Complex PTSD  $F [1, 14523] = 0.57, p = 0.452$ ; presence of borderline personality disorder  $F [1, 7476] = 0.79, p = 0.374$ ; severity of suicidality  $F [2, 11652] = 0.22, p = 0.800$ ; severity of self-injury  $F [2, 1083117] = 0.77, p = 0.464$ ). Table 1 presents the means, standard deviations, and baseline differences between the two conditions for the continuous predictors and moderators and the PTSD scores at post-treatment and the six-month's follow-up. No significant differences were found at baseline between the two conditions, except for the severity of dissociative symptoms, with a significantly higher mean

score in the EMDR therapy only condition ( $t [8926] = 2.10, p = .035$ ). As for the DES, a significant difference was found at pre-treatment between the two conditions, analyses with and without outliers on the DES were performed. As the outcomes did not lead to different conclusions, the presented results are with outliers included.

Table 1 The pooled means, standard deviations and pooled t-scores for continuous variables pre-treatment and the PTSD severity at post-treatment and at six month's follow-up

Variable	EMDR condition <i>M (Sd)</i>	STAIR-EMDR condition <i>M (Sd)</i>	<i>t</i>	<i>df**</i>	<i>p</i>
PTSD pre-treatment	39.34 (9.61)	37.61 (8.32)	1.05	119	.295
Dissociation pre-treatment	28.12 (19.62)	21.38 (13.40)	2.10	8926	.035
Emotion Regulation Problems pre-treatment	117.05 (27.14)	110.55 (21.86)	1.36	3632	.174
Interpersonal Problems pre-treatment	1.70 (0.61)	1.59 (0.54)	1.00	4991	.316
Self-esteem pre-treatment	88.83 (28.83)	80.97 (27.62)	1.46	4919	.146
PTSD post-treatment	18.26 (14.10)	18.06 (13.34)			
PTSD six months' follow- up	16.27 (12.76)	15.89 (13.64)			

\*significant value  $p < .05$

\*\* the 50 imputations cause high degrees of freedom

Table 2 presents the results of the hierarchical regression analyses identifying potential predictors and moderators using the CAPS-5 at post-treatment as the dependent variable and the CAPS at pre-treatment as a covariate. The CAPS total score explained 24.1 % of the variance on the post-treatment score, which was a significant effect ( $F [1,111.83] = 33.38, p < .001; \beta = .490$ ). In the second block, we entered the condition, in the third block all predictors were entered, and in the fourth block the interactions between the separate DSO symptoms and conditions were entered, all explaining low, non-significant differences of the variance. In this final analysis, pre-treatment PTSD severity proved the best predictor of treatment outcomes ( $\beta = .41, p < .000$ ) and led to a positive predictive effect of dissociative experiences on PTSD treatment outcomes, with pre-treatment PTSD severity as a covariate ( $\beta = .28, p = .009$ ; see Table 2). The other predictors and moderators in the model did not

lead to a significant difference. We conducted a Benjamini-Hochberg correction on the outcomes to control for false positives (significance level  $(k/m) \cdot \alpha$ , with  $\alpha = .05$ ), showing that the lowest  $p$ -value (.012 for dissociation) is not lower than the corrected significance level (.0083). This means that the predictive value of dissociative experiences on PTSD treatment outcomes should be interpreted with caution.

Table 2 Pooled outcome of hierarchical regression analysis with CAPS scores at posttreatment as the dependent variable

Pooled	<i>B</i>	<i>SE</i>	$\beta$	<i>T</i>	<i>p</i>	FMI
Block 1						
Constant	-10.534	5.011		-2.102	.036	.085
CAPS pretreatment	.745	.128	.490	5.810	.000	.108
Block 2						
Constant	-11.276	5.323		-2.118	.034	.108
CAPS pretreatment	.751	.129	.495	5.798	.000	.113
Condition	1.096	2.388	.040	.459	.646	.154
Block 3						
Constant	-5.112	6.702		-.763	.446	.181
CAPS pretreatment	.624	.148	.411	4.222	.000	.126
Condition	2.107	2.451	.077	.860	.390	.212
Suicidality	2.104	2.062	.104	1.020	.308	.229
Self-injury	1.766	1.567	.112	1.127	.260	.242
BPD	-1.150	3.232	-.033	-.356	.722	.197
Dissociation	.225	.086	.283	2.604	.009	.283
Emotion Regulation	-.121	.074	-.221	-1.633	.103	.229
Interpersonal Problems	3.238	2.537	.136	1.276	.202	.236
Self-esteem	-.021	.066	-.044	-.322	.747	.253
Block 3						
Constant	-1.455	7.919		-.184	.854	.156
CAPS pretreatment	.629	.149	.414	4.225	.000	.127
Condition	-7.275	11.630	-.267	-.626	.532	.185
Suicidality	2.011	2.079	.099	.967	.334	.227
Self-injury	2.024	1.629	.128	1.242	.215	.258
BPD	-1.184	3.249	-.034	-.364	.716	.193
Dissociation	.224	.089	.282	2.518	.012	.305
Emotion Regulation	-.133	.099	-.241	-1.343	.180	.223
Interpersonal Problems	2.470	3.314	.104	.745	.456	.244
Self-esteem	-.036	.087	-.075	-.417	.677	.229
Condition x Emotion	.043	.153	.178	.279	.781	.280
Regulation						
Condition x Interpersonal Problems	1.738	5.377	.111	.323	.747	.271
Problems						
Condition x self-esteem	.021	.123	.070	.170	.865	.238

CAPS = Clinician-administered PTSD scale, BPD = Borderline Personality Disorder, B = Unstandardized regression coefficient, SE = Standard error,  $\beta$  = standardized regression coefficient, FMI = Fraction of missing information.

The model with the CAPS-5 total scores as a covariate and the CAPS score at six months' follow-up as the dependent variable explained 19.5 % of the variance in the post-treatment score, which is a significant effect ( $F$ -change [1, 97.29] = 21.62,  $p < .001$ ;  $\beta = .441$ ; see Table 3). In the second, third, and fourth blocks, we entered the condition, predictors, and interactions between separate DSO symptoms and conditions, all adding low percentages and a non-significant explanation of the variance. None of the potential predictors and moderators caused a significant difference in the model

Table 3 Pooled outcome of hierarchical multiple regression with CAPS scores at six month's follow-up as the dependent variable and pretreatment PTSD score as the covariate

Pooled	<i>B</i>	<i>SE</i>	$\beta$	<i>T</i>	<i>p</i>	FMI
Block 1						
Constant	-8.623	5.278		-1.634	.103	.197
CAPS pretreatment	.641	.134	.441	4.777	.000	.208
Block 2						
Constant	-9.125	5.649		-1.615	.107	.229
CAPS pretreatment	.645	.136	.444	4.745	.000	.217
Condition	.742	2.428	.028	.305	.760	.203
Block 3						
Constant	-3.642	7.127		-.511	.609	.260
CAPS pretreatment	.609	.161	.419	3.792	.000	.246
Condition	1.695	2.483	.064	.683	.495	.215
Suicidality	-.171	2.235	-.009	-.076	.939	.330
Self-injury	2.258	1.654	.149	1.365	.173	.305
BPD	-4.474	3.482	-.135	-1.285	.199	.293
Dissociation	.095	.086	.124	1.102	.271	.268
Emotion Regulation	-.138	.079	-.263	-1.758	.079	.295
Interpersonal Problems	2.172	2.623	.095	-.828	.408	.270
Self-esteem	.056	.065	.122	.867	.386	.219
Block 3						
Constant	.732	8.397		.087	.931	.234
CAPS pretreatment	.612	.162	.421	3.783	.000	.246
Condition	-9.899	11.533	-.379	-.858	.391	.152
Suicidality	-.303	2.234	-.016	-.136	.892	.317
Self-injury	2.501	1.722	.165	1.453	.147	.322
BPD	-4.527	3.511	-.137	-1.289	.198	.294
Dissociation	.100	.088	.130	1.130	.259	.281
Emotion Regulation	-.183	.103	-.348	-1.778	.076	.270
Interpersonal Problems	1.914	3.297	.084	.580	.562	.219
Self-esteem	.068	.089	.147	.769	.442	.243
Condition x Emotion Regulation	.116	.146	.505	.790	.430	.196
Regulation						
Condition x Interpersonal Problems	.799	5.334	.054	.150	.881	.243
Problems						
Condition x self-esteem	-.032	.123	-.110	-.264	.792	.217

CAPS = Clinician-administered PTSD scale, BPD = Borderline Personality Disorder, B = Unstandardized regression coefficient, SE = Standard error,  $\beta$  = standardized regression coefficient, FMI = Fraction of missing information.



## Discussion

This study investigated potential predictors and moderators of PTSD treatment outcomes among patients with a history of childhood abuse who were treated within two outpatient mental health settings and compared the results of phase-based treatment with those of direct trauma-focused treatment for this target group. Our first hypothesis, that the presence of a borderline personality disorder or the severity of suicidality, self-injury, or dissociative experiences at pre-treatment would predict less favorable PTSD treatment effects, was partly supported. The results showed that the severity of PTSD symptoms at the start of treatment was the best predictor of less beneficial PTSD treatment outcomes. When corrected for pretreatment PTSD severity, only dissociative symptoms predicted worse PTSD treatment outcomes but only post-treatment and when corrected for false positives these results did not hold true, which means that these should be interpreted with caution. In the long term, at the six-month follow-up, dissociative symptoms were not found to be associated with worse PTSD treatment outcomes. This indicates that none of the patient characteristics measured prior to treatment were predictive of less favorable post-treatment treatment outcomes, except for PTSD severity. This also holds true for the severity of dissociative symptoms which was found to have an albeit disputable significant impact on treatment outcomes, but only a immediately post-treatment and not on the long term. This means that pre-treatment characteristics should not be a reason to withhold patients a PTSD treatment or to deliver another type of (e.g., stabilizing) treatment form. Our second hypothesis, stating that DSO symptoms (i.e., interpersonal problems, problems in affect regulation, and negative self-concept) moderate the relationship between treatment conditions and treatment outcomes, was not supported by the present data. Based on these data, the choice for a trauma-focused treatment or a phase-based treatment should not depend on the severity of interpersonal problems, emotion regulation problems or negative self-concept.

This study is the first to examine self-injury and suicidality as potential predictors of PTSD outcomes. Hence, besides pretreatment PTSD severity, we only found dissociative symptoms to be predictive of PTSD treatment outcomes; however, this predictive effect did not persist in the long term and did not hold true when correcting for false positives. This could be explained by the fact that dissociative symptoms diminish in response to trauma-focused treatment (Van Vliet et al., 2021). The finding that DSO symptoms did not moderate between PTSD treatment outcomes and conditions is consistent with the results of a study that compared 16 sessions of Prolonged Exposure therapy (PE) with eight sessions of PE preceded by eight sessions of STAIR in the same target group (Hoeboer et al., 2021). Our results showed that even when STAIR was added to trauma-focused treatment (instead of replacing a part of the trauma-focused treatment), the severity of the separate DSO symptoms did not moderate between the treatment conditions and PTSD treatment outcomes. In other words, the severity of DSO symptoms does not seem to predict whether a patient will profit more from phase-based treatment than from trauma-focused treatment, or vice versa.

The finding that the presence of a borderline personality disorder was not found to be a predictor of PTSD treatment outcomes is in line with the results of a meta-analysis of patients with regular PTSD, which showed that psychotherapy for PTSD in general is effective in patients with borderline personality disorder (Slotema et al., 2020). This suggests that irrespective of the type of trauma background, the presence of BPS may not influence the results of treatment outcomes for PTSD. In contrast to the results of a meta-analysis showing that dissociative phenomena are not predictive of PTSD treatment outcomes (Hoeboer et al., 2020), we found that dissociation symptoms were predictive of worse posttreatment PTSD outcomes. This difference may be explained by differences in target groups, because childhood trauma has been found to be associated with the presence of more severe dissociative symptoms than other trauma types (Schalinski and Teicher, 2015). Hoeboer et al.

(2020) included studies on patients with PTSD from all types of trauma backgrounds.

Furthermore, self-injury and suicidality did not predict PTSD treatment outcome.

One of the strengths of the current study is that it is one of the first to identify multiple potential predictors and moderators in the treatment of a patient group with PTSD related to childhood abuse, without excluding patients with a borderline personality disorder and/or self-injurious or suicidal behavior. Second, in line with the Complex PTSD guidelines (ISTSS, 2012), STAIR was used as an add-on to trauma-focused therapy within the phase-based treatment condition rather than as a replacement for (a part of) the trauma-focused sessions. The third strength is the six-month follow-up PTSD measurements, rendering it possible to determine the impact of a variety of predictor and moderator variables on the long-term effects of trauma-focused treatment. Conversely, a limitation of the present study is that the sample size was small, and there were missing data (data were imputed) that decreased statistical power, restricted the number of predictors and moderators that could be included, and limited the ability to examine higher-order interactions. In addition, suicidal and self-injurious behaviors were only measured by single items, which also limited the conclusions. One noteworthy aspect for discussion pertains to the source of these findings, which were derived from a dataset originating from an RCT that has been used for various analyses, including one based on the personalized advantage index, PAI (van Vliet et al., in press). However, an essential distinction lies in the fact that the present study aimed to assess the actual predictive value of a wide variety of variables, previously assumed to have a differential impact on treatment outcomes. This differs from the PAI study, a distinct analytical approach that sought to investigate a broader question of whether certain patients with childhood-related PTSD and potential symptoms of complex PTSD would benefit more from a phased treatment approach, whereas others might benefit more from a direct trauma-focused approach. This was achieved by utilizing all variables measured in the study and

employing machine learning techniques to identify the combination of variables with the strongest predictive value. Although it is important to acknowledge that relying on a singular dataset for different analyses carries the inherent risk of over-publication of results (Šupak Smolčić, 2013), it is also important to establish that the results of both studies converge on the notion that there are no compelling grounds to favor phase-based treatment over trauma-focused treatment.

The fact that both the severity of PTSD symptoms and the severity of dissociative symptoms were predictive of less favorable PTSD treatment outcomes (the latter only at post-treatment and not at follow-up) suggests that individuals who develop severe PTSD symptoms as a result of exposure to adverse childhood events have a relatively worse long-term treatment prognosis. Conceivably, PTSD treatment results for this specific patient group were not optimal. To this end, future studies should focus on improving the treatment outcomes for this target group to enhance the effects of trauma-focused PTSD treatment. This should not be STAIR, because Complex PTSD symptoms were not found to moderate between PTSD treatment outcome and the EMDR condition preceded by STAIR or the EMDR-only condition. Since no clear moderators were found that influenced the relationship between treatment conditions and PTSD treatment outcomes, future studies should focus on investigating other possible moderators or possible combinations of factors that may influence treatment outcomes on one treatment or the other, rather than separate symptoms.

In conclusion, the present findings provide valuable insights into treatment predictors and moderators for patients with severe PTSD related to childhood abuse, addressing unresolved questions involving ongoing discussions on the treatment of these patients. The results of this study, although with some limitations (e.g. size of the sample and the amount of missing data), suggest that trauma-focused treatments can lead to improved outcomes in patients with PTSD related to childhood abuse. However, individuals with severe PTSD

symptoms may experience less favorable outcomes. The same holds true for dissociative symptoms, but this turned out to only pertain to their status immediately after treatment, and not in the longer run, and not when corrected for false positives. Further research is necessary to replicate these findings and develop treatments for patients at risk of achieving less profitable outcomes. Nonetheless, these and findings of other recent studies on this topic converge to suggest that even patients with severe forms of PTSD profit from evidence-based trauma-focused therapies.

## References

- Achterhof, R., Huntjens, R. J. C., Meewisse, M-L., & Kiers, H. A. L. (2019). Assessing the application of latent class and latent profile analysis for evaluating the construct validity of complex posttraumatic stress disorder: cautions and limitations. *European Journal of Psychotraumatology*, *10*(1), [1698223].  
<https://doi.org/10.1080/20008198.2019.1698223>
- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: Author.
- Barkham, M., Hardy, G. E. & Startup, M. (1996). The IIP-32: A short version of the Inventory of Interpersonal Problems. *British Journal of Clinical Psychology*, *35*, 21-35. <https://doi.org/10.1111/j.2044-8260.1996.tb01159.x>
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory II*. San Antonio, TX: Psychological corporation.
- Boeschoten, M. A., Van der Aa, N., Bakker, A., Ter Heide, F. J. J., Hoofwijk, M. C., Jongedijk, R. A., Van Minnen, A., Elzinga, B. M., & Olf, M. (2018). Development and Evaluation of the Dutch Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). *European Journal of Psychotraumatology*, *9*(1), 1546085.  
<https://doi.org/10.1080/20008198.2018.1546085>
- Bohus, M., Dyer, A. S., Priebe, K., Krüger, A., Kleindienst, N., Schmahl, C., Niedtfeld, I., & Steil, R. (2013). Dialectical behaviour therapy for post-traumatic stress disorder after childhood sexual abuse in patients with and without borderline personality disorder: a randomised controlled trial. *Psychotherapy Psychosomatics*, *82*(4), 221-33.  
<https://doi.org/10.1159/000348451>
- Carlson, E. B., & Putnam, F. W. (1993). An update on the Dissociative Experiences Scale. *Dissociation*, *6*(1), 16-27.

- Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., Herman, J. L., Lanius, R., Stolbach, B. C., Spinazolla, J., Van der Kolk, B. A., & Van der Hart, O. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in adults*. <https://terrorvictimresponse.ca/wp-content/uploads/ISTSS-Expert-Concesnsus-Guidelines-for-Complex-PTSD-Updated-060315.pdf>
- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han, H. (2002). Skills training in affective and interpersonal regulation followed by exposure: A phase-based treatment for PTSD related to childhood abuse. *Journal of Consulting and Clinical Psychology, 70*(5), 1067–1074. <https://doi.org/10.1037//0022-006x.70.5.1067>
- Cloitre, M., Stovall-McClough, K. C., Nooner, K., Zorbas, P., Cherry, S., Jackson, C. L., Gan, W., & Petkova, E. (2010). Treatment for PTSD related to childhood abuse: A randomized controlled trial. *American Journal of Psychiatry, 167*(8), 915–924. <https://doi.org/10.1176/appi.ajp.2010.09081247>
- De Jongh, A., Resick, P. A., Zoellner, L. A., van Minnen, A., Lee, C. W., Monson, C. M., Foa, E. B., Wheeler, K., Broeke, E. T., Feeny, N., Rauch, S. A., Chard, K. M., Mueser, K. T., Sloan, D. M., van der Gaag, M., Rothbaum, B. O., Neuner, F., de Roos, C., Hehenkamp, L. M., Rosner, R., ... Bicanic, I. A. (2016). Critical analysis of the current guidelines for Complex PTSD in adults. *Depression and Anxiety, 33*(5), 359–369. <https://doi.org/10.1002/da.22469>
- De Jongh, A., & Ten Broeke, E. (2013). *Handboek EMDR, een geprotocolleerde behandelmethode voor de gevolgen van psychotrauma [EMDR Manual: A Protocolized Treatment Method for the Consequences of Psychotrauma]* (6th ed.). Benelux Pearson Education BV.
- DeRubeis, R. J., Cohen, Z. D., Forand, N. R., Fournier, J. C., Gelfand, L. A., & Lorenzo-

- Luaces, L. (2014). The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration. *PLoS one*, 9(1), e83875. <https://doi.org/10.1371/journal.pone.0083875>
- First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B. W., & Benjamin, L. S. (1997). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Press.
- Foa, E. B., Riggs, D. S., Dancu, C. V., & Rothbaum, B. O. (1993). Reliability and validity of a brief instrument for assessing posttraumatic stress disorder. *Journal of Traumatic Stress*, 6, 459–73. <https://doi.org/10.1002/jts.2490060405>
- Foa, E. B., Ehlers, A., Clark, D. M., Tolin, D. F., & Orsillo, S. M. (1999). The Posttraumatic Cognitions Inventory (PTCI). Development and validation. *Psychological Assessment*, 11(3), 303-314. <https://psycnet.apa.org/doi/10.1037/1040-3590.11.3.303>
- Frazier, P. A., Tix, A. P., & Barron, K. E. (2004). Testing moderator and mediator effects in counseling psychology research. *Journal of Counseling Psychology*, 51, 115e134. <https://psycnet.apa.org/doi/10.1037/0022-0167.51.1.115>
- Graham, J. W. (2009). Missing data analysis: making it work in the real world. *Annual review of psychology*, 60, 549-576. <https://doi.org/10.1146/annurev.psych.58.110405.085530>
- Graham, J.W. (2012). *Missing data: Analysis and design*. Springer.
- Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology and Behavioral Assessment*, 26, 41-54. <https://psycnet.apa.org/doi/10.1023/B:JOBA.0000007455.08539.94>
- Harned, M. S., Rizvi, S. L., & Linehan, M. M. (2010). Impact of co-occurring posttraumatic



stress disorder on suicidal women with borderline personality disorder. *American Journal of Psychiatry*, *167*, 1210–1217.

<https://doi.org/10.1176/appi.ajp.2010.09081213>

Herman, J. L., (1992). Complex PTSD: A syndrome of survivors of prolonged and repeated trauma. *Journal of Traumatic Stress*, *5*, 377-391.

Hoeboer, C. M., De Kleine, R. A., Molendijk, M. L., Schoorl, M., Oprel, D. A. C., Mouthaan, J., Van der Does, W., & Van Minnen, A. (2020). Impact of dissociation on the effectiveness of psychotherapy for post-traumatic stress disorder: meta-analysis. *BJPsych open*, *6*(3), e53. <https://doi.org/10.1192/bjo.2020.30>

Hoeboer, C. M., de Kleine, R. A., Oprel, D. A. C., Schoorl, M., van der Does, W., & van Minnen, A. (2021). Does complex PTSD predict or moderate treatment outcomes of three variants of exposure therapy?. *Journal of Anxiety Disorders*, *80*, 102388. <https://doi.org/10.1016/j.janxdis.2021.102388>

Horowitz, L. M., Alden, L. E., Wiggins, J. S., & Pincus, A.L. (2000). *Inventory of Interpersonal Problems*. Psychological Corporation.

IBM Corp. Released 2017. *IBM SPSS Statistics for Windows, Version 25.0*. IBM Corp.

International Society for Traumatic Stress (2018). ISTSS Guidelines Position Paper on Complex PTSD in Adults. Retrieved from [https://istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS\\_CPTSD-Position-Paper-\(Adults\)\\_FNL.pdf.aspx](https://istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_CPTSD-Position-Paper-(Adults)_FNL.pdf.aspx)

Karatzias, T., Murphy, P., Cloitre, M., Bisson, J., Roberts, N., Shevlin, M., Hyland, P., Maercker, A., Ben-Ezra, M., Coventry, P., Mason-Roberts, S., Bradley, A., & Hutton, P. (2019). Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. *Psychological Medicine*, *49*(11), 1761–1775. <https://doi.org/10.1017/S0033291719000436>

- Kolk, B.A. van der, Roth, S., Pelcovitz, D., Sunday, S. & Spinazzola, J. (2005). Disorders of extreme stress: the empirical foundation of a complex adaptation to trauma. *Journal of Traumatic Stress, 18*, 389-399. <https://doi.org/10.1002/jts.20047>
- Kraemer, H.C. (2013), Discovering, comparing, and combining moderators of treatment on outcome after randomized clinical trials: a parametric approach. *Statistical Medicine, 32*, 1964-1973. <https://doi.org/10.1002/sim.5734>
- Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical Psychology & Psychotherapy, 18*(1), 75–79. <https://doi.org/10.1002/cpp.693>
- Lysenko, L., Schmahl, C., Bockhacker, L., Vonderlin, R., Bohus, M., & Kleindienst, N. (2018). Dissociation in Psychiatric Disorders: A Meta-Analysis of Studies Using the Dissociative Experiences Scale. *American Journal of Psychiatry, 175*(1), 37-46. <https://doi.org/10.1176/appi.ajp.2017.17010025>
- Raabe, S., Ehring, T., Marquenie, L., Arntz, A., & Kindt, M. (2022). Imagery Rescripting as a stand-alone treatment for posttraumatic stress disorder related to childhood abuse: A randomized controlled trial. *Journal of Behavior Therapy and Experimental Psychiatry, 77*, 101769. <https://doi.org/10.1016/j.jbtep.2022.101769>
- Resick, P. A., Bovin, M. J., Calloway, A. L., Dick, A. M., King, M. W., Mitchell, K. S., Suvak, M. K., Wells, S. Y., Stirman, S. W., & Wolf, E. J. (2012). A critical evaluation of the complex PTSD literature: implications for DSM-5. *Journal of Traumatic Stress, 25*(3), 241–251. <https://doi.org/10.1002/jts.21699>
- Rink, J., & Lipinska, G. (2020). Evidence of distinct profiles of ICD-11 post-traumatic stress disorder (PTSD) and complex PTSD in a South African sample. *European Journal of*

*Psychotraumatology*, 11(1), 1818965.

<https://doi.org/10.1080%2F20008198.2020.1818965>

RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA

URL <http://www.rstudio.com/>.

Schalinski, I., & Teicher, M. H. (2015). Type and timing of childhood maltreatment and severity of shutdown dissociation in patients with schizophrenia spectrum disorder.

*PLoS One*, 10(5), e0127151. <https://doi.org/10.1371/journal.pone.0127151>

Slotema, C. W., Wilhelmus, B., Arends, L. R., & Franken, I. H. A. (2020) Psychotherapy for posttraumatic stress disorder in patients with borderline personality disorder: a

systematic review and meta-analysis of its efficacy and safety. *European Journal of*

*Psychotraumatology*, 11(1). <https://doi.org/10.1080%2F20008198.2020.1796188>

Stein, D. J., Koenen, K. C., Friedman, M. J., Hill, E., McLaughlin, K. A., Petukhova, M.,

Ruscio, A. M., Shahly, V., Spiegel, D., Borges, G., Bunting, B., Caldas-de-Almeida, J.

M., de Girolamo, G., Demyttenaere, K., Florescu, S., Haro, J. M., Karam, E. G.,

Kovess-Masfety, V., Lee, S., Matschinger, H., ... Kessler, R. C. (2013). Dissociation

in posttraumatic stress disorder: evidence from the world mental health

surveys. *Biological Psychiatry*, 73(4), 302–312.

<https://doi.org/10.1016/j.biopsych.2012.08.022>

Supak Smolčić V. (2013). Salami publication: definitions and examples. *Biochemia Medica*,

23(3), 237-41. <https://doi.org/10.11613/bm.2013.030>

Van Buuren, S. (2012). *Flexible Imputation of Missing Data*. CRC Press.

Van Emmerik, A. A. P., Schoorl, M., Emmelkamp, P. M. G., & Kamphuis, J. H. (2007).

Psychometrische kenmerken van de Nederlandstalige Posttraumatische Cognities

Inventarisatielijst (PTCI). *Gedragstherapie [Behavior Therapy]*, 40, 269–84.

Van IJzendoorn, M. H., & Schuengel, C. (1996). The measurement of dissociation in normal

- and clinical populations: Meta-analytic validation of the Dissociative Experiences Scale (DES). *Clinical Psychology Review*, *16*(5), 365-382.  
[https://psycnet.apa.org/doi/10.1016/0272-7358\(96\)00006-2](https://psycnet.apa.org/doi/10.1016/0272-7358(96)00006-2)
- Van Minnen, A., Harned, M. S., Zoellner, L., & Mills, K. (2012). Examining potential contraindications for prolonged exposure therapy for PTSD. *European Journal of Psychotraumatology*, *3*. <https://doi.org/10.3402/ejpt.v3i0.18805>
- Van Vliet, N. I., Huntjens, R. J. C., Van Dijk, M. K., & de Jongh, A. (2018). Phase-based treatment versus immediate trauma-focused treatment in patients with childhood trauma-related posttraumatic stress disorder: Study protocol for a randomized controlled trial. *Trials*, *19*(1), 1–10. <https://doi.org/10.1186/s13063-018-2508-8>
- Van Vliet, N. I., Huntjens, R. J. C., Dijk, M. K. Van, Bachrach, N., Meewisse, M., & Jongh, A. De. (2021). Phase-based treatment versus immediate trauma-focused treatment for post-traumatic stress disorder due to childhood abuse : randomised clinical trial. *British Journal of Psychiatry Open*, *7*(6), E211.  
<https://doi.org/10.1192%2Fbjo.2021.1057>
- Warner, R. M. (2013). *Applied statistics: From bivariate through multivariate techniques (2nd ed.)*. Sage Publications, Inc.
- Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., Keane, T. M. (2013). *The Life Events Checklist for DSM-5 (LEC-5)*. Retrieved from National Center for Posttraumatic Stress Disorder ([www.ptsd.va.gov](http://www.ptsd.va.gov) [2013]).
- Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., Keane, T. M., & Marx, B. P. (2018). The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment*, *30*(3), 383–395.  
<https://doi.org/10.1037/pas0000486>

Weertman, A., Arntz, A., Dreesen, L., Van Velzen, C., & Vertommen, S. (2003). Short-interval test-retest interrater reliability of the Dutch version of the structured clinical interview for DSM-IV for personality disorders (SCID-II). *Journal of Personality Disorders, 17*(6), 562-7. <https://doi.org/10.1521/pedi.17.6.562.25359>

World Health Organization (2018). *The ICD-11 for mortality and morbidity statistics*. World Health Organization. Guidelines for the management of conditions specifically related to stress. Geneva: World Health Organization. (<https://icd.who.int/browse11/l-m/en>).

Zlotnick, C., Johnson, D. M., Yen, S., Battle, C. L., Sanislow, C. A., Skodol, A. E., Grilo, C. M., McGlashan, T. H., Gunderson, J. G., Bender, D. S., Zanarini, M. C., & Shea, M. T. (2003). Clinical features and impairment in women with borderline personality disorder (BPD) with posttraumatic stress disorder (PTSD), BPD without PTSD, and other personality disorders with PTSD. *The Journal of Nervous and Mental Disease, 191*(11), 706–713. <https://doi.org/10.1097/01.nmd.0000095122.29476.ff>

**Predicting optimal treatment outcomes in phase-based treatment and direct trauma-focused treatment among patients with posttraumatic stress disorder stemming from childhood abuse**

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**Abstract**

Research over the last few decades has demonstrated the effectiveness of various treatments for posttraumatic stress disorder (PTSD). However, the question of which treatment works best remains, especially for patients with PTSD stemming from childhood abuse. Using the Personalized Advantage Index (PAI), we explored which patients benefit more from phase-based treatment and which benefit more from direct trauma-focused treatment. Data were obtained from a multicenter randomized controlled trial (RCT) comparing a phase-based treatment condition (i.e., eye-movement desensitization and reprocessing [EMDR] therapy preceded by Skills Training in Affect and Interpersonal Regulation [STAIR];  $n = 57$ ) and a direct trauma-focused treatment (EMDR only;  $n = 64$ ) among individuals with PTSD related to childhood abuse. Machine learning techniques were used to examine all pretreatment variables included in the trial as potential predictors and moderators, with selected variables combined to build the PAI model. The utility of the PAI was tested by comparing actual posttreatment outcomes of individuals who received PAI-indicated treatment with those allocated to a non-PAI-indicated treatment. Although eight pretreatment variables between PTSD treatment outcome and treatment condition were selected as moderators, there was no significant difference between participants assigned to their PAI-indicated treatment and those randomized to a non-PAI-indicated treatment,  $d = 0.25$ ,  $p = .213$ . Hence, the results of this study do not support the need for personalized medicine for patients with PTSD and a history of childhood abuse. Further research with larger sample sizes and external validation is warranted.

## Introduction

Exposure to prolonged or repeated traumatic events during childhood is a risk factor for the development of complex posttraumatic stress disorder (CPTSD; Rink & Lipinska, 2020), a diagnostic classification added to the 11th revision of the *International Classification of Diseases (ICD-11*; World Health Organization [WHO], 2019). In addition to typical PTSD symptoms (e.g., intrusions, avoidance, arousal), CPTSD entails symptoms of affect dysregulation, negative self-concept, and interpersonal problems. The *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013), however, does not recognize CPTSD as a separate diagnostic classification, and studies on the distinction between CPTSD and PTSD differ in their results. Some studies have found great variability in clinical presentations among adult individuals with PTSD and CPTSD (Achterhof et al., 2019), whereas other studies have found a clear distinction between these patient groups (e.g., Rink & Lipinska, 2020). Apart from the inconsistencies surrounding the diagnosis of CPTSD, there is also discussion about the treatment of patients who are at risk for developing CPTSD symptoms, such as those with PTSD related to childhood abuse (Cloitre, 2016; De Jongh et al., 2016).

Some experts have argued that people with PTSD who experience interpersonal traumatization in childhood and report symptoms that fall into some or all of the typical CPTSD symptom domains could lack the psychological stability to face traumatic memories and tolerate the emotional arousal associated with trauma-focused treatments (Cloitre et al., 2011), such as prolonged exposure therapy (PE; Foa et al., 2007) or eye-movement desensitization and reprocessing (EMDR; Shapiro, 2018). As such, in 2012, an International Society of Traumatic Stress Studies (ISTSS) working group recommended that individuals with PTSD related to childhood abuse and symptoms of CPTSD should be treated using a “phase-based” treatment model rather than immediate trauma-focused therapy (ISTSS, 2012).



The phase-based treatment model is based on the notion that it is important to increase safety, establish a therapeutic relationship, teach patients about stress management, and affect regulation skills during the first phase of treatment (i.e., before the phase during which exposure to trauma memories occurs; Cloitre et al., 2002). A well-evaluated treatment that has shown efficacy as a first-phase treatment for patients with PTSD related to childhood abuse is Skills Training in Affect and Interpersonal Regulation (STAIR; Cloitre et al., 2002). Several recent studies have shown that evidence-based immediate trauma-focused therapy for PTSD and phase-based treatment, in the form of trauma-focused treatment preceded by STAIR, produce equivalent treatment outcomes in patients with PTSD stemming from childhood abuse (Oprel et al., 2021; Raabe et al., 2022; Van Vliet et al., 2021). These outcomes suggest that a phase-based treatment approach may not be more effective than an evidence-based, direct trauma-focused treatment for PTSD in this patient group.

Although head-to-head comparisons of these therapies have not shown significant differences regarding general treatment outcomes, individual patients may respond differently to these two therapies depending on their characteristics. Until now, studies on predictors and moderators in patients with PTSD or CPTSD related to childhood abuse are scarce. Hoeboer, De Kleine et al. (2021) studied the presence of a CPTSD diagnosis and separated CPTSD symptoms into potential predictors and moderators in this population but did not find any predictors of PTSD treatment outcomes or moderators of associations between treatment condition and the PTSD treatment outcome. However, the authors only assessed single potential predictors and moderators and did not examine a combination of predictors and moderators as a best possible prediction. It is possible that a combination of predictors and moderators could prove superior in predicting and selecting the best available treatment for a given individual as part of a more personalized treatment plan. Such personalized treatment has also been recommended in recent ISTSS guidelines, which suggest that a preparation

phase or other non–trauma-focused intervention may be used in addition to a trauma-focused phase based on certain individual patient characteristics (ISTSS, 2019).

One way to use a combination of pretreatment characteristics to predict the optimal treatment for a given individual and the magnitude of this advantage is the Personalized Advantage Index (PAI; DeRubeis et al., 2014). To the best of our knowledge, until now, only one published study has used this method in this population (i.e., individuals with PTSD or CPTSD stemming from childhood trauma) for the comparison of a phase-based treatment and direct trauma-focused treatment. In this study, Hoeboer, Oprel et al. (2021) used data from an RCT (Oprel et al., 2021) to compare PE alone, intensified PE, and PE plus phase-based treatment with PE as the trauma-focused component (i.e., STAIR followed by PE) in 149 patients. The findings indicated that higher levels of depressive symptoms, less social support, more overall psychopathology, and higher degrees of childhood sexual abuse severity were predictors of poorer treatment outcomes in the standalone trauma-focused treatment conditions compared with phase-based treatment. In addition, more emotion regulation difficulties, lower general health status, and higher baseline PTSD symptoms were predictors of poorer treatment outcomes in participants who received phase-based treatment compared with those who received trauma-focused treatment alone. Randomization to optimal treatment based on these predictors resulted in significantly larger PTSD symptom improvements compared with suboptimal treatment condition randomization, with medium effect sizes.

To date, no studies using PAI analysis to examine the moderating effects of combined pretreatment patient characteristics have examined EMDR as the trauma-focused treatment and STAIR as an additional treatment (i.e., instead of as a replacement for part of the trauma-focused treatment, as in Hoeboer, Oprel et al. [2021]). The purpose of the present study was, therefore, to use machine learning to explore whether some patients with childhood trauma–related PTSD and possible symptoms of CPTSD would benefit more from a phase-based

treatment approach whereas others would benefit more from a direct trauma-focused approach. More specifically, our aim was to contribute to a personalized treatment approach by identifying the optimal treatment option for each individual patient and provide an estimate of the advantage that would be gained by offering a patient the most appropriate treatment.

## **Method**

### *Participants and procedure*

This study used data from a multicenter RCT (Van Vliet et al., 2017) to compare EMDR as a standalone trauma-focused therapy to EMDR therapy preceded by STAIR (i.e., phase-based treatment) in patients with PTSD related to childhood abuse. A total of 121 patients from two mental health institutions in the Netherlands, Dimence GGZ and GGZ Oost-Brabant, were found to be eligible for inclusion. Patients were enrolled after providing written informed consent if they were between 18 and 65 years of age and had been diagnosed with PTSD as measured using the Clinician-Administered PTSD scale for *DSM-5* (CAPS-5; Weathers et al., 2013a). In addition, participants were required to be survivors of repeated sexual and/or physical abuse that occurred before 18 years of age and perpetrated by a caretaker or person in a position of authority before the age of 18. Patients were ineligible for inclusion if they reported acute suicidality, as assessed using Item 9 of the Beck Depression Inventory–II (BDI-II; Beck et al., 1996), and direct crisis intervention was needed or if they demonstrated insufficient mastery of the Dutch language. In addition, participants were excluded if they (a) had received at least eight sessions of any well-evaluated treatment for PTSD in the past year, (b) reported being a victim of ongoing physical and/or sexual abuse, (c) reported severe alcohol or drugs use, or (d) had an intellectual disability. All included patients were randomly assigned to STAIR–EMDR ( $n = 57$ ) or EMDR only ( $n = 64$ ). The study design was registered (NTR5991) and approved by the Medical Ethics Committee of Twente (NL 56641.044.16

CCMO). Further details on the trial methodology and patient sample can be found in Van Vliet et al. (2018, 2021). All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All patients received the required information about the study to decide whether to participate. Written informed consent was obtained after the procedure had been fully explained.

Therapy sessions were delivered twice a week for 90 min each. STAIR was conducted according to the protocol described by Cloitre et al. (2002) and consisted of eight sessions. EMDR was conducted according to the Dutch protocol (De Jongh & Ten Broeke, 2013) and consisted of 16 sessions. In both treatment conditions, patients first received one 90-min session consisting of psychoeducation and constructed a hierarchy of relevant traumatic experiences. Following treatment, patients were not allowed to receive psychological therapy during the 6-month follow-up period. For a more detailed description of these two treatments, see Van Vliet et al. (2018).

### *Measures*

#### *Outcome measure: PTSD symptoms*

PTSD symptom severity, as assessed using the CAPS-5 (Weathers et al., 2013a), was the primary study outcome. The CAPS-5 is a semistructured interview containing 20 questions rated on a scale from 0 (*no complaints*) to 4 (*invalidating complaints*). Because the CAPS is the gold standard for diagnosing PTSD and evaluating symptom severity, we only included total scores in the present analyses. To ensure that the research assistants scored the CAPS-5 correctly and similarly, we calculated interrater reliability using the intraclass correlation coefficient (ICC) and found it to be excellent,  $ICC = .999$ . The Dutch version of CAPS-5 has demonstrated excellent internal reliability (Cronbach's  $\alpha = .90$ ; Boeschoten et al., 2018).

*Pretreatment variables*

To increase the potential feasibility of this model, we decided to reduce the number of variables by applying multiple variable selection steps. Supplementary Tables 1 and 2 show the indexed predictors and moderators at pretreatment. For most questionnaires, the total pretreatment score was used for the moderator and predictor analyses. For some questionnaires, separate subscales were used based on sufficient subscale reliability; subsequently, the correlations between all scales were explored to avoid multicollinearity (see Supplementary Table 3 for information on subscale-specific inclusion and exclusion).

**Demographic characteristics.** The following demographics were included in the study: age, sex, educational attainment, employment status, and marital status.

**Self-report PTSD symptoms.** The 17-item Dutch version of the PTSD Symptom Scale–Self Report, developed as a brief measure of PTSD symptom frequency in trauma survivors, was administered before treatment began (Arntz, 1993). Participants were asked to rate symptom frequency on a scale of 0 (*never*) to 3 (*more than five times a week*). The English version (Foa et al., 1993) and Dutch version (Arntz, 1993) have demonstrated good psychometric properties. In the present sample, internal consistency was high at baseline, Cronbach's  $\alpha = .83$ .

**Physical and/or sexual abuse.** Physical abuse and/or sexual abuse were determined using the Life Events Checklist for *DSM-5* (LEC-5; Weathers et al., 2013b). Participants were asked whether they had experienced various traumatic events and, if so, to indicate their level of exposure (i.e., whether it happened to them or if they heard about or witnessed it).

**Suicidality.** Suicidality was determined using BAI Item 9 (Beck et al., 1996). Patients who indicated that they would commit suicide whenever they had the chance were excluded from study participation, as they required direct crisis intervention. In the current analysis, the presence of suicidal thoughts was used as a dichotomous value.

**Borderline personality disorder (BPD).** The presence of a BPD was determined using the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II; First et al., 1997), which is considered the gold standard for assessing personality disorders. The Dutch translation and adaptation have demonstrated good interrater reliability ( $M = .84$ ; Lobbestael et al., 2011) and test–retest reliability (.63; Weertman et al., 2005). We only used the SCID dichotomously to determine whether the patient fulfilled the diagnostic criteria for a personality disorder; therefore, we were unable to calculate Cronbach’s alpha for this measure. The severity of self-injury was indexed using Items 97 and 98.

**Dissociative symptoms.** The presence of the dissociative PTSD subtype was determined using the CAPS-5 interview (Weathers et al., 2013). Self-reported dissociative symptom severity was measured using the Dissociative Experiences Scale (DES-II; Carlson & Putnam, 1993), which asks respondents to rate items on a visual analog scale ranging from 0 to 100. The DES-II has demonstrated good psychometric properties (Van IJzendoorn & Schuengel, 1996). In the present sample, internal consistency for the DES-II was excellent at baseline, Cronbach’s  $\alpha = .93$ .

**CPTSD.** CPTSD was measured using the 38-item version of the Structured Interview for Disorders of Extreme Stress (SIDES; Ford et al., 2006; Scoboria et al., 2008). It is important to note that when the study began, the current *ICD-11* CPTSD diagnosis had not yet been established (WHO, 2019), and the SIDES represents criteria related to previous operationalizations of a CPTSD diagnosis. Thus, we used the Inventory of Interpersonal Problems (IIP; Horowitz et al., 2000), Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004), and Posttraumatic Cognitions Inventory (PTCI; Foa et al., 1999) to assess symptoms included in the current CPTSD diagnostic criteria. The SIDES has demonstrated good psychometric properties as a dichotomous measure (i.e., interrater reliability = .81 [Pelcovitz et al., 1997], Cronbach’s  $\alpha = .86$  [Spinazzola, 2019]). The SIDES was solely used

dichotomously to determine whether patients fulfilled the CPTSD diagnostic criteria; therefore, we were unable to calculate Cronbach's alpha for this measure.

The IIP consists of 32 items that are rated on a scale of 0 (*not experienced at all*) to 4 (*very strongly experienced*); the measure's eight subscales were used in the present analyses (see Supplementary Table 1). The IPP has shown satisfactory psychometric properties (Barkham & Hardy, 1996). In the present sample, internal consistency ranged from poor to good across most subscales at baseline, Cronbach's  $\alpha$ s = .64–.83; the Domineering/Controlling subscale demonstrated unacceptable internal consistency, Cronbach's  $\alpha$  = .42, whereas the Socially Inhibited, Cronbach's  $\alpha$  = .68, and Intrusive/Needy subscales, Cronbach's  $\alpha$  = .64, were questionable.

The DERS consists of 36 items that are rated on a scale of 1 (*never*) to 5 (*almost always*), and the measure has been well-validated (Gratz & Roemer, 2004). In the present sample, the DERS demonstrated good internal consistency at baseline, Cronbach's  $\alpha$  = .92.

The PTCI is a 33-item scale, rated on a scale of 0 (*totally disagree*) to 7 (*totally agree*). Both the English and Dutch versions of the measure have demonstrated good psychometric properties (Foa et al., 1999; Van Emmerik et al., 2007). In the present sample, internal consistency for the PTCI subscales was good to excellent at baseline, Cronbach's  $\alpha$ s = .86–.94.

**General psychopathology.** The Brief Symptom Inventory (De Beurs & Zitman, 2006; Derogatis, 1975) was used to measure the symptoms of general psychopathology. This self-report instrument includes 53 items that are scored on a scale of 0–4, with higher scores indicating more severe symptoms. The reliability, validity, and utility of the BSI have been tested in many research studies, and the Dutch version has demonstrated good psychometric properties (De Beurs & Zitman, 2006). In the present study, Cronbach's alpha values ranged

from .76 to .86 for most subscales except the Psychoticism subscale, which demonstrated questionable internal consistency, Cronbach's  $\alpha = .69$ .

## Data analysis

### *Data preprocessing*

All analyses were performed using RStudio (RStudio Team, 2020). First, the data were checked for missing values for baseline pretreatment variables. Ten individuals were excluded from the study because they had too many missing values for the baseline variables (i.e., 50.0% or higher). Using Fisher's exact test, we found no significant differences between patients who were included in the study and those who were excluded with regard to any demographic characteristic except educational attainment, such that individuals with lower levels of educational attainment were more likely to be included in the study than those with mid- and higher-level attainment.

The final dataset consisted of 105 individuals (EMDR:  $n = 64$ , STAIR-EMDR:  $n = 57$ ). There are no clear guidelines regarding the size of data sets suitable for machine learning, though some research suggests that 300 patients per treatment arm may be sufficient (Luedtke et al., 2019). As this indicates the present sample may be too small for analyses based on machine learning, this study can best be regarded as an attempt to explore the opportunities and directions for further research. Missing data were imputed using an imputation method based on the random forest algorithm (i.e., the R package *missForest*; Stekhoven & Bühlmann, 2012). The advantage of random forest-based imputation is its ability to deal with mixed data types and complex interactions (Stekhoven & Bühlmann, 2012; Tang & Ishwaran, 2017). Highly correlated variables (i.e.,  $r > .70$ ) were excluded from the statistical analyses to avoid multicollinearity (Kuhn & Johnson, 2013); for highly correlated variables, the research team collectively decided which variables should be removed and which should not. To



remove distributional skewness, outliers were winsorized, and continuous variables were transformed using the Box–Cox method when necessary (Box & Cox, 1964; Kuhn, 2008). Continuous variables were centered and standardized, and categorical variables were centered by recoding the categories around 0 (i.e., -0.5 and 0.5; see Supplementary Table 3 for details about included and excluded variables and transformations for each variable). After data preprocessing, a set of 39 variables was used for model building.

Of the 105 participants, 66 (62.9%) had no missing values for pretreatment variables, and 88 (83.8%) had no missing outcome values. All missing values were imputed, and the imputation performance was quite satisfactory when applied to the nonmissing dataset with artificially introduced missing values. The normalized root mean squared error (NRMSE) was .15, and the proportion of falsely classified (PFC) was .22.

#### *Outcome transformation*

There was a small, insignificant difference in PTSD symptom severity between participants randomized to EMDR (i.e., standalone trauma-focused treatment) and STAIR–EMDR (i.e., phase-based treatment) at baseline (Supplementary Table 1). To avoid this baseline difference affecting our model-building process, we corrected the outcome variable using the following procedure: PTSD symptom severity at baseline was used to build a regression function with posttreatment PTSD symptom severity as the dependent variable (Fiske et al., 1970; Mintz et al., 1979). For further analyses, the residuals of this regression function were used as the outcome variable (i.e., the residual gain score). To interpret the selected moderators and evaluate PAI predictions, actual posttreatment PTSD symptom severity scores were used.

#### *Variable selection*

Following best practices, we applied two variable selection steps to find robust moderators and predictors of treatment response: random forest (RF; Garge et al., 2013; Stekhoven & Bühlmann, 2012) and elastic net regularization (ENR; Friedman et al., 2010). RF is a

recursive partitioning method based on the construction of so-called “trees” of variables. At each split in a tree, a subset of variables is considered (James et al., 2003). To adjust RF for identifying moderators, the model function that determines a split can be extended with treatment (i.e.,  $y = x \times \text{treatment}$ ). The results of the RF procedure include an overall summary of the predictive importance of each variable, which is determined through permutation tests (Garge et al., 2013; James et al., 2003). Variables were selected on the basis of surpassing the permutation threshold. ENR is a penalized regression that combines the least absolute shrinkage and selection operator (LASSO) and ridge regression methods. ENR is particularly useful for datasets that include many variables that are highly correlated (Kuhn & Johnson, 2013), as it shrinks some coefficients of variables toward 0 (ridge regression) and some coefficients of variables to exactly 0, resulting in the exclusion of these variables (LASSO regression). The amount of shrinkage is determined by the tuning parameter lambda. The other tuning parameter is alpha, where 0 corresponds to ridge and 1 to LASSO. These parameters were determined using a 10-fold cross-validation (CV; James et al., 2003). ENR is particularly useful for identifying prognostic variables. To determine moderators, a prognostic model was created for each treatment condition, and the coefficients of the variables in these models were calculated. Variables were selected as potential moderators based on their existence (a) in only one model or (b) in both models, with negative values in one model and positive values in the other (Cohen et al., 2019).

The predictive variables identified using the RF and ENR variable selection methods were analyzed using a backward elimination approach with multiple bootstrapped samples (Austin & Tu, 2004). The bootstrap approach was performed with 1,000 bootstrapped samples. Variables selected in the best model fit and with a  $p$  value lower than .05 in the final model were used to build the PAI. The benefit of this approach is that it allows for the best combination of variables to be included, resulting in the simplest model (Kuhn & Johnson,

2013). Specific interaction effects with treatment were investigated for the identified moderators. These prescriptive associations can be ordinal, meaning that one treatment is superior for all levels of the moderator, or they can be disordinal, meaning that the superiority of a treatment depends on the level of the moderator.

#### *Generating personalized treatment recommendations*

Selected variables (i.e., predictors and moderators) were used to generate personalized treatment recommendations using the PAI approach (DeRubeis et al., 2014). First, a regression model was built using the residual gain score as the dependent variable. Second, with this regression model, individual outcome predictions were made for each treatment using 10-fold CV, which was chosen because this reduces the risk of overfitting (James et al., 2003). The PAI reflected the difference between these two predictions for EMDR and STAIR–EMDR. The size of this PAI indicates the strength of the optimal treatment advantage over the less optimal one (DeRubeis et al., 2014).

#### *PAI evaluation*

To determine the clinical utility of the PAI, a *t* test was conducted to compare the actual posttreatment outcomes of individuals who received PAI-indicated treatment and those who received nonindicated treatment. Following recommendations by DeRubeis et al. (2014), this comparison was repeated for individuals with the highest 60.0% PAI scores. Similar comparisons were then made within the two treatment conditions—EMDR and STAIR–EMDR—separately. For example, posttreatment PTSD symptom severity was compared for participants who received PAI-indicated standalone EMDR and those whose PAI indicated standalone EMDR but who received STAIR–EMDR (i.e., nonindicated).

## **Results**

### *Variable selection*

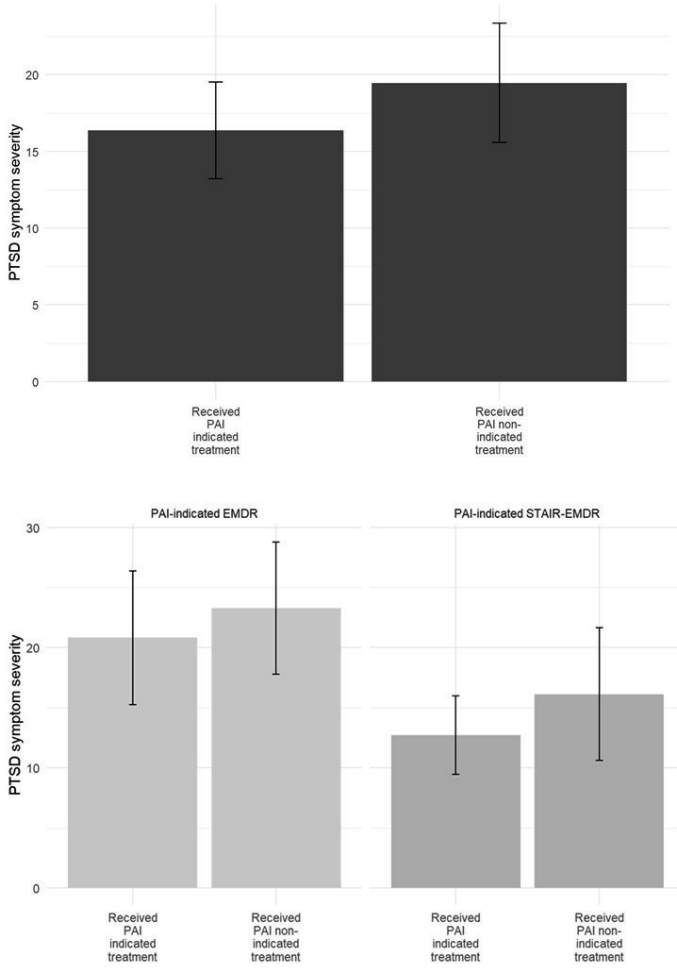
Supplementary Table 4 provides an overview of the variables selected for the variable selection approaches and the final selected variables after the bootstrap approach. The following combination of moderators was identified: the presence of a BPD, suicidal thoughts, marital status, IIP Self-Sacrificing subscale score, IIP Vindictive/Self-Centered, subscale score, IIP Cold/Distant subscale score, BSI Hostility subscale score, and DES-II score. Supplementary Figure 1 illustrates the moderating effect of these variables. Individuals with a BPD diagnosis, suicidal thoughts, high score IPP Cold/Distant subscale score, high BSI Hostility subscale score, and high DES-II score demonstrated significantly lower posttreatment PTSD symptom severity in the EMDR therapy condition than in the STAIR–EMDR condition. Individuals who were not married reported higher posttreatment PTSD severity scores in the STAIR–EMDR condition than in the EMDR condition. The IPP Self-Sacrificing and Vindictive/Self-Centered subscales were so-called ordinal moderators, indicating that all scores were linked to different levels of a superior effect of one treatment above the other. In these cases, STAIR–EMDR was superior, meaning that participants in this condition demonstrated lower posttreatment PTSD symptom severity scores, and the degree of superiority was more pronounced when these IPP subscale scores were lower.

#### *Personalized treatment recommendations*

The identified predictors and moderators were combined into a final regression model, and predictions for STAIR–EMDR and EMDR were calculated for each individual. The associated  $R^2$  value of these predictions was .17, indicating a modest goodness of fit for the regression model. The STAIR–EMDR and EMDR predictions were then used to calculate individual PAI scores. As illustrated in Figure 1, there was a nonsignificant difference between posttreatment PTSD symptom severity scores for individuals who received PAI-indicated treatment versus those who received non-PAI-indicated treatment. On average, there was an average advantage of 3.1 points between receiving indicated ( $M = 16.37, n = 60$ )

versus nonindicated treatment ( $M = 19.47$ ,  $n = 45$ ),  $d = 0.25$ ,  $p = .213$ . When the highest 60.0% of PAI scores were selected, this advantage effect increased to 5.2 points on average (indicated:  $M = 14.00$ , nonindicated:  $M = 19.17$ ),  $d = 0.41$ ,  $p = .112$ . A closer inspection of Figure 1 illustrates that for individuals who received PAI-indicated EMDR, posttreatment PTSD symptom severity scores were 3.4 points lower compared to those who received a nonindicated treatment. In addition, participants who received PAI-indicated STAIR-EMDR demonstrated a posttreatment symptom severity score that was, on average, 2.5 points lower compared with those assigned to the nonindicated treatment. However, none of the posttreatment comparisons between participants who received PAI-indicated treatment and non-PAI-indicated treatment were statistically significant.

**Figure 1**  
*Comparison of posttreatment posttraumatic stress disorder (PTSD) symptom severity for individuals randomized to their indicated treatment versus those randomized to a nonindicated treatment.*



*Note:* EMDR = eye-movement desensitization and reprocessing; PAI = Personalized Advantage Index; STAIR = Skills Training in Affect and Interpersonal Regulation.

## Discussion

The purpose of the present study was to use machine learning to determine whether some individuals with PTSD stemming from childhood abuse would benefit more from a phase-based treatment approach whereas others would benefit more from a direct trauma-focused approach. The study represents a secondary analysis of data collected during an RCT. To this end, we identified the predicted optimal treatment option for each patient by developing a PAI and calculated the potential advantage that could be gained by offering the most appropriate treatment according to this index score. To our knowledge, this is the first PAI analysis to compare phase-based treatment that includes EMDR with EMDR alone as a direct trauma-focused treatment in a sample of individuals with PTSD related to childhood abuse; therefore, this study represents the first effort to come to a more personalized treatment approach for this patient population, although our sample may have been too small for this purpose (Luedtke et al., 2019). Therefore, we used data from a recent RCT (Van Vliet et al., 2021) that compared a direct trauma-focused treatment approach (i.e., EMDR) with a phase-based treatment approach (i.e., STAIR-EMDR). No significant differences in posttreatment symptom severity scores were found between individuals who received a PAI-indicated treatment and those who received a non-PAI-indicated treatment. The effect sizes were small to medium in size, with a Cohen's  $d$  of 0.25 for comparisons between indicated and nonindicated treatment and a Cohen's  $d$  of 0.41 for comparisons between indicated and nonindicated treatment for the highest 60.0% of PAI scores. These effect sizes were similar in size (i.e., small to medium) to those reported in other PAI studies (e.g., Cohen et al., 2019; Schwartz et al., 2021). The fact that no clinically meaningful difference was found means that there was no overall difference between the EMDR condition and the STAIR-EMDR, and there are no reliable moderators between treatment condition and PTSD treatment outcome. Thus, the effects of both

treatments appeared to be robust, indicating that patients can benefit from either condition, and patients with PTSD related to childhood abuse do not need a phase-based treatment.

The nonsignificant outcome differences between the indicated versus nonindicated treatments are in contrast with Hoeboer, Oprel et al.'s (2021) study, which demonstrated a combination of patient characteristics that was significantly indicative of optimal treatment selection in PTSD. An explanation may be that the total sample size in that study was larger than the sample size in the present study, which may have increased the likelihood of detecting significant differences. In addition, in the study by Hoeboer, Oprel et al. (2021), different pretreatment variables were available and selected as potential predictors and moderators, which may also have led to different outcomes. Another explanation for this difference may be the study design. In contrast to our study, in which the number of trauma-focused sessions for both conditions was the same, Hoeboer, Oprel, and colleagues (2021) offered fewer trauma-focused sessions in the phase-based condition than in the direct trauma-focused condition. According to our results, the PAI analysis did not show significant differences between the two conditions with the same dose of trauma-focused treatment or with the addition of STAIR in one of the two conditions. This suggests that this group of patients may benefit from both treatments. Another possible explanation for the nonsignificant results could be that offering trauma-focused treatment by itself is sufficient to reduce the typical symptom levels commonly associated with a history of repeated early childhood traumatization, including affective dysregulation, disturbances in relationships, and negative self-concept (e.g., Voorendonk et al., 2020). If this is the case, having a history of childhood abuse and/or symptoms of CPTSD should not be a primary factor in determining the need for a phase-based treatment.

Further, we examined the moderator results in more detail and compared these with those reported in the only other PAI study pertaining to this patient group (Hoeboer, Oprel et



al., 2021). This examination showed that the common pretreatment variables that led to different moderating effects between the two studies, were emotion regulation difficulties and interpersonal problems. Although Hoeboer, Oprel et al.'s (2021) PAI analysis showed a moderating effect of difficulties in emotion regulation, our results did not. These differences may be explained by differences in study design and sample size. Whereas Hoeboer, Oprel et al. (2021) did not detect any moderating effects for interpersonal problems as indexed by the IIP, we did find some moderating effects for some IIP subscales, specifically the Intrusive/Needy, Vindictive/Self-Centered, and Cold/Distant subscales. This might indicate that treatment choice should be based on specific interpersonal problems and not total scores for these variables.

Given that little is known about predictors and moderators of PTSD treatment outcomes, this study makes a substantial contribution to the literature. For example, individuals with a BPD reported lower posttreatment PTSD symptom severity scores in EMDR compared with STAIR–EMDR (see Supplementary Figure 1 for more details). A strength of the present study is that we explored a broad spectrum of possible moderators, leading to the best predictive model. Another study strength is that STAIR was applied as an add-on treatment, which is in line with the international treatment guidelines for CPTSD (ISTSS, 2012), rather than replacing part of the trauma-focused treatment with another component.

Several study limitations should also be discussed. The most important limitation was the relatively small sample size. The RCT from which data were drawn was not designed for this analysis; therefore, it could be considered an exploratory study. The small sample size reduced the likelihood of detecting significant differences and elevated the risk of overfitting the model. Based on a simulation study (Luedtke et al., 2019), much larger sample sizes (i.e., 300 per treatment arm) may be required for multivariable prediction models, although this

remains an important subject for future studies to explore and confirm. Similar studies using larger sample sizes are needed to determine whether these PAI results remain nonsignificant. A few studies have used larger sample sizes in the field of affective disorders (Delgadillo et al., 2020; Schwartz et al., 2021), with results indicating that treatment selection based on machine learning may improve treatment outcomes and support clinical decision-making. Moreover, once significant treatment selection effects in a larger population are found, external validation in different populations and treatment settings will be an essential step to gaining a better understanding of individual patient characteristics that influence PTSD treatment outcomes.

Although the initial ISTSS guidelines for CPTSD (Cloitre et al., 2012) were adapted based on criticism from the field (e.g., De Jongh et al., 2016; ISTSS, 2018) and currently state that CPTSD treatment should primarily focus on facilitating the processing of the childhood memories, the guidelines still leave room for “personalized medicine” for a possibly limited group of people who might still benefit from a stabilization phase prior to trauma treatment. The current results do not provide evidence of added value in using personalized medicine approaches to assign patients with PTSD and a history of childhood abuse to phase-based treatment, although this study may well have been insufficiently powered to detect the need for personalized medicine. Given no clear or consistent characteristics warranting an extended treatment approach, the results suggest that clinicians should provide trauma-focused treatment, as several studies have shown that direct trauma-focused treatments are safe for patients with severe PTSD and/or CPTSD and a history of childhood abuse (Opres et al., 2020; Raabe et al., 2022; Van Vliet et al., 2021).

## References

- Achterhof, R., Huntjens, R. J. C., Meewisse, M. L., & Kiers, H. A. L. (2019). Assessing the application of latent class and latent profile analysis for evaluating the construct validity of complex posttraumatic stress disorder: cautions and limitations. *European Journal of Psychotraumatology*, *10*(1), 1698223. <https://doi.org/10.1080/20008198.2019.1698223>
- American Psychiatric Association. (2017). *Clinical practice guideline for the treatment of PTSD*. <https://www.apa.org/ptsd-guideline/ptsd.pdf>
- Arntz, A. (1993). *Dutch translation of the PSS-SR*. Universiteit Maastricht.
- Austin, P. C., & Tu, J. V. (2004). Bootstrap methods for developing predictive models. *The American Statistician*, *58*(2), 131–137. <https://doi.org/10.1198/0003130043277>
- Barkham, M., Hardy, G. E., & Startup, M. (1996). The IIP-32: A short version of the inventory of interpersonal problems. *British Journal of Clinical Psychology*, *35*(1), 21–35. <https://doi.org/10.1111/j.2044-8260.1996.tb01159.x>
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory–II*. Psychological Corporation.
- Boeschoten, M. A., Van der Aa, N., Bakker, A., Ter Heide, F. J. J., Hoofwijk, M. C., Jongedijk, R. A., Van Minnen, A., Elzinga, B. M. & Olf, M. (2018). Development and Evaluation of the Dutch Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). *European Journal of Psychotraumatology*, *9*(1), Article 1546085. [doi:10.1080/20008198.2018.1546085](https://doi.org/10.1080/20008198.2018.1546085)
- Box, G. E. P., & Cox, D. R. (1964). An analysis of transformations. *Journal of the royal statistical society, Series B (Methodological)*, *26*(2), 211–252. <https://doi.org/10.1111/j.2517-6161.1964.tb00553.x>
- Carlson, E. B., & Putnam, F. W. (1993). An update on the Dissociative Experiences Scale.

*Dissociation: Progress in the Dissociative Disorders*, 6(1), 16–27.

- Cloitre, M. (2016). Commentary on De Jongh et al. (2016) critique of ISTSS complex PTSD guidelines: Finding the way forward. *Depression and Anxiety*, 33(5), 355–356.  
<https://doi.org/10.1002/da.22493>
- Cloitre, M., Courtois, C. A., Charuvastra, A., Carapezza, R., Stolbach, B. C., & Green, B. L. (2011). Treatment of complex PTSD: Results of the ISTSS expert clinician survey on best practices. *Journal of Traumatic Stress*, 24(6), 615–627.  
<https://doi.org/10.1002/jts.20697>
- Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., Herman, J. L., Lanius, R., Stolbach, B. C., Spinazolla, J., Van der Kolk, B. A., & Van der Hart, O. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in adults*.  
<https://terrorvictimresponse.ca/wp-content/uploads/ISTSS-Expert-Concesnus-Guidelines-for-Complex-PTSD-Updated-060315.pdf>
- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han, H. (2002). Skills training in affective and interpersonal regulation followed by exposure: A phase-based treatment for PTSD related to childhood abuse. *Journal of Consulting and Clinical Psychology*, 70(5), 1067–1074. <https://doi.org/10.1037/0022-006X.70.5.1067>
- Cohen, Z. D., Kim, T. T., Van, H. L., Dekker, J., & Driessen, E. (2019). A demonstration of a multi-method variable selection approach for treatment selection: Recommending cognitive-behavioral versus psychodynamic therapy for mild to moderate adult depression. *Psychotherapy Research: Journal of the society for Psychotherapy Research*, 30(2), 137–150. <https://doi.org/10.1080/10503307.2018.1563312>
- De Beurs, E. (2006). *Brief Symptom Inventory*. PITS.
- De Beurs, E., & Zitman, F. G. (2006). De Brief Symptom Inventory (BSI): De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90 [Reliability

and validity of a handy alternative for the SCL-90]. *Maandblad geestelijke volksgezondheid [Monthly Magazine for Mental Health]*, 61, 120–141.

- De Jongh, A., Resick, P. A., Zoellner, L. A., van Minnen, A., Lee, C. W., Monson, C. M., Foa, E. B., Wheeler, K., Ten Broeke, E., Feeny, N., Rauch, S. A. M., Chard, K. M., Mueser, K. T., Sloan, D. M., Van der Gaag, M., Rothbaum, B. A., Neuner, F., De Roos, C., Hehenkamp, L. M. J.,...Bicanic, I. A. (2016). Critical analysis of the current treatment guidelines for complex PTSD in adults. *Depression and Anxiety*, 33(5), 359–69. <https://doi.org/10.1002/da.22469>
- De Jongh, A., & Ten Broeke, E. (2013). *Handboek EMDR, een geprotocolleerde behandelmethode voor de gevolgen van psychotrauma [EMDR Manual: A protocolized treatment method for the consequences of psychotrauma]* (6th ed.). Benelux Pearson Education BV.
- Delgadillo, J., & Gonzalez Salas Duhne, P. (2020). Targeted prescription of cognitive–behavioral therapy versus person-centered counseling for depression using a machine learning approach. *Journal of Consulting and Clinical Psychology*, 88(1), 14–24. <https://doi.org/10.1037/ccp0000476>
- Derogatis, L. R. (1975). *Brief Symptom Inventory (BSI)*. Clinical Psychometric Research. <https://doi.org/10.1037/t00789-000>
- DeRubeis, R. J., Cohen, Z. D., Forand, N. R., Fournier, J. C., Gelfand, L. A., & Lorenzo-Luaces, L. (2014) The Personalized Advantage Index: Translating research on prediction into individualized treatment recommendations. A demonstration. *PLoS one*, 9(1), Article e83875. <https://doi.org/10.1371/journal.pone.0083875>
- First, M. B., Gibbon, M., Spitzer, R. L., Williams, J. B. W., & Benjamin, L. S. (1997). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. American Psychiatric Press.

- Fiske, D. W., Hunt, H. F., Luborsky, L., Orne, M. T., Parloff, M. G., Reiser, M. F., & Tuma, A. H. (1970). Planning of research on effectiveness of psychotherapy. *American Psychologist*, 25(8), 727–737. <https://doi.org/10.1037/h0037877>
- Foa, E. B., Ehlers, A., Clark, D. M., Tolin, D. F., & Orsillo, S. M. (1999). The Posttraumatic Cognitions Inventory (PTCI). Development and validation. *Psychological Assessment*, 11(3), 303–314. <https://doi.org/10.1037/1040-3590.11.3.303>
- Foa, E. B., Hembree, E. A., & Rothbaum, B. O. (2007). *Prolonged exposure therapy for PTSD: Emotional processing of traumatic experiences: Therapist guide*. Oxford University Press.
- Foa, E. B., Riggs, D. S., Dancu, C. V., & Rothbaum, B. O. (1993). Reliability and validity of a brief instrument for assessing posttraumatic stress disorder. *Journal of Traumatic Stress*, 6(4), 459–473. <https://doi.org/10.1007/BF00974317>
- Ford, J., Stockton, P., Kaltman, S., & Green, B. L. (2006). Disorders of extreme stress (DESNOS) symptoms are associated with type and severity of interpersonal trauma exposure in a sample of healthy young women. *Journal of Interpersonal Violence*, 21(11), 1399–1416. <https://doi.org/10.1177/0886260506292992>
- Friedman, J., Hastie, T., & Tibshirani, R. (2010). Regularization paths for generalized linear models via coordinate descent. *Journal of Statistical Software*, 33(1), 1–22. <https://doi.org/10.18637/jss.v033.i01>
- Garge, N. R., Bobashev, G., & Eggleston, B. (2013). Random forest methodology for model-based recursive partitioning: The mobForest package for R. *BMC Bioinformatics*, 14(1), 125. <https://doi.org/10.1186/1471-2105-14-125>
- Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology Behavioral Assessment*, 26(1),

41–54. <https://doi.org/10.1023/B:JOBA.0000007455.08539.94>

Hoeboer, C. M., De Kleine, R. A., Oprel, D. A. C., Schoorl, M., Van der Does, W., Van Minnen, A. (2021). Does complex PTSD predict or moderate treatment outcomes of three variants of exposure therapy? *Journal of Anxiety Disorders*, *80*, Article 102388. <https://doi.org/10.1016/j.janxdis.2021.102388>

Hoeboer, C. M., Oprel, D. A. C., Kleine, R. A. De, Schwartz, B., Deisenhofer, A., Schoorl, M., Does, W. A. J. Van Der, & Minnen, A. Van. (2021). Personalization of treatment for patients with childhood-abuse-related posttraumatic stress disorder. *Journal of Clinical Medicine*, *10*(19), 1–15. <https://doi.org/10.3390/jcm10194522>

Horowitz, L. M., Alden, L. E., Wiggins, J. S., & Pincus, A. L. (2000). *Inventory of Interpersonal Problems*. Psychological Corporation.

International Society for Traumatic Stress Studies (2019). *ISTSS guidelines position paper on complex PTSD in adults*. [http://www.istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS\\_CPTSD-Position-Paper-\(Adults\)\\_FNL.pdf.aspx](http://www.istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_CPTSD-Position-Paper-(Adults)_FNL.pdf.aspx)

James, G., Witten, D., Hastie, T. & Tibshirani, R. (2003). *An Introduction to Statistical Learning with Applications in R*. Springer.

Kuhn, M. (2008). Building predictive models in R using the caret package. *Journal of Statistical Software*, *28*(5), 1–26. <https://doi.org/10.18637/jss.v028.i05>

Kuhn, M., & Johnson, K. (2013). *Applied Predictive Modeling* (Vol. 26). Springer.

Luedtke, A., Sadikova, E., & Kessler, R. C. (2019). Sample size requirements for multivariate models to predict between-patient differences in best treatments of major depressive disorder. *Clinical Psychological Science*, *7*(3), 445–461. <https://doi.org/10.1177/2167702618815>

- Mintz, J., Luborsky, L., & Christoph, P. (1979). Measuring the outcomes of psychotherapy: Findings of the Penn Psychotherapy Project. *Journal of Consulting and Clinical Psychology, 47*(2), 319–334. <https://doi.org/10.1037/0022-006X.47.2.319>
- Oprel, D. A. C., Hoeboer, C. M., Schoorl, M., Kleine, R. A. D., Cloitre, M., Wigard, I. G., Van Minnen, A., & Van der Does, W. (2021). Effect of prolonged exposure, intensified prolonged exposure and STAIR+prolonged exposure in patients with PTSD related to childhood abuse: A randomized controlled trial. *European Journal of Psychotraumatology, 12*(1), Article 1851511. <https://doi.org/10.1080/20008198.2020.1851511>
- Pelcovitz, D., Van der Kolk, B., Roth, S., Mandel, F., Kaplan, S., & Resick, P. (1997). Development of a criteria set and a structured interview for Disorders of Extreme Stress (SIDES). *Journal of Traumatic Stress, 10*(1), 3–16. <https://doi.org/10.1023/a:1024800212070>
- Raabe, S., Ehring, T., Marquenie, L., Arntz, A., & Kindt, M. (2022). Imagery rescripting versus STAIR plus imagery rescripting for PTSD related to Childhood Abuse: A randomized controlled trial. *Journal of Behavior Therapy and Experimental Psychiatry, 77*, Article 101769. <https://doi.org/10.1016/j.jbtep.2022.101769>
- Rink, J., & Lipinska, G. (2020). Evidence of distinct profiles of *ICD-11* post-traumatic stress disorder (PTSD) and complex PTSD in a South African sample. *European Journal of Psychotraumatology, 11*(1), Article 1818965. <https://doi.org/10.1080/20008198.2020.1818965>
- RStudio Team. (2020). *RStudio: Integrated Development for R* [software program]. <http://www.rstudio.com/>.
- Schwartz, B., Cohen, Z. D., Rubel, J. A., Zimmermann, D., Wittmann, W. W., & Lutz, W.



- (2021). Personalized treatment selection in routine care: Integrating machine learning and statistical algorithms to recommend cognitive behavioral or psychodynamic therapy. *Psychotherapy Research*, 31(1), 33–51.  
<https://doi.org/10.1080/10503307.2020.1769219>
- Scoboria, A., Ford, J., Lin, H., & Frisman, L. (2008). Revision of the Structured Interview for Disorders of Extreme Stress (SIDES): An exploratory and confirmatory factor analytic approach. *Assessment*, 15(4), 404–425. <https://doi.org/10.1177/1073191108319005>
- Shapiro, F. (2018). *Eye movement desensitization and reprocessing (EMDR): Basic principles, protocols and procedures* (3rd ed). Guilford Press.
- Spinazzola, J. (2019). *Structured Interview for Disorders of Extreme Stress (SIDES) & Self-Report Inventory for Disorders of Extreme Stress (SIDES-SR)* [Unpublished manuscript]. <https://complextrauma.org/wp-content/uploads/2019/03/SIDES-Manual-Spinazzola-2019.pdf>
- Stekhoven, D. J., & Bühlmann, P. (2012). Missforest—non-parametric missing value imputation for mixed-type data. *Bioinformatics*, 28(1), 112–118.  
<https://doi.org/10.1093/bioinformatics/btr597>
- Tang, F., & Ishwaran, H. (2017). Random forest missing data algorithms. *Statistical analysis and Data Mining*, 10(6), 363–377. <https://doi.org/10.1002/sam.11348>
- Van Emmerik, A. A. P., Schoorl, M., Emmelkamp, P. M. G., & Kamphuis, J. H. (2007). Psychometrische kenmerken van de Nederlandstalige Posttraumatische Cognities Inventarisatielijst (PTCI) [psychometric characteristics of the Dutch Posttraumatic Cognitions Inventory]. *Gedragstherapie* [Behavior Therapy], 40, 269–84.
- Van IJzendoorn, M. H., & Schuengel, C. (1996). The measurement of dissociation in normal and clinical populations: Meta-analytic validation of the Dissociative Experiences Scale

- (DES). *Clinical Psychology Review*, 16(5), 365–382. [https://doi.org/10.1016/0272-7358\(96\)00006-2](https://doi.org/10.1016/0272-7358(96)00006-2)
- Van Vliet, N. I., Huntjens, R. J. C., Van Dijk, M. K., Bachrach, N., Meewisse, M. L., & De Jongh, A. (2021). Phase-based treatment versus immediate trauma-focused treatment for post-traumatic stress disorder due to childhood abuse: Randomised clinical trial. *British Journal of Psychiatry Open*, 7(6), Article E211. <https://doi.org/10.1192/bjo.2021.1057>
- Van Vliet, N. I., Huntjens, R. J. C., Van Dijk, M. K., & de Jongh, A. (2018). Phase-based treatment versus immediate trauma-focused treatment in patients with childhood trauma-related posttraumatic stress disorder: Study protocol for a randomized controlled trial. *Trials*, 19(1), 1–10. <https://doi.org/10.1186/s13063-018-2508-8>
- Voorendonk, E. M., De Jongh, A., Rozendaal, L., & Van Minnen, A. (2020). Trauma-focused treatment outcome for complex PTSD patients: Results of an intensive treatment programme. *European Journal of Psychotraumatology*, 11(1), 1783955. <https://doi.org/10.1080/20008198.2020.1783955>
- Weertman, A., Arntz, A., Dreessen, L., Van Velzen, C., & Vertommen, S. (2003). Short-interval test-retest interrater reliability of the Dutch version of the Structured Clinical Interview for *DSM-IV* personality disorders (SCID-II). *Journal of Personality Disorders*, 17(6), 562–567. <https://doi.org/10.1521/pedi.17.6.562.25359>
- Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013a). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. <https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp>
- Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013b). *The Life Events Checklist For DSM-5 (LEC-5)*. [https://www.ptsd.va.gov/professional/assessment/te-measures/life\\_events\\_checklist.asp](https://www.ptsd.va.gov/professional/assessment/te-measures/life_events_checklist.asp)

World Health Organization (2019). *The ICD-11 for mortality and morbidity statistics*.

(<https://icd.who.int/browse11/l-m/en>).

**Predictors of treatment dropout in patients with  
posttraumatic stress disorder due to childhood abuse**

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**Abstract***Background*

Knowledge about patient characteristics predicting treatment dropout for post-traumatic stress disorder (PTSD) is scarce, whereas more understanding about this topic may give direction to address this important issue.

*Method*

Data were obtained from a randomized controlled trial in which a phase-based treatment condition (Eye Movement Desensitization and Reprocessing [EMDR] therapy preceded by Skills Training in Affect and Interpersonal Regulation [STAIR];  $n = 57$ ) was compared with a direct trauma-focused treatment (EMDR therapy only;  $n = 64$ ) in people with a PTSD due to childhood abuse. All pre-treatment variables included in the trial were examined as possible predictors for dropout using machine learning techniques.

*Results*

For the dropout prediction, a model was developed using Elastic Net Regularization. The ENR model correctly predicted dropout in 81.6 % of all individuals. Males, with a low education level, suicidal thoughts, problems in emotion regulation, high levels of general psychopathology and not using benzodiazepine medication at screening proved to have higher scores on dropout.

*Conclusions*

Our results provide directions for the development of future programs in addition to PTSD treatment or for the adaptation of current treatments, aiming to reduce treatment dropout among patients with PTSD due to childhood abuse.

**Keywords:** PTSD, Childhood abuse, EMDR, Dropout, Predictors, Machine learning

## 1. Introduction

Posttraumatic stress disorder (PTSD) has a major impact on social and occupational functioning and individuals' quality of life (Alonso et al., 2004). In addition, individuals with PTSD are at great risk of attempting suicide (Kessler, 2000; Panagioti, Gooding, & Tarrier, 2012; Sareen et al., 2007). Although many treatments targeting PTSD have proven to be effective (e.g. Mavranouzouli et al., 2020), a recent meta-analysis of randomized controlled trials (RCTs) found an average dropout rate of 21% for guideline-recommended PTSD treatments (Varker et al., 2021). This is problematic as untreated PTSD compared to treated PTSD may lead to a worse prognosis, and many societal consequences (Usman, Rehman, Bakhtawar, & Bhatti, 2015). Considering the societal impact of PTSD, it is important to ensure that individuals suffering from PTSD complete their treatment because evidence-based PTSD treatments significantly improve their prognosis (Usman et al., 2015). Completing treatment may be of particular importance for those with a history of childhood abuse since they are at risk of displaying more severe symptoms of PTSD or developing symptoms of Complex PTSD (ISTSS, 2012; Rink & Lipinska, 2020).

In order to establish a Complex PTSD diagnosis individuals need to experience symptoms of "Disturbances in Self-Organization" (DSO; i.e., problems with affect regulation, negative self-concept, and interpersonal problems; World Health Organization, 2018), in addition to all diagnostic criteria of PTSD. It has been suggested that existing evidence-based trauma-focused therapies may lead to less favorable outcomes and more dropout in patients with a history of childhood abuse (Cloitre, Koenen, Cohen, and Han, 2002; Cloitre et al., 2012; Karatzias et al., 2019), and that these patients are at risk of developing Complex PTSD (Rink & Lipinska, 2020). Previous attempts to decrease the dropout rate from PTSD treatments in this target group by adding treatment programs that specifically target Complex PTSD symptoms in addition to actual trauma-focused treatment (Cloitre et al., 2002; Cloitre

et al., 2010) did not lead to less dropout compared to only applying direct trauma-focused treatment (Oprel et al., 2021; Raabe et al., 2022; Van Vliet et al., 2021). The identification of patient characteristics that predict early treatment termination is essential for developing new target strategies to prevent dropout.

Most meta-analyses studying potential predictors of dropout regarding PTSD treatments focus on the kind of therapy as a predictive factor (i.e., Bradley, Greene, Russ, Dutra, & Westen, 2005; Bisson et al. 2007; Hembree et al. 2003; Imel, Laska, Jakupcak, & Simpson, 2013; Lewis, Roberts, Gibson, & Bisson, 2020). As far as we know, only Varker et al. (2021) performed a meta-analysis in which they also considered patient characteristics in the comparison of several PTSD treatments among patients with military and civilian trauma. PTSD chronicity, PTSD severity, medication use, age, employment status, relationship status, sex, baseline depression scores, or baseline anxiety scores were included separately as possible predictors, but none of the included patient characteristics were found to be predictive of dropout. To this end, given the scarcity of studies and variables considered so far and the lack of meta-analytic support for specific comorbid symptoms as potential predictors for treatment dropout, more research on patient characteristics predicting dropout is needed. As, until now, not one specific characteristic has been found to be predictive of dropout, it may be even more important to determine whether a combination of characteristics may be predictive.

The purpose of the present study was to identify patients who are at risk of dropping out, and to identify patient characteristics that predict the dropout of PTSD treatments in patients with PTSD related to childhood abuse. To achieve this aim, we used machine learning techniques. One advantage of machine learning techniques is that all available pretreatment variables and variable combinations are examined (Chekroud et al., 2021), thus not limiting the number of possible predictors. Another advantage is that it is particularly

appropriate for identifying small effects in predicting outcomes (Chekroud et al., 2021). For the current study, the dataset of a multi-center randomized controlled trial was used, that compared a phase-based treatment with a direct-trauma-focused treatment in patients with PTSD related to a history of childhood abuse (Van Vliet, Huntjens, Van Dijk, & De Jongh, 2017; Van Vliet et al., 2021).

## **2. Method**

### *2.1 Design and Participants*

A total of 121 patients were recruited in two mental health organizations; Dimence GGZ and GGZ Oost-Brabant. Included patients were aged between 18 and 65 years, and diagnosed with PTSD based on the Clinician-Administered PTSD scale for DSM-5 (CAPS-5; Weathers et al., 2013). Participants had to be a victim of repeated sexual and/or physical abuse before the age of 18 by a caretaker or a person in a position of authority, which was identified by the Life Events Checklist for the DSM-5 (LEC-5; Weathers et al., 2013). Patients were excluded when they did not master the Dutch language sufficiently, or in case of acute suicidality for which direct crisis intervention was needed, as assessed by an item of the Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1996). In addition, patients were excluded if they had received at least eight sessions of any well-evaluated treatment for PTSD in the past year, reported being a victim of ongoing physical and/or sexual abuse, reported severe use of alcohol or drugs, or had an intellectual disability. The study design was registered in a national trial registry and approved by the medical ethics committee Twente NL. Further details on the trial methodology and patient sample can be found in the study protocol (Van Vliet et al., 2018) and main outcome paper of the study (Van Vliet et al., 2021).

### *2.2 Interventions*

After patients were found to be eligible for participation in the study, they were randomized to two treatment conditions: both contained 16 sessions of EMDR (Eye Movement



Desensitization and Reprocessing) as the trauma-focused treatment, and in one condition these sixteen sessions of EMDR were preceded by eight sessions of the first phase treatment STAIR (in total 24 sessions). Both the STAIR and the EMDR therapy were delivered twice a week for 90 minutes. STAIR was conducted according to the program described by Cloitre and her colleagues (Cloitre, Koenen, Cohen, & Han, 2002). EMDR therapy was conducted according to the protocol by Shapiro using the Dutch translation of the treatment protocol (De Jongh and Ten Broeke, 2013). Before actual treatment, patients first received one 90-minute session consisting of psycho-education in which a hierarchy of relevant traumatic experiences was determined. For a full description of the two treatments, see Van Vliet et al. (2018).

### *2.3 Measures*

#### *2.3.1 Drop out*

Patients were considered to have dropped out if they discontinued treatment prematurely after the first session, which included psychoeducation and case conceptualization just before the actual treatment began. This applies to cases where the patient did not complete the total number of treatment sessions as per the study's requirements (see the study protocol; Van Vliet et al., 2018), and failed to complete treatment for all the traumas that were selected for treatment during the first treatment session. The outcome variable was a dichotomous variable: dropout versus completer status.

#### *2.3.2. Pre-treatment variables*

Tables 1 and 2 show an overview of the pre-treatment variables and the differences between the two groups (dropout versus completer status). The reasons given by the patients for dropout are shown in Supplementary Table 1.

##### *2.3.2.1 Demographic characteristics*

The following demographic characteristics were determined in the study: Gender, level of education, employment status, marital status, and age.

TABLE 1  
*Continuous baseline variables pre-treatment for completers and dropouts and comparison of the means*

Variables pre-treatment	Completer (n = 90) Mean (Sd)	Dropout (n = 21) Mean (Sd)	t	df	p
Age	37.91 (12.72)	34.59 (10.57)	1.11	109	.27
CAPS-5	38.32 (9.27)	39.57 (8.27)	-0.57	109	.57
SIDES	31.28 (11.73)	34.19 (14.31)	-0.98	109	.33
PSS-SR	29.03 (9.02)	31.19 (7.09)	-1.03	109	.31
DES	23.55 (14.82)	26.06 (14.64)	-0.70	109	.49
DERS	112.79 (24.87)	120.52 (22.15)	-1.31	109	.19
PTCI Self-Esteem	3.98 (1.40)	4.29 (1.07)	-0.96	109	.34
IIP	1.63 (0.57)	1.71 (0.53)	-0.59	109	.56
BSI	1.83 (0.72)	2.09 (0.75)	-1.47	109	.14

*CAPS-5 = Clinician Administered PTSD Scale for DSM-5, SIDES = Structured Interview for Disorders of Extreme Stress-Revised, PSS-SR = PTSD Symptoms Scale-self report, DES = Dissociative Experiences Scale, DERS = Difficulties in Emotion Regulation Scale, PTCI = Posttraumatic Cognitions Inventory, IIP = Inventory of Interpersonal Problems, BSI = Brief Symptom Inventory.*

TABLE 2  
Categorical baseline variables for completers and dropouts and comparison of the amounts

Variable	Completer (n = 90)	Dropout (n = 21)	$\chi^2$ / Fisher's exact	df	p
Gender					
Woman	65	11			
Man	25	10	2.25	1	.13
Education					
Low	42	12			
Middle	33	9	4.06	2	.13
High	15	0			
Employment					
unemployed	54	14			
employed	25	5	.33	2	.85
student	11	2			
Living together	53	12			
Married	40	8	0.00	1	1.00
Sexual Abuse	69	14	0.08	1	.78
Physical Abuse	69	16	0.45	1	.50
Dissociative subtype	31	6	0.00	1	1.00
Complex PTSD	22	10	0.66	1	.80
Borderline personality disorder	16	5	3.40	1	.07
Self-injury			0.11	1	.74
no self-injury	53	12			
doubtful	14	3	.09	2	.96
self-injury	23	6			
Suicidality					
no suicidality	27	1			
suicidality	63	20	5.75	1	.02*
Psychiatric medication use	48	13			
Benzodiazepine medication use at screening	22	2	0.22	1	.64
			2.24	1	.24

\*p<0.05

### 2.3.2.2. PTSD variables

PTSD symptom severity at the start of the treatment was measured with the CAPS-5 (Weathers et al., 2013). The CAPS-5 is a clinical interview that includes 20 items on a 5-point Likert scale, resulting in a total score of between 0 and 80. The CAPS-5 has good psychometric properties (Weathers et al., 2017; see for the Dutch version Boeschoten et al., 2018). The inter-rater reliability was assessed by calculating the interclass correlation coefficient, which was .999, which is an excellent score.

### 2.3.2.3. Suicidality

Item 9 of the BDI-II (Beck, Steer, & Brown, 1996) was used to measure suicidality. The scale of this item ranges from 0 to 3, with 0 for the absence of suicidal thoughts, 1 for indicating the presence of suicidal thoughts, but no intention to carry them out, and, 2 for indicating suicidal thoughts accompanied by a clear intention to commit suicide. Patients were excluded when they scored a 3 on this scale, which said that they would commit suicide whenever they had the chance. In that case they were assigned to a direct crisis intervention. In the current analysis, suicidality was used as a dichotomous value: absence (score of 0) or presence of suicidality (score of 1 or 2).

### 2.3.2.3. Borderline personality disorder

The Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID-II interview; First, Spitzer, Gibbon, Williams, & Benjamin, 1997; Weertman, Arntz, Dreessen, Van Velzen, and Vertomme, 2005) was used to determine the presence of a borderline personality disorder. The psychometric properties are fair to good for this instrument.

Self-Injury: The severity of self-injury was determined by items 97 and 98 of the Dutch version of the SCID-II interview (Weertman et al., 2005), with 1 for absent, 2 for doubtful, and 3 for present.

### 2.3.2.5 Dissociative symptoms

The severity of dissociative symptoms was indexed using the Dissociative Experiences Scale (DES-II; Carlson and Putnam, 1993; Cronbach's  $\alpha = .93$  in the present study at baseline). This is a 28-item self-report questionnaire with scores ranging from 0 to 100 (Van IJzendoorn & Schuengel, 1996). The presence of a dissociative subtype of PTSD was determined using the CAPS-5 (Weathers et al., 2013).

#### 2.3.2.6 Complex PTSD

The presence and severity of Complex PTSD was measured by the Structured Interview for Disorders of Extreme Stress (SIDES; Scorbodia, Ford, Lin, & Frisman, 2008), the 38-item version developed by Ford et al. (2006). The SIDES has good psychometric properties as a dichotomous measure in determining whether Complex PTSD is present or not (SIDES Manual by Spinazzola, 2019).

#### 2.3.2.7 Interpersonal difficulties

Interpersonal difficulties were indexed using the Inventory of Interpersonal Problems (IIP; Horowitz, Alden, Wiggins, & Pincus, 2000). The psychometric properties of the IIP are satisfying (Barkham & Hardy, 1996). The IIP contains 32 items that can be scored on a 5-point scale from 0 (not at all) to 4 (very strongly). The reliability at baseline in this study was high (Cronbach's  $\alpha = .85$ ).

#### 2.3.2.8 Emotion regulation

Difficulties in emotion regulation were measured with the Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004), a questionnaire that has been validated in clinical populations (Fox, Axelrod, Paliwal, Sleeper, & Sinha, 2007; Gratz, Tull, Baruch, Bornovalova, Lejuez, 2008) and nonclinical populations (Gratz and Roemer, 2004; Johnson et al., 2008). Each item of the DERS is rated on a 5-point scale. The reliability in this study at baseline was high (Cronbach's  $\alpha = .92$ ).

#### 2.3.2.9 Problems in self-esteem

To index problems in self-esteem the self-esteem subscale of the Posttraumatic Cognitions Inventory (PTCI; Foa, Ehlers, Clark, Tolin, & Orsillo, 1999) was used. Items are scored on a Likert scale from 1 (“I totally disagree”) to 7 (“I totally agree”), and psychometric properties for the Dutch version (Van Emmerik, Schoorl, Emmelkamp, & Kamphuis, 2007) are good. The PTCI score for self-esteem showed a high reliability at baseline in this study (Cronbach's  $\alpha = .94$ ).

#### 2.3.2.10 General Psychopathology

The Brief Symptom Inventory (Derogatis, 1975; De Beurs, 2006) was used to measure the severity of general psychopathology symptoms. The severity of each item can be rated on a 5-point scale from 0 (not at all) to 4 (a lot). The Dutch version has good psychometric properties (De Beurs & Zitman, 2006; Cronbach's  $\alpha = .95$  at baseline in the present study).

### **3. Statistical analysis**

All analyses were carried out using RStudio (RStudio Team, 2020). The R code used is available in the Supplementary Material.

#### *3.1 Data Pre-Processing*

Following Cohen et al. (2019) individuals with less than 50% missing pre-treatment values were included in this study. As a result, ten individuals were excluded. For the remaining 111 participants, variables with missing data were imputed using a random forest imputation algorithm (R package ‘MissForest’, Stekhoven and Bühlmann, 2012). The benefits of this approach are that no pre-processing is required and that it is robust for noisy data and multicollinearity, so that it can be applied to mixed data types (Tang & Ishwaran, 2017; Stekhoven and Bühlmann, 2012). The imputation method was verified by applying this method to the non-missing dataset with completely at random removed values. After imputing the missing values, the performance was assessed using the normalized root mean squared

error (NRMSE) and the proportion of falsely classified (PFC), which is defined by comparing the complete values with the imputed values (Stekhoven and Bühlmann, 2012).

In case of highly correlated variables ( $\text{cor.} > 0.70$ ), one of the variables was dropped to avoid redundancy and multicollinearity. The decision which variable to remove was made by the research team. Outliers were winsorized and continuous variables with a non-normal distribution were transformed using the Box-Cox method (Box and Cox, 1964; R package 'Caret'; Kuhn, 2008). Finally, continuous variables were standardized and categorical variables were centered (see Table 3 for details about transformations for each variable). This data pre-processing procedure resulted in a dataset of 111 participants with 22 pre-treatment variables. Dropouts did not differ significantly between patients who received STAIR-EMDR (21.8%) and EMDR only therapy (16.1%;  $\chi^2(1) = 6.00, p = .440$ ). A prognostic model for dropout was developed independently of treatment conditions because the subsample of dropouts was too small to create a prescriptive model for dropout depending on the treatment conditions.

Table 3  
Variable transformation

Variable	Included	Reason excluded	Transformation
Sex	yes		Centered (male: -0.5, female: 0.5)
Education	yes		Centered (low: -0.5, middle: 0; high: 0.5)
Employment	yes		Centered (unemployed: -0.5, student: 0; employed: 0.5)
Age	yes		Transformed (lambda 0.4)
Married	yes		Centered (not married: -0.5, married: 0.5)
Living together	no	Substantial overlap with variable Married	
LEC-5 Sexual Abuse	yes		Centered (no sexual abuse: -0.5, sexual abuse: 0.5)
LEC-5 Physical Abuse	yes		Centered (no physical abuse: -0.5, physical abuse: 0.5)
Dissociative subtype	yes		Centered (no dissociative subtype: -0.5, dissociative subtype: 0.5)
BDI-II item 9 Suicidal thoughts	yes		Centered (no suicidal thoughts: -0.5, suicidal thoughts: 0.5)
Complex posttraumatic stress disorder (PTSD)_	yes		Centered (no complex PTSD: -0.5, complex PTSD: 0.5)
SCID-II item 97 and 98 Borderline personality disorder (BPD)	yes		Centered (no BPD: -0.5, BPD: 0.5)
Kind of Personality Disorder	no	Substantial overlap with variable Presence BPD	
Self-injury	yes		Centered (no self-injury: -0.5, doubtful: 0; self-injury: 0.5)
Posttraumatic stress disorder (PTSD)_	no	Near-zero variance	
Psychoactive medication use at screening	yes		Centered (no Psychoactive medication: -0.5, Psychoactive medication: 0.5)
Benzodiazepine medication use at screening	yes		Centered (no Benzodiazepine medication: -0.5, Benzodiazepine medication: 0.5)
CAPS-5 total score	yes		
SIDES total score	yes		
PSS-SR total score	yes		
DES total score	yes		Winsorized 2 high outliers; Transformed (lambda 0.4)
BSI total score	yes		
PTCI total score	no	Subscale included	
PTCI Self-Esteem	yes		Transformed (lambda 1.2)
DERS total score	yes		Transformed (lambda 1.5)
IIP total score	yes		

Note. Transformations were performed with the BoxCox method.

BDI-II, Beck Depression Inventory; CAPS-5, Clinician-Administered PTSD scale for DSM-5; SIDES, Structured Interview for Disorders of Extreme Stress; PSS-SR, PTSD Symptoms Scale-Self Report; DES-II, Dissociative Experiences Scale; BSI, Brief Symptom Inventory; PTCI, Posttraumatic Cognitions Inventory; DERS, Difficulties in Emotion Regulation Scale; IIP, Inventory of Interpersonal Problems; SCID-II, Structured Clinical Interview for DSM-IV Axis II; LEC-5, Life Events Checklist for DSM-5.



### *3.2 Imbalanced dataset*

After data pre-processing, the ratio between dropout and completers was checked, because it was expected that the dataset would be imbalanced due to a relatively smaller proportion of dropouts compared to completers. This is of importance as an imbalanced dataset causes classification performance problems in machine learning algorithms (Japkowicz & Stephen, 2002). To deal with this class imbalance, the proven effective synthetic minority oversampling technique (SMOTE) was applied (Chawla et al., 2002). This method over-samples the minority class (i.e., dropout), by artificially creating new samples using the nearest neighbours of the cases, and under-samples the majority class (Chawla et al., 2002).

### *3.3 Model building*

For the dropout prediction, a model was developed using Elastic Net Regularization (ENR, R package ‘glmnet’, Friedman et al., 2010). ENR is a combination of ridge regression and lasso regression where alpha is the tuning parameter between ridge regression (alpha = 0) and lasso (alpha = 1; Kuhn & Johnson, 2013). Another tuning parameter is the lambda which determines the shrinkage or penalty of the coefficients, the larger its value the stronger the shrinkage (Kuhn & Johnson, 2013). The alpha and lambda were determined using 10-fold cross-validation, where the selected alpha was based on the highest area under the curve (AUC; James et al., 2013). After determination of the alpha and lambda, the final model was built.

### *3.4 Model evaluation*

The model was evaluated on the initial (imbalanced) dataset using three different measures: accuracy, the area under the curve (AUC), and the Brier score. The selected variables in the final model were evaluated for significance and variable importance. The variable importance was calculated using the vip package (Greenwell & Boehmke, 2020). The accuracy is the percentage of correct dropout predictions ranging from 0% (worst prediction) to 100% (best

prediction). The AUC refers to the overall performance of a classifier. When the AUC is 1, predictions are 100% correct, and when the AUC is 0, all predictions are incorrect (James et al., 2013). The Brier score can be described as a parameter that measures the accuracy of probabilistic predictions ranging from 0 (best prediction) to 1 (worst prediction; Brier, 1950).

## **4. Results**

### *4.1 Data Pre-Processing*

The total sample consisted of 111 patients. From that number, 80 individuals (72%) had no missing data and the percentage of missing baseline variables was 2.5 percent. All patients who dropped out prematurely and were assessed after dropping out still fulfilled the diagnostic criteria for PTSD. The number of sessions before dropping out was registered and the median of the number of sessions before dropping out was 4 sessions. The missing values were imputed and the performance of the imputation method was acceptable (NRMSE = .15; PFC .26).

### *4.2 Imbalanced dataset and dropout rate*

The dropout rate in this study was 19%, indicating that the distribution between dropout and completers was unequal, leading to an imbalanced dataset. To balance the dataset, SMOTE was applied. After applying SMOTE, the dropout rate was 43%.

### *4.3 Model building*

The final ENR model selected the following variables for dropout risk: suicidality, benzodiazepine medication use at screening, education, gender, sexual abuse, Borderline personality disorder, PTCI Self-Esteem, SIDES, DERS, complex PTSD, BSI, DES, and CAPS-5 scores.

### *4.4 Predictor evaluation*

The best ENR model ( $\alpha = 0.25$ ,  $\lambda = 0.18$ ) correctly predicted 81.6 % of all individuals (accuracy). For this model, the AUC was 0.85 and the Brier score was 0.31, indicating sufficient predictions. The sensitivity and specificity are 75% and 87%, respectively. Predictors were evaluated based on both significance and variable importance. Based on significance (i.e., p-value lower than 0.05), the main variables for risk of dropout in the model were gender, education, suicidality, score on the DERS, score on the BSI and benzodiazepine medication use at screening. The (i.e., an importance score greater than or close to 1), the main variables of the model were suicidality, education, and benzodiazepine use at screening (for a total overview of the variable importance, see Table 4). More specifically, low education level, presence of suicidal thoughts, and not using benzodiazepine medication during screening were most strongly related to dropout risk according to both significance and variable importance. Given our focus on prediction, we will further focus on these three variables with the highest variable importance score and not on all significant variables.

Table 4  
*Variable importance indicators*

Variable	Importance
Suicidality	1.22
Benzodiazepine medication use at screening	1.14
Education	.97
Complex PTSD	.89
Gender	.68
SIDES	.37
DERS	.35
Sexual Abuse	.34
PTCI Self-Esteem	.32
Borderline personality disorder	.26
BSI	.24
DES	.10
CAPS-5	.07

## 5. Discussion

The purpose of the present study was to identify patients with PTSD related to childhood abuse who are at risk of dropping out of treatment. Therefore, we applied machine learning techniques to analyze all available pre-treatment variables from a recent RCT. The best model was able to correctly predict dropout in 81.6% of the individuals. We consider our research endeavor to be a promising approach for identifying individuals at risk of dropout and, to this end, could be considered a first step in developing models for predicting patient groups that are at an elevated risk of dropout. This makes it possible to develop interventions that support these patients during treatment and prevent them from dropping out; for example, extra nursing support or treatment in clinical settings.

Our model evaluation indicated that the within-sample predictions were accurate based on three different measures (accuracy, AUC, and Brier score). To this end, the combination of pretreatment suicidality, low education, and non-use of benzodiazepines was found to be a risk factor for dropout. Interestingly, from their meta-analysis Guina et al. (2015) concluded that the use of benzodiazepines is contraindicated for the treatment of PTSD. They found that the use of benzodiazepines is associated with poor treatment outcomes. To this end, the lack of experienced treatment benefits and the inability to use benzodiazepines as missed opportunities to ease and regulate feelings of tension may explain why patients discontinued therapy. Also, regarding the other predictors, it is conceivable that this could have prompted the patient to discontinue treatment early. This holds true, for instance, if one conceives suicidality as an indicator of feelings of entrapment or hopelessness, and a low level of education as a possible indicator of higher trait impulsivity or low frustration tolerance. However, before speculating too much on how these factors together might explain the increased risk of treatment dropout, more research is needed to first try and replicate these results and rule out the possibility of chance. Our method is the first step toward developing personalized medicine to prevent dropouts from PTSD treatment. Our findings further suggest that one of the ways to reduce dropout rates may be to intensify trauma treatments, as most patients in this study dropped out in an early stage (between the third and fourth treatment sessions) and other studies found that a more intensive PTSD treatment can lead to a lower dropout rate (for example, Hoppen, Kip et al., 2023; Van Woudenberg et al., 2018). Clearly, replication studies are needed to provide reliable evidence for out-of-sample prediction accuracy for use in clinical practice.

The first strength of this study is that, to our knowledge, this is the first study to analyze predictors of dropout among patients with PTSD related to childhood abuse using machine learning, which has the advantage that it takes into account all possible pre-treatment

variables. A second strength is that we handled an imbalanced dataset by applying the proven effective synthetic minority oversampling technique (SMOTE; Chawla et al., 2002), which provides more opportunities to compare dropouts with completers, as in most studies, there is a large difference between the sample sizes of both groups. As in any study, some limitations of this study need to be noted. The first limitation is that the study sample was quite small, thereby limiting the possibility of distinguishing between the two treatment conditions (Luedtke et al., 2019). Future studies should focus on examining patient characteristics that might predict dropout by machine learning, using larger patient samples and including more types of trauma-focused therapies. A second limitation is the missing data for which we had to impute the data, leading to less reliable outcomes. However, the performance of our imputation method proved reliable (REF), which was verified in this study. Third, we were not able to externally validate the data on an independent dataset to answer the question of whether this model leads to significant effects in new samples (Bleeker et al., 2003; van Bronswijk et al., 2021). Before these outcomes are confirmed by external validation, the results cannot be generalized to clinical practice. Although we attempted to overcome this using 10-fold cross-validation, it is unknown how this model will perform on a truly independent dataset. For example, Isaksson et al. (2008) argued that cross-validation was unreliable for classifying small samples.

In conclusion, this study identified a combination of variables predicting the dropout rate of patients with PTSD due to childhood abuse in trauma-focused treatments. A challenging task for future research is to examine whether these results can be replicated in larger patient samples. Another challenge is to examine these potential dropout predictors in a more profound way; although our study may help identify patients who are at risk of dropping out of therapy, the results do not reveal the mechanisms that explain the elevated risk. Experimental studies are required to elucidate the exact mechanisms involved, which could be

fundamental for future preventive interventions. Developments in the field of machine learning are moving rapidly, and for follow-up research, it may be interesting to look at other models that use tidy modeling.

## References

- Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., de Girolamo, G., Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J. M., Katz, S. J., Kessler, R. C., Kovess, V., Lépine, J. P., Ormel, J., Polidori, G., Russo, L. J., Vilagut, G., Almansa, J., ... ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project (2004). Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica. supplementum*, (420), 38–46. <https://doi.org/10.1111/j.1600-0047.2004.00329.x>
- Barkham, M., Hardy, G. E. and Startup, M. (1996). The IIP-32: A short version of the Inventory of Interpersonal Problems. *British Journal of Clinical Psychology*, 35, 21-35. <https://doi.org/10.1111/j.2044-8260.1996.tb01159.x>
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory II*. Psychological corporation.
- Bisson, J. I., Ehlers, A., Matthews, R., Pilling, S., Richards, D., & Turner, S. (2007). Psychological treatments for chronic post-traumatic stress disorder. Systematic review and meta-analysis. *The British Journal of Psychiatry: The journal of mental science*, 190, 97–104. <https://doi.org/10.1192/bjp.bp.106.021402>
- Bleeker, S., Moll, H., Steyerberg, E., Donders, A., Derksen-Lubsen, G., Grobbee, D., & Moons, K. (2003). External validation is necessary in prediction research: A clinical example. *Journal of Clinical Epidemiology*, 56(9), 826–832. [https://doi.org/10.1016/S0895-4356\(03\)00207-5](https://doi.org/10.1016/S0895-4356(03)00207-5)
- Boeschoten, M. A., Van der Aa, N., Bakker, A., Ter Heide, F. J. J., Hoofwijk, M. C.,



- Jongedijk, R. A., Van Minnen, A., Elzinga, B. M., & Olf, M. (2018). Development and Evaluation of the Dutch Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). *European Journal of Psychotraumatology*, 9(1), 1546085.  
<https://doi.org/10.1080/20008198.2018.1546085>
- Box, G., & Cox, D. (1964). An Analysis of Transformations. *Journal of the Royal Statistical Society. Series B (Methodological)*, pp. 211–252. <https://doi.org/10.1111/j.2517-6161.1964.tb00553.x>
- Bradley, R., Greene, J., Russ, E., Dutra, L., & Westen, D. (2005). A multidimensional meta-analysis of psychotherapy for PTSD. *The American Journal of Psychiatry*, 162(2), 214–227. <https://doi.org/10.1176/appi.ajp.162.2.214>
- Brier, G. W. (1950). Verification of forecasts expressed in terms of probability. *Monthly Weather Review*, 78(1), 1–3.
- Carlson, E. B., & Putnam, F. W. (1993). An update on the Dissociative Experiences Scale. *Dissociation*, 6(1), 16-27.
- Chawla, N. V., Bowyer, K. W., Hall, L.O., & Kegelmeyer, W.P. (2002). SMOTE: synthetic minority over-sampling technique. *Journal of Artificial Intelligence Research*, 16, 321–57. <https://doi.org/10.48550/arXiv.1106.1813>
- Chekroud, A. M., Bondar, J., Delgadillo, J., Doherty, G., Wasil, A., Fokkema, M., Cohen, Z., Belgrave, D., DeRubeis, R., Iniesta, R., Dwyer, D., & Choi, K. (2021). The promise of machine learning in predicting treatment outcomes in psychiatry. *World Psychiatry : Official journal of the World Psychiatric Association (WPA)*, 20(2), 154–170.  
<https://doi.org/10.1002/wps.20882>
- Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., Herman, J. L., Lanius, R., Stolbach, B. C., Spinazolla, J., Van der Kolk, B. A., & Van der Hart, O. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in*

*adults*. <https://terrorvictimresponse.ca/wp-content/uploads/ISTSS-Expert-Concesnus-Guidelines-for-Complex-PTSD-Updated-060315.pdf>

- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han H. (2002). Skills training in affective and interpersonal regulation followed by exposure: a phase-based treatment for PTSD related to childhood abuse. *Journal of Consulting and Clinical Psychology, 70*(5), 1067-74. <https://doi.org/10.1037//0022-006x.70.5.1067>
- Cloitre, M., Stovall-McClough, K. C., Nooner, K., Zorbas, P., Cherry, S., Jackson, C. L., Gan, W., & Petkova, E. (2010). Treatment for PTSD related to childhood abuse: a randomized controlled trial. *The American Journal of Psychiatry, 167*(8), 915–924. <https://doi.org/10.1176/appi.ajp.2010.09081247>
- Cohen, Z. D., Kim, T. T., Van, H. L., Dekker, J. J., & Driessen, E. (2019). A demonstration of a multi-method variable selection approach for treatment selection: Recommending cognitive–behavioural versus psychodynamic therapy for mild to moderate adult depression. *Psychotherapy Research, 1*–14. <https://doi.org/10.1080/10503307.2018.1563312>
- De Beurs E. Brief Symptom Inventory. Handleiding. Leiden: PITS; 2006.
- De Beurs, E., & Zitman, F. G. (2006). De Brief Symptom Inventory (BSI): De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90 [reliability and validity of a handy alternative for the SCL-90]. *Maandblad Geestelijke Volksgezondheid [monthly magazine for mental health], 61*, 120-141.
- De Jongh, A., & Ten Broeke, E. (2013). Handboek EMDR, een geprotocolleerde behandelmethode voor de gevolgen van psychotrauma [EMDR manual: A protocolized Treatment Method fort he Consequences of Psychotrauma] (6th ed.). Benelux Pearson Education BV.

- Derogatis, L. R. (1975). Brief Symptom Inventory (BSI). *Clinical Psychometric Research*, 49. <https://psycnet.apa.org/doi/10.1037/t00789-000>
- First, M. B., Spitzer, R. L., Gibbon, M., Williams, J. B. W., & Benjamin, L. S. (1997). *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. American Psychiatric Press.
- Foa, E. B., Riggs, D. S., Dancu, C. V., & Rothbaum, B. O. (1993). Reliability and validity of a brief instrument for assessing posttraumatic stress disorder. *Journal of Traumatic Stress*, 6, 459-473. <https://psycnet.apa.org/doi/10.1002/jts.2490060405>
- Foa, E. B., Ehlers, A., Clark, D. M., Tolin, D. F., & Orsillo, S. M. (1999). The Posttraumatic Cognitions Inventory (PTCI). Development and validation. *Psychological Assessment*, 11(3), 303-314. <https://psycnet.apa.org/doi/10.1037/1040-3590.11.3.303>
- Ford, J., Stockton, P., Kaltman, S., & Green, B. L. (2006). Disorders of extreme stress (DESNOS) symptoms are associated with type and severity of interpersonal trauma exposure in a sample of healthy young women. *Journal of Interpersonal Violence*, 21, 1399-1416. <http://doi.org/10.1177/0886260506292992>
- Fox, H. C., Axelrod, S. R., Paliwal, P., Sleeper, & Sinha, R. (2007). Difficulties in emotion regulation and impulse control during cocaine abstinence. *Drug and Alcohol Dependence*, 89(2-3), 298-301.
- Friedman, J., Hastie, T., & Tibshirani, R. (2010). Regularization paths for generalized linear models via coordinate descent. *Journal of Statistical Software*, 33(1), 1. [doi:10.18637/jss.v033.i01](https://doi.org/10.18637/jss.v033.i01)
- Gratz, K. L., & Roemer, L. (2004). Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the Difficulties in Emotion Regulation Scale. *Journal of Psychopathology Behavioral Assessment*, 26, 41-54. <https://psycnet.apa.org/doi/10.1023/B:JOBA.0000007455.08539.94>

- Gratz, K. L., Tull, M. T., Baruch, D. E., Bornovalova, M. A., & Lejuez, C. W. (2008). Factors associated with co-occurring borderline personality disorder among inner-city substance users: the roles of childhood maltreatment, negative affect intensity / reactivity, and emotion dysregulation. *Comprehensive Psychiatry*, 49, 603-15.  
<http://doi.org/10.1016/j.comppsy.2008.04.005>
- Greenwell BM, Boehmke BC (2020). “Variable Importance Plots—An Introduction to the vip Package.” *The R journal*, 12(1), 343–366. <https://doi.org/10.32614/RJ-2020-013>.
- Guina, J., Rossetter, S. R., DeRhodes, B. J., Nahhas, R. W., & Welton, R. S. (2015). Benzodiazepines for PTSD: A Systematic Review and Meta-Analysis. *Journal of Psychiatric Practice*, 21(4), 281-303. <https://doi.org/10.1097/pr.0000000000000091>
- Hembree, E. A., Foa, E. B., Dorfman, N. M., Street, G. P., Kowalski, J., & Tu, X. (2003). Do patients drop out prematurely from exposure therapy for PTSD? *Journal of Traumatic Stress*, 16(6), 555–562. <https://doi.org/10.1023/b:jots.0000004078.93012.7d>
- Hoppen, T. H., Kip, A., & Morina, N. (2023). Are psychological interventions for adult PTSD more efficacious and acceptable when treatment is delivered in higher frequency? A meta-analysis of randomized controlled trials. *Journal of Anxiety Disorders*, 95, 102684. <https://doi.org/10.1016/j.janxdis.2023.102684>
- Horowitz, L. M., Alden, L. E., Wiggins, J. S., & Pincus, A. L. (2000). Inventory of Interpersonal Problems. Psychological Corporation.
- Imel, Z. E., Laska, K. M., Jakupcak, M., & Simpson, T. L. (2013). Meta-analysis of dropout in treatments for posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*, 81(3), 394-404. <https://doi.org/10.1037/a0031474>
- Isaksson, A., Wallman, M., Göransson, H., & Gustafsson, M.G. (2008). Cross-validation and

- bootstrapping are unreliable in small sample classification. *Pattern Recognition Letters*, 29, 1960-1965.
- James, G., Witten, D., Hastie, T. & Tibshirani, R. (2003), *An Introduction to Statistical Learning with Applications in R*. Springer.
- Japkowicz N., & Stephen S. (2002). The class imbalance problem: a systematic study. *Intelligent Data Analysis*, 6(5), 429–449.
- Johnson, K. A., Zvolensky, M. J., Marshall, E. C., Gonzalez, A., Abrams, K., & Vujanovic, A. A. (2008). Linkages between cigarette smoking outcome expectancies and negative emotional vulnerability. *Addictive Behaviors*, 33, 1416-24.  
<https://doi.org/10.1016%2Fj.addbeh.2008.05.001>
- Karatzias, T., Murphy, P., Cloitre, M., Bisson, J., Roberts, N., Shevlin, M., Hyland, P., Maercker, A., Ben-Ezra, M., Coventry, P., Mason-Roberts, S., Bradley, A., & Hutton, P. (2019). Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. *Psychological Medicine*, 49(11), 1761–1775.  
<https://doi.org/10.1017/S0033291719000436>
- Kessler, R. C. (2000). Posttraumatic stress disorder: the burden to the individual and to society. *Journal of Clinical Psychiatry*, 61(5), 4-12; discussion 13-4. PMID: 10761674.
- Kuhn, M. (2008). Building Predictive Models in R Using the caret Package. *Journal of Statistical Software*, 28(5), 1-26. <https://doi.org/10.18637/jss.v028.i05>
- Kuhn, M., & Johnson, K. (2013). *Applied Predictive Modeling* (Vol. 26). Springer.
- Lewis, C., Roberts, N. P., Gibson, S., & Bisson, J. I. (2020). Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: Systematic review and meta-analysis. *European Journal of Psychotraumatology*, 11(1), 1709709.  
<https://doi.org/10.1080%2F20008198.2019.1709709>

- Luedtke, A., Sadikova, E., & Kessler, R. C. (2019). Sample size requirements for multivariate models to predict between-patient differences in best treatments of major depressive disorder. *Clinical Psychological Science* 7, 445–461.
- Mavranezouli, I., Megnin-Viggars, O., Daly, C., Dias, S., Welton, N. J., Stockton, S., Bhutani, G., Grey, N., Leach, J., Greenberg, N., Katona, C., El-Leithy, S., & Pilling, S. (2020). Psychological treatments for post-traumatic stress disorder in adults: a network meta-analysis. *Psychological Medicine*, 50(4), 542–555.  
<https://doi.org/10.1017/S0033291720000070>
- McKinney, J. M., Hirsch, J. K., & Britton, P. C. (2017). PTSD symptoms and suicide risk in veterans: Serial indirect effects via depression and anger. *Journal of Affective Disorders*, 214, 100-07. <https://doi.org/10.1016/j.jad.2017.03.008>
- Oprel, D. A. C., Hoeboer, C. M., Schoorl, M., de Kleine, R. A., Cloitre, M., Wigard, I. G., van Minnen, A., & van der Does, W. (2021). Effect of Prolonged Exposure, intensified Prolonged Exposure and STAIR+Prolonged Exposure in patients with PTSD related to childhood abuse: a randomized controlled trial. *European Journal of Psychotraumatology*, 12(1), 1851511.  
<https://doi.org/10.1080/20008198.2020.1851511>
- Panagioti, M., Gooding, P. A., & Tarrier, N. (2012). A meta-analysis of the association between posttraumatic stress disorder and suicidality: the role of comorbid depression, *Comprehensive Psychiatry*, 53(7), 915-930.  
<https://doi.org/10.1016/j.comppsy.2012.02.009>
- Raabe, S., Ehring, T., Marquenie, L., Arntz, A., & Kindt, M. (2022). Imagery Rescripting versus STAIR plus Imagery Rescripting for PTSD related to Childhood Abuse: A randomized controlled trial. *Journal of Behavior Therapy and Experimental Psychiatry*, 77. <https://doi.org/10.1016/j.jbtep.2022.101769>

- Rink, J., & Lipinska, G. (2020). Evidence of distinct profiles of ICD-11 post-traumatic stress disorder (PTSD) and complex PTSD in a South African sample. *European Journal of Psychotraumatology*, *11*(1), 1818965.  
<https://doi.org/10.1080%2F20008198.2020.1818965>
- RStudio Team (2020). *RStudio: Integrated Development for R*. RStudio.  
<http://www.rstudio.com/>
- Sareen, J., Cox, B. J., Stein, M. B., Afifi, T. O., Fleet, C., & Asmundson, G. J. (2007). Physical and mental comorbidity, disability, and suicidal behavior associated with posttraumatic stress disorder in a large community sample. *Psychosomatic Medicine*, *69*(3), 242–8. <https://doi.org/10.1097/psy.0b013e31803146d8>
- Scobordia, A., Ford, J. Lin, H., & Frisman, L. (2008). Revision of the Structured Interview for Disorders of Extreme Stress (SIDES): an exploratory and confirmatory factor analytic approach. *Assessment*, *15*, 404–425. <https://doi.org/10.1177/1073191108319005>
- Spinazzola, J. (2019). *Structured Interview for Disorders of Extreme Stress (SIDES) & Self-Report Inventory for Disorders of Extreme Stress (SIDES-SR)*. Unpublished manuscript available from <https://complextrauma.org/wp-content/uploads/2019/03/SIDES-Manual-Spinazzola-2019.pdf>
- Stekhoven, D. J., & Bühlmann, P. (2012). Missforest—non-parametric missing value imputation for mixed-type data. *Bioinformatics*, *28*(1), 112–118.  
<https://doi.org/10.1093/bioinformatics/btr597>
- Tang, F., & Ishwaran, H. (2017). Random Forest missing data algorithms. *Statistical Analysis and Data Mining*, *10*(6), 363–77. <https://doi.org/10.1002%2Fsam.11348>
- Usman, M., Rehman, A., Bakhtawar N., & Bhatti, A. B. H. (2015). Prognosis of PTSD in treated vs. non-treated groups. *Journal of Pakistan Psychiatric Society*, *12*(1).
- Van Bronswijk, S. C., Bruijnicks, S. J., Lorenzo-Luaces, L., Derubeis, R. J., Lemmens, L. H.,

- Peeters, F. P., & Huibers, M. J. (2021). Cross-trial prediction in psychotherapy: External validation of the Personalized Advantage Index using machine learning in two Dutch randomized trials comparing CBT versus IPT for depression. *Psychotherapy and Research, 31*(1), 78-91. <https://doi.org/10.1080/10503307.2020.1823029>
- Van Emmerik, A. A. P., Schoorl, M., Emmelkamp, P. M. G., & Kamphuis, J. H. (2007). Psychometrische kenmerken van de Nederlandstalige Posttraumatische Cognities Inventarisatielijst (PTCI). *Gedragstherapie [Behavior Therapy], 40*, 269-84.
- Van Vliet, N. I., Huntjens, R. J. C., Van Dijk, M. K., & De Jongh, A., (2018). Phase-based treatment versus immediate trauma-focused treatment in patients with childhood trauma-related posttraumatic stress disorders: Study protocol for a randomized controlled trial. *Trials, 19* (1), 1-10. <https://doi.org/10.1186/s13063-018-2508-8>
- Van Vliet, N. I., Huntjens, R. J. C., Van Dijk, M. K., Bachrach, N., Meewisse, M. L., & De Jongh, A. (2021). Phase-based treatment versus immediate trauma-focused treatment for post-traumatic stress disorder due to childhood abuse: Randomised clinical trial. *British Journal of Psychiatry Open, 7*(6), E211. <https://doi.org/10.1192%2Fbjpo.2021.1057>
- Van Woudenberg, C., Voorendonk, E. M., Bongaerts, H., Zoet, H. A., Verhagen, M., Lee, C. W., van Minnen, A., & De Jongh, A. (2018). Effectiveness of an intensive treatment programme combining prolonged exposure and eye movement desensitization and reprocessing for severe post-traumatic stress disorder. *European Journal of Psychotraumatology, 9*(1), 1487225. <https://doi.org/10.1080/20008198.2018.1487225>
- Van IJzendoorn, M. H., & Schuengel, C. (1996). The measurement of dissociation in normal and clinical populations: Meta-analytic validation of the Dissociative Experiences Scale (DES). *Clinical Psychology Review, 16*(5), 365-382. [https://psycnet.apa.org/doi/10.1016/0272-7358\(96\)00006-2](https://psycnet.apa.org/doi/10.1016/0272-7358(96)00006-2)



- Varker, T., Jones, K. A., Arjmand, H. A., Hinton, M., Hiles, S. A., Freijah, I., Forbes, D., Kartal, D., Phelps, A., Bryant, R. A., McFarlane, A., Hopwood, M., & O'Donnell, M. (2021). Dropout from guideline-recommended psychological treatments for posttraumatic stress disorder: A systematic review and meta-analysis. *Journal of Affective Disorders Reports, 4*, 100093-100093. <https://doi.org/10.1016/j.jadr.2021.100093>
- Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013). *The Life Events Checklist for DSM-5 (LEC-5)*. National Center for Posttraumatic Stress Disorder. Retrieve from [www.ptsd.va.gov](http://www.ptsd.va.gov)
- Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., Keane, T. M., & Marx, B. P. (2018). The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment, 30*(3), 383–395. <https://doi.org/10.1037/pas0000486>
- Weertman, A., Arntz, A., Dreessen, L., Van Velzen, C., & Vertommen, S. (2003). Short-interval test-retest interrater reliability of the Dutch version of the structured clinical interview for DSM-IV personality disorders (SCID-II). *Journal of Personality Disorders, 17*(6), 562–7. <https://doi.org/10.1521/pedi.17.6.562.25359>
- World Health Organization (2018). *The ICD-11 for mortality and morbidity statistics*. World Health Organization. Guidelines for the management of conditions specifically related to stress. Geneva: World Health Organization. (<https://icd.who.int/browse11/l-m/en>).

**Cost-effectiveness analysis of the treatment of  
posttraumatic stress disorder related to childhood abuse.  
Comparison of phase-based treatment and direct trauma-  
focused treatment.**

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**Abstract***Background*

Policymakers, health insurers, and health care providers are becoming increasingly interested in cost-effectiveness analyses (CEA's) when choosing between possible treatment alternatives.

*Objective*

The current study compared the cost-effectiveness and cost-utility of a phased-based treatment approach that includes a preparatory stabilization phase with direct trauma-focused treatment in patients with PTSD with a history of childhood abuse.

*Method*

A cost-effectiveness analysis was conducted based on data from a randomized controlled trial of 121 patients with PTSD due to childhood abuse. A phase-based treatment (Eye Movement Desensitization and Reprocessing [EMDR] therapy preceded by Skills Training in Affect and Interpersonal Regulation [STAIR]; n = 57) was compared with a direct trauma-focused treatment (EMDR therapy only; n = 64). The primary outcome of cost-effectiveness was the proportion of patients with remitted PTSD. Quality-adjusted life years (QALY) were used as the primary outcome measure for cost-utility analysis.

*Results*

Although the results of the cost-effectiveness analyses yielded no statistically significant differences between the two groups, the mean societal costs per patient differed significantly between the STAIR-EMDR and EMDR therapy groups (€19.599 vs. €13.501; M cost differences = €6.098, CI (95%) = [€117 ; €12.644]).

*Conclusions*

STAIR-EMDR is not cost-effective compared with EMDR-only therapy. Since trauma-focused treatment is less time-consuming, non-trauma-focused phase-based, treatment does not seem to be a viable alternative for the treatment of PTSD due to adverse childhood events.

Keywords: PTSD, CEA, Childhood abuse, EMDR, STAIR

## 1. Introduction

Post-traumatic stress disorder (PTSD) is a mental health condition that may result from one or more traumatic events and is characterized by intrusive and recurrent memories of trauma, avoidance of trauma-related stimuli, numbing and/or negative changes in mood or cognition, and changes in reactivity and arousal (APA, 2013). PTSD has been found to have a major impact on work disability and quality of life, resulting in economic burden (Von der Warth et al., 2020). This condition can result in functional impairment and reduced societal productivity (Alonso et al., 2004); however, frequent physical and mental comorbidities also exert a strong socioeconomic influence on individuals with PTSD (Pacella et al., 2013). Owing to the impact of PTSD on societal costs and quality of life, the APA PTSD Treatment Guidelines (APA, 2017) and the WHO Guidelines for the Management of Conditions Specifically Related to Stress (WHO, 2013) emphasize the importance of cost-effectiveness studies for future treatment guideline recommendations.

Only one study has systematically reviewed economic evaluations and cost analyses, using PTSD as a diagnostic criterion (Von der Warth, 2020). Of the 31 included studies, only 13 performed a full economic evaluation with cost-effectiveness and cost-utility analyses, indicating that the intervention costs were measured in relation to effectiveness. Only four of these studies were performed in the European healthcare system. Of the 13 studies with a fully performed economic evaluation, only two also calculated costs from a societal perspective, as recommended by international guidelines (Chang et al., 2018; Le et al., 2014), instead of only a mental health payer's perspective. In addition, some evidence-based PTSD treatments, including EMDR therapy, were not included in the review (Von der Warth et al., 2020), whereas EMDR therapy was found to be the most cost-effective PTSD treatment among 10 different PTSD treatments in another large study (Mavranezouli et al., 2020). Thus, economic evaluations of PTSD therapies from a societal perspective are lacking in Europe.

The latter may even be more true for severe forms of PTSD, for which patients with a history of childhood abuse are at risk (Cloitre et al., 2012; Rink & Lipinska, 2020).

There is an ongoing debate about the treatment of individuals with PTSD due to childhood abuse, which revolves around the question of whether they need phase-based treatment instead of treatment according to international treatment guidelines for PTSD (i.e., by EMDR or prolonged exposure therapy; Cloitre, 2015; De Jongh et al., 2016). Phase-based treatment involves an initial stage that precedes trauma-focused therapy, of which Skills Training in Affect and Interpersonal Regulation (STAIR) is the most extensively studied approach. Within the STAIR phase, the therapeutic objectives include: (1) promoting emotional awareness of feelings and their triggers in daily life; (2) teaching emotion regulation strategies (3) encouraging the adaptive utilization of emotions and enhancing distress tolerance (4) supporting the identification and modification of dysfunctional interpersonal schemas (5) facilitating the identification of adaptive and achievable social goals with in various relationships and interpersonal contexts, and (6) achieving a sense of self-efficacy in both emotional and social domains (Haasija & Cloitre, 2015). STAIR can be followed with any form of trauma-focused treatment.

A recent study examined the cost-effectiveness of prolonged exposure (PE) therapy preceded by STAIR among patients with PTSD related to childhood abuse (Kullberg et al., 2023). Unfortunately, the researchers did not answer the question of whether the addition of STAIR to trauma-focused treatment leads to economic benefits because of the skills gained during the preparation phase. However, they replaced part of the trauma-focused sessions with STAIR, which was intended to be used as an addition to trauma-focused treatment (10). Hence, a study comparing the cost-effectiveness of phase-based treatments with direct trauma-focused treatments is warranted.

The purpose of the present study was to perform secondary analyses based on data from our randomized controlled trial (16) to assess the cost-effectiveness of phase-based treatment (i.e., EMDR therapy preceded by STAIR: Skills Training in Affective and Interpersonal Regulation) compared with direct trauma-focused treatment (i.e., EMDR therapy) in patients with severe PTSD due to repeated sexual and/or physical abuse during childhood, with STAIR as an actual addition to EMDR therapy.

## **2. Method**

### *2.1 Design and Participants*

Our economic evaluation was focused on the balance between costs and health outcomes of phase-based treatment (STAIR-EMDR;  $n = 57$ ) compared to direct trauma-focused treatment (EMDR therapy;  $n = 64$ ) in individuals with PTSD due to childhood abuse (Van Vliet et al., 2021). For this randomized controlled trial patients were recruited from two mental health organizations in the Netherlands (Dimence GGZ and GGZ Oost-Brabant). After patients signed a written informed consent form, and were eligible to participate in the study ( $N = 121$ ), they were randomly assigned to one of the two treatment conditions. The power calculation was based on a repeated-measures ANOVA, with the treatment condition as the between-subjects factor and time as the within-subjects factor (Van Vliet et al., 2018). The inclusion criteria were a) age between 18 and 65 years, b) PTSD as measured by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013), and c) PTSD related to repeated sexual and/or physical abuse before the age of 18 by a caretaker or a person in a position of authority. This was indexed using the LEC-5 (Weathers et al., 2013). The exclusion criteria were: insufficient mastery of the Dutch language, acute suicidality for which direct crisis intervention was needed (as assessed by item 9 of the Beck Depression Inventory-II [Beck, 1996]), when patients had received any well-evaluated treatment for

PTSD for at least eight sessions in the past year, when they reported being a victim of ongoing physical and/or sexual abuse, in case of severe use of alcohol or drugs, or in case of an intellectual disability. The study design was registered in (<https://onderzoekmetmensen.nl/nl/trial/22074>) NL5836 and approved by the medical ethics committee Twente NL 56641.044.16 CCMO. Details regarding the comparison of the effects of the two conditions have been previously published (Van Vliet et al., 2021).

### *2.2 Interventions*

The phase-based intervention involved eight sessions of STAIR and 16 sessions of EMDR therapy whereas the direct trauma-focused treatment involved only 16 sessions of EMDR therapy. Both interventions were delivered twice a week for 90 minutes each. Before each therapy every patient received a first session of 90 minutes consisting of psycho-education and determining relevant traumatic experiences for PTSD treatment. STAIR was performed according to the method described by Cloitre et al. (2002). EMDR therapy was performed according to the standard EMDR protocol (Shapiro, 2018; De Jongh & Ten Broeke, 2019). After the treatment, patients were not allowed to receive psychological therapy during six months follow-up. For a complete description of these two treatments, see Van Vliet et al. (2018).

### *2.3 Outcome measures*

Two economic analyses were performed; a cost-effectiveness analysis and a cost-utility analysis. Primary outcome measure of the cost-effectiveness analysis was the proportion of participants with remitted PTSD. Presence of PTSD was measured using the CAPS-5 (Weathers et al., 2013). This interview includes 20 items on a 5-point Likert scale, resulting in a total score between 0 and 80. The CAPS-5 has good psychometric properties (Weathers et al., 2017).



Quality-adjusted life years (QALY) were used as primary outcome measure for the cost-utility analysis. A QALY of 1 assumes a year of life lived in perfect health (1 Year of Life  $\times$  1 Utility = 1 QALY) and a score between 0 and 1 indicates a year of life lived in a state of less than this perfect health (Drummond et al., 1997). The economic evaluation was conducted from a societal perspective; relevant costs in and outside the healthcare sector were prospectively assessed for 9 months for all the included participants. Costs and health outcomes were not discounted due to the follow-up period of less than one year, which is in accordance with Dutch guidelines that advise the adjustment of calculated effects and costs from one year to the next year to consider any changes (Zorginstituut Nederland, 2015b). QALYs were derived from the EQ-5D-3L (EuroQol, 1990), which is a commonly applied self-administered instrument. The EQ-5D consists of five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with three levels (from no problems to many problems concerning the dimension). It also includes a VAS that asks participants to rate their health today from 0 (worst imaginable health) to 100 (best imaginable health). Subsequently, utilities were calculated by applying Dolan's algorithm (Dolan, 1997).

#### *2.4 Cost study*

Supplemental Table 1 provides an overview of the various types of costs assessed during the study (including the follow-up time). Cost aspects directly related to STAIR and EMDR therapy were assessed in detail, including the costs of contact between participants and therapists (individual sessions), supervision of therapists during the study, materials and housing. The various types of costs within the healthcare sector were related to the range of healthcare service participants used during the study. In addition, various types of costs outside the healthcare sector were assessed. Costs of informal care were based on the monetary valuation of the time invested by relatives or acquaintances in helping or assisting

the participants (such as household work or visiting healthcare professionals). By means of the friction cost method, the costs of productivity losses due to illness-related absence from work were estimated (Koopmanschap et al., 1995). Furthermore, the costs related to changes in the amount of voluntary (unpaid) work conducted by participants were considered.

Information on healthcare consumption was collected using a detailed case record form adapted to the context of the current study. The case record form assessed, among others, admissions to hospitals, contacts with healthcare professionals, and absence from work. The case record form was administered to all participants at baseline, at the end of treatment (2 or 3 months after baseline in the EMDR therapy and STAIR-EMDR groups respectively), and six and nine months after baseline.

Unit prices (i.e., the price of one unit of each included cost type) were based mainly on Dutch standard prices (Zorginstituut Nederland, 2015a) to facilitate comparisons with other economic evaluations. The true costs of the resources used were estimated when standard prices were not available. All unit prices were based on the price level of the Euro in the year 2020. The reference prices established for previous years were adjusted to the 2020 prices by applying the consumer price index.

The presence of PTSD diagnosis, the EQ-5D-3L and the case record form for health care consumption were administered to all participants at baseline, at the end of treatment (2 or 3 months after baseline in the EMDR therapy and STAIR-EMDR groups respectively), and 6 and 9 months after baseline.

### *2.5 Economic analyses*

The economic evaluation design included cost-effectiveness and cost-utility analyses. In these types of analyses, costs and health outcomes are used to calculate the incremental cost-effectiveness ratio (ICER) relative to one or more alternatives (Drummond et al., 2005). The

formula used for calculating the ICER is presented below (with the proportion of participants with remitted PTSD as the outcome measure).

$$\text{ICER} = \frac{(C_{\text{STAIR-EMDR}} - C_{\text{EMDR}})}{(\text{PTSD}_{\text{STAIR-EMDR}} - \text{PTSD}_{\text{EMDR}})}$$

$C_{\text{STAIR-EMDR}}$  = mean costs in the STAIR-EMDR group

$C_{\text{EMDR}}$  = mean costs in the EMDR group

$\text{PTSD}_{\text{STAIR-EMDR}}$  = proportion of participants with remitted PTSD in the STAIR-EMDR group

$\text{PTSD}_{\text{EMDR}}$  = proportion of participants with remitted PTSD in the EMDR group

### 2.6 Statistical procedures

The bootstrap method (Efron & Tibshirani, 1993) was applied to provide information on the uncertainty of the results of the economic evaluation. To deal with participants for whom not all data were available for various measurements, multiple imputation with a bootstrap approach (Oostenbrink, 2005) was used. In the planned sensitivity analysis, an alternative approach for handling missing data was applied to verify the results.

ICERs were calculated for each of the 2500 bootstrap iterations and simulated values of the mean estimates for the cost and outcome differences were added to the cost-effectiveness planes (Black, 1990). Finally, cost-effectiveness acceptability curves (CEACs; Fenwick et al., 2004) were calculated. CEACs inform decision makers on the probability that an intervention will be cost-effective, which depends on the willingness to pay per additional unit of health outcome.

Confidence intervals for cost and effect differences were assessed using bootstrap techniques. Cost outcomes in the EMDR group assessed for two months between the baseline and the end of treatment were extrapolated to three months. The analyses were conducted using SPSS (version 25), R (2022), and CEA-plus (version 2.1).

### 3. Results

Of the 121 participating patients 40 completed the entire treatment (15 in the STAIR-EMDR condition and 25 in the EMDR condition), 58 patients lost their PTSD diagnosis before the end of the maximum amount of treatment sessions (i.e. early completers; 29 in the STAIR-EMDR condition and 29 in the EMDR only condition), and 23 dropped out of treatment before the maximum amount of sessions were reached, and without losing their PTSD diagnostic status (13 in the STAIR-EMDR condition and 10 in the EMDR only condition). In the STAIR-EMDR condition one serious non-study-related adverse event was reported, which included short hospitalization after a suicide attempt. In the EMDR condition two non-study-related adverse events were reported (one due to increased suicidal ideations during the follow-up, and one due to increased psychotic experiences after changes in medication).

#### *3.1 Costs and healthcare utilisation*

A selection of the various types of costs (in and outside the healthcare sector) generated by the two groups during the nine months of the study is presented in Supplemental Table 2.

Only the most relevant cost types, or those that contributed considerably to the total costs ( $\geq 1\%$  of the total costs in at least one group), are presented here. These costs are based on the data of participants for whom at least one cost measurement was available during the study (for participants who did not use specific types of costs or information was missing, and €0 was applied when calculating group means for this overview).

Supplemental Table 2 also displays information on the utilization of healthcare services; the percentage of participants using each cost type is provided. The mean costs directly related to the studied interventions were €2.436 and € 1.686 per participant in the STAIR-EMDR and EMDR groups, respectively. Costs related to hospital admissions, sheltered living, psychologist contacts, and psychotherapist contacts contributed considerably

to the overall costs within the healthcare sector. Outside the healthcare sector, costs related to informal care and productivity losses were relatively high.

### 3.2 Total costs

An overview of the mean total societal costs during the various measurement periods of this study is provided in Table 1. In addition, the number of participants available for each measurement is presented.

Table 1. Mean total societal costs (€) during the study

Measurement (in months)	STAIR-EMDR		EMDR		Mean cost differences (95% CI) <sup>2</sup>
	Mean total costs	n	Mean total costs	n	
0-3	€12,682	33	€8,261	44	€4,421 (€491 , €4,609)
3-6	€4,493	35	€3,126	41	€1,367 (-€562, €2,170)
6-9	€2,734	41	€1,755	38	€979 (-€206, €1,251)
0-9 <sup>1</sup>	€19,599	38	€13,501	41	€6,098 (€117 , €12,644)

<sup>1</sup> Mean total societal costs during 9 months, estimates based on the multiple imputation plus bootstrap approach used to account for missing data

<sup>2</sup> 95% confidence interval (CI) for the mean cost differences between the groups, Lower and upper boundaries of the CI are presented

The mean total societal costs of the STAIR-EMDR group were significantly higher than those of the EMDR group for the 0 to 3 months measurement (as demonstrated by the 95% CI). The differences in mean total societal costs between the groups were not statistically significant for the two subsequent measurements. The mean total societal costs during the nine months of the study were 19.599 and 13.501 for the STAIR-EMDR and EMDR therapy groups, respectively. The difference between the groups in mean total societal costs during the nine months was statistically significant.

### 3.3 Health outcomes

The results of the health outcomes of the participants included in the economic analyses are presented in Table 2.

Table 2. PTSD outcomes and QALYS during 9 months<sup>1</sup>

Outcome measure	STAIR-EMDR		EMDR		Mean differences (95% CI <sup>2</sup> )
	Mean (SD)	n	Mean (SD)	n	
PTSD <sup>3</sup>	0.83 (0.06)	38	0.64 (0.08)	41	0.19 (-0.01, 0.39)
QALY	0.43 (0.04)	30	0.45 (0.03)	35	-0.02 (-0.13, 0.09)

<sup>1</sup> Estimates were based on the multiple imputation plus bootstrap approach used to account for missing data

<sup>2</sup> 95% confidence interval (CI) for the mean difference between groups. Lower and upper boundaries of the CI are presented

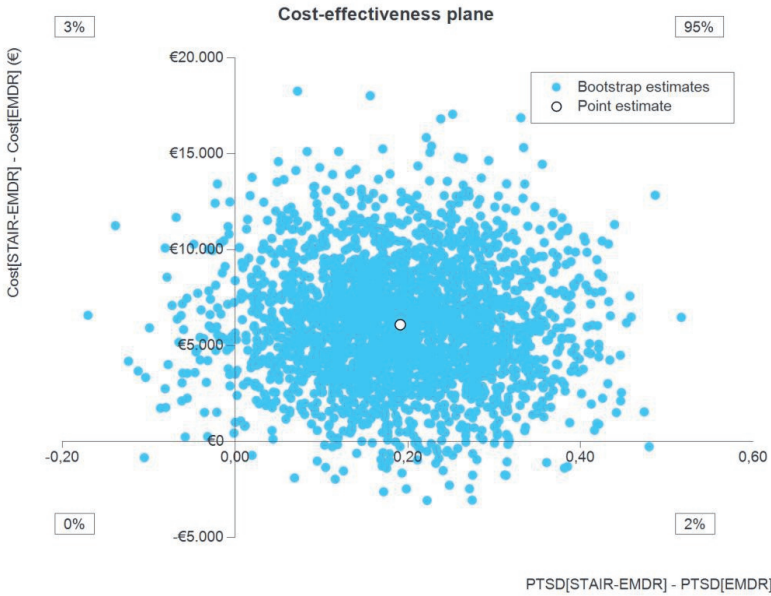
<sup>3</sup> Proportion of participants with remitted PTSD (at the last measurement).

Analyses of the included outcome measures, remitted PTSD, and QALYs revealed no statistically significant differences between the two groups. PTSD outcomes tended to favor of the STAIR-EMDR group, but QALY outcomes were slightly worse in this group.

### 3.4 Cost-effectiveness analyses

The cost-effectiveness analyses were based on the data of participants for whom sufficient information was available on both costs and health outcomes (at least 50% of the data available). The results of the cost-effectiveness analysis with remitted PTSD as the primary outcome measure are presented in the cost-effectiveness plane (CEP) in Figure 1. Information is provided on the point estimate of the ICER, and percentage of bootstrap simulations located in each quadrant of the CEP.

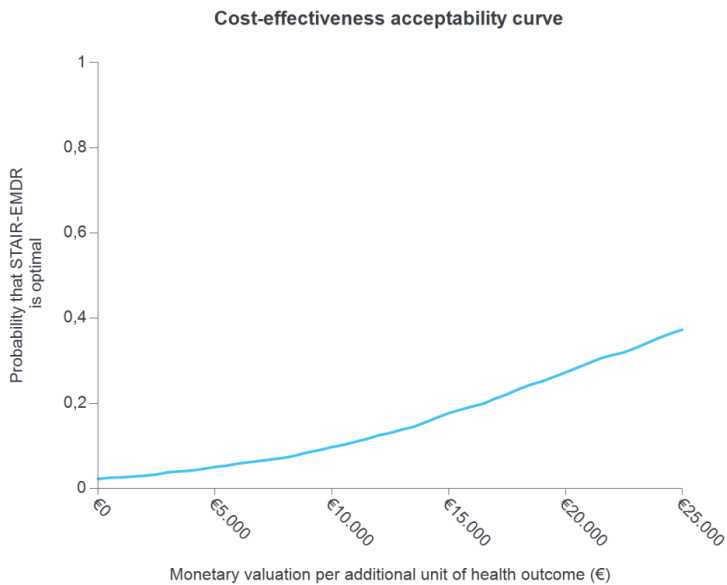
Figure 1. Cost-effectiveness analysis with remitted PTSD as outcome measure



The point estimate is located in the northeast quadrant, which indicates higher costs and better PTSD outcomes in the STAIR-EMDR group. Approximately 95% of bootstrap simulations were located in the northeast quadrant. Interpretation of the results of this cost-effectiveness analysis depends on how much decision makers are willing to pay for an additional unit of health outcome (remitted PTSD). The probability that the intervention will be optimal for increasing willingness to pay per additional unit of health outcome indicates that STAIR-

EMDR is not likely to be cost-effective compared to EMDR (Figure 2). The probability that STAIR-EMDR is optimal starts at only .03 for a monetary threshold of €0, and slowly increases for values up to €25.000. Even at these high monetary values, the probability that STAIR-EMDR is optimal increases to only .37.

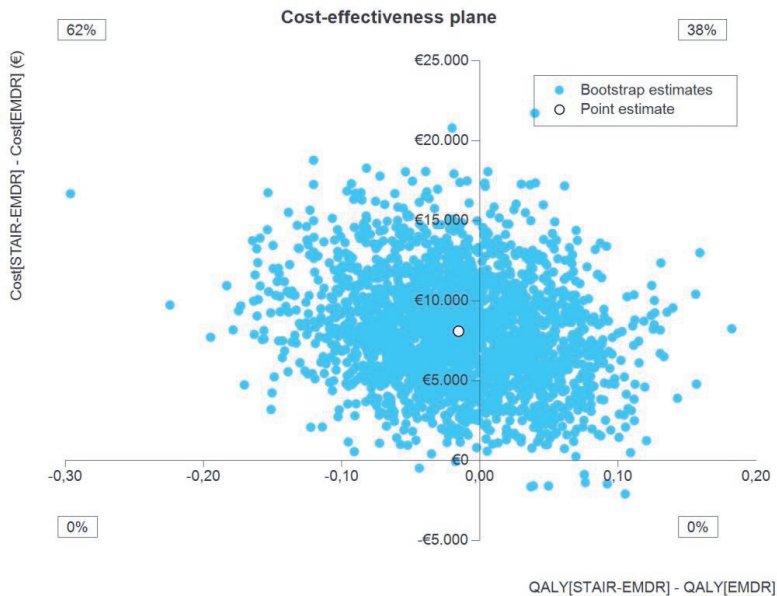
Figure 2. Cost-effectiveness acceptability curve (with remitted PTSD as primary outcome)



The results of the economic analysis using QALYs as the primary outcome measure are presented in the cost-effectiveness plane in Figure 3. The point estimate is located in the northwest quadrant, which indicates that costs were higher and QALY outcomes were worse in the STAIR-EMDR group. In total 62% of the bootstrap simulations were in the northwest quadrant. Overall, these results indicate that STAIR-EMDR is not cost-effective when focusing on the QALY outcomes.



Figure 3. Cost-effectiveness analyses with QALY as outcome measure



### 3.5 Sensitivity analysis

In the current study, the data were incomplete for a substantial proportion of the participants. In the planned sensitivity analysis, the influence of the applied approach on dealing with missing data was compared to the results of a complete case analysis. The results indicated that the complete case analysis was associated with a lower probability of STAIR-EMDR being optimal than the standard analysis. The results of the sensitivity analysis are therefore not presented in more detail here, but are available on request.

## 4. Discussion

To our knowledge, this is the first economic head-to-head comparison of phase-based treatment and direct trauma-focused treatment in patients with PTSD related to childhood abuse, with EMDR as the trauma-focused element and the preparation phase as an actual addition to EMDR therapy. The results indicate that STAIR-EMDR was not cost-effective

compared to EMDR therapy alone. The outcome measures of remitted PTSD and QALY's yielded no significant differences between the two treatment conditions, while the mean societal costs per patient differed significantly between the STAIR-EMDR and EMDR therapy groups (€19.599 vs. €13.501).

In contrast to the purported assumption that STAIR would increase day-by-day functioning by addressing interpersonal and emotion regulation problems (Haasija & Cloitre, 2015), the present results do not show the advantage of adding this treatment to EMDR therapy in terms of cost-effectiveness. In contrast to the study of Kullberg et al. (2023), we found a significant difference in mean societal costs between phase-based and direct trauma-focused conditions, with higher societal costs for phase-based treatment. The costs for PE and STAIR-PE appeared to be much higher (€ 4479 and € 4464, respectively) than those for EMDR and STAIR-EMDR (€ 1686 and € 2436, respectively). This is consistent with the conclusion of Mavranouzouli et al. (2020), who found that EMDR is a less expensive intervention than PE.

Consistent with previous detailed analyses of the same dataset (Van Vliet et al., 2021), we found no difference in the treatment effects between the two conditions. These outcomes are comparable to those reported in a previous study (Raabe et al., 2021). The QALY's from the present study for both STAIR-EMDR and EMDR therapy alone were comparable to the QALY's for EMDR calculated by Mavranouzouli et al. (2020). However, the QALY outcomes in the study by Mavranouzouli et al. were measured over a different period of time (three years) than in our study (nine months), so in comparing both outcomes, many assumptions had to be made, which leaves much uncertainty. The QALY's for EMDR seem somewhat lower than those for Prolonged Exposure from the study by Kullberg et al. (2023); however, also in this case, many assumptions had to be made. This may have been because our sample had more severe symptoms.

A strength of the present study is that we performed a full economic evaluation with a cost-effectiveness analysis and a cost-utility analysis of both treatment forms, evaluating the costs in relation to the effectiveness of the interventions, as recommended by the national and international guidelines for health cost evaluations (EUnetHTA, 2015; Zorginstituut Nederland, 2015b). Second, in addition to healthcare costs, societal costs such as productivity losses and care by relatives or acquaintances were assessed. These costs reflect the use of resources from other sectors of society and their increased usefulness (EUnetHTA, 2015). By considering these costs, we avoided artificially lowering costs by shifting medical costs to informal societal care costs.

One limitation of this study was the number of missing values, which may have limited the power of statistical calculations, leading to less reliable outcomes. Of the 57 participants in the STAIR-EMDR condition and 64 participants in the EMDR therapy condition, only 38 (66.7 %) and 41 (64.1%) participants, respectively, remained in the cost-effectiveness measurements at the six-month follow-up. The main reason for the incomplete data was the measurement dropout of patients during the study, despite our preventive efforts. As we used advanced methods to deal with incomplete data, patient data could still be included in our analyses when at least half of the measurements were available. A second limitation was the generalizability of these findings to other healthcare systems. Other countries and continents may have other healthcare organizations and costing methods, potentially leading to considerable differences in costs between studies of different healthcare systems. A third limitation is the relatively short study period (nine months), which precludes the visibility of societal gains in the long term. For decision makers, outcomes assessed over longer periods (at least one to two years) may prove more relevant for policy decisions.

In conclusion, although phase-based treatment and EMDR therapy alone demonstrated no difference in effectiveness in achieving remission of PTSD symptoms and improving

Quality-Adjusted Life Years, the societal costs of phase-based treatment were found to be significantly higher than those of the trauma-focused therapy approach. Where cost and time are issues, EMDR therapy alone would be the choice of treatment; however, some individuals might benefit from a longer treatment with an additional focus on skill-building.

## References

- Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., de Girolamo, G., Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J. M., Katz, S. J., Kessler, R. C., Kovess, V., Lépine, J. P., Ormel, J., Polidori, G., Russo, L. J., Vilagut, G., Almansa, J., ... ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project (2004). Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatrica Scandinavica. Supplementum*, (420), 38–46. <https://doi.org/10.1111/j.1600-0047.2004.00329.x>
- Ament, A., & Evers, S. (1993). Cost of illness studies in health care: a comparison of two cases. *Health Policy*, 26(1), 29–42. [https://doi.org/10.1016/0168-8510\(93\)90076-2](https://doi.org/10.1016/0168-8510(93)90076-2)
- American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders, DSM-5. Washington, DC: Author.
- American Psychiatric Association (2017). Clinical Practice Guideline for the treatment of PTSD. Retrieved from <https://www.apa.org/ptsd-guideline/ptsd.pdf>
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory II*. San Antonio, TX: Psychological corporation.
- Black, W. C. (1990). The CE plane: a graphic representation of cost-effectiveness. *Medical Decision Making*, 10, 212-214. <https://doi.org/10.1177/0272989x9001000308>
- CEA-plus BV. Released 2019. CEA-plus, software for cost-effectiveness analysis, Version 2.1. Enschede: CEA-plus BV.
- Chang, W. L., Andersen, C. J., Berisha, B. S., Estrup, O., & Wang, S. J. (2018). Economic

- evaluation of a bio-psycho-social intervention for comorbid disorders in a traumatized population in post-war Kosovo. *Journal of Rehabilitation Medicine*, 50(5), 444–450. <https://doi.org/10.2340/16501977-2322>
- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han, H. (2002). Skills training in affective and interpersonal regulation followed by exposure: A phase-based treatment for PTSD related to childhood abuse. *Journal of Consulting and Clinical Psychology*, 70(5), 1067–1074. <https://doi.org/10.1037//0022-006x.70.5.1067>
- Cloitre, M., Stovall-McClough, K. C., Noonan, K., Zorbas, P., Cherry, S., Jackson, C. L., Gan, W., & Petkova, E. (2010). Treatment for PTSD related to childhood abuse: a randomized controlled trial. *The American Journal of Psychiatry*, 167(8), 915–924. <https://doi.org/10.1176/appi.ajp.2010.09081247>
- Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., Herman, J. L., Lanius, R., Stolbach, B. C., Spinazolla, J., Van der Kolk, B. A., & Van der Hart, O. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in adults*. <https://terrorvictimresponse.ca/wp-content/uploads/ISTSS-Expert-Concesensus-Guidelines-for-Complex-PTSD-Updated-060315.pdf>
- Cloitre M. (2015). The "one size fits all" approach to trauma treatment: should we be satisfied?. *European Journal of Psychotraumatology*, 6, 27344. <https://doi.org/10.3402%2Ffejpt.v6.27344>
- De Jongh, A., & Ten Broeke, E. (2019). *Handboek EMDR: een geprotocolleerde behandelmethode voor de gevolgen van psychotrauma [Handbook EMDR: a protocolled treatment method for the consequences of psychotrauma]*. Amsterdam: Pearson Assessment and Information B.V.
- De Jongh, A., Resick, P. A., Zoellner, L. A., van Minnen, A., Lee, C. W., Monson, C. M., Foa, E. B., Wheeler, K., Ten Broeke, E., Feeny, N., Rauch, S. A. M., Chard, K. M.,

- Mueser, K. T., Sloan, D. M., Van der Gaag, M., Rothbaum, B. A., Neuner, F., De Roos, C., Hehenkamp, L. M. J.,...Bicanic, I. A. (2016). Critical analysis of the current treatment guidelines for complex PTSD in adults. *Depression and Anxiety*, 33(5), 359–69. <https://doi.org/10.1002/da.22469>
- Dolan, P. (1997). Modeling valuations for EuroQol health states. *Medical Care*, 35, 1095-1108. <https://doi.org/10.1097/00005650-199711000-00002>
- Drummond, M. F., O'Brien, B., Stoddart, G. L., Torrance, G. W. (1997). *Methods for the economic evaluation of health care programmes (2nd ed)*. Oxford Medical Publications: Oxford.
- Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B. J., & Stoddart, G. L. (2005). *Methods for the economic evaluation of health care programmes (3rd ed)*. Oxford University Press.
- Efron, B., & Tibshirani, R. J. (1993). *An introduction to the bootstrap*. Chapman & Hall.
- European Network for Health Technology Assessment (2015). *Methods for health economic evaluations, a guideline based on current practices in Europe*. Retrieved from: [https://www.eunethta.eu/wp-content/uploads/2018/03/Methods\\_for\\_health\\_economic\\_evaluations.pdf](https://www.eunethta.eu/wp-content/uploads/2018/03/Methods_for_health_economic_evaluations.pdf)
- EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy*, 16, 199-208. [https://doi.org/10.1016/0168-8510\(90\)90421-9](https://doi.org/10.1016/0168-8510(90)90421-9)
- Fenwick, E., O'Brien, B. J., & Briggs, A. (2004). Cost-effectiveness acceptability curves-facts, fallacies and frequently asked questions. *Health Economics*, 13, 405-415. <https://doi.org/10.1002/hec.903>
- Haasija, M. C., Cloitre, M. (2015). STAIR Narrative Therapy: A skills focused approach to trauma-related distress. *Current Psychiatry Reviews*, 11(3), 172-179. <http://dx.doi.org/10.2174/1573400511666150629105544>

- IBM Corp. Released 2017. *IBM SPSS Statistics for Windows*, Version 25.0. IBM Corp.
- Koopmanschap, M. A., Rutten, F. F. H., Van Ineveld, B. M., & Van Roijen, L. (1995). The friction cost method for measuring indirect costs of disease. *Journal of Health Economics*, *14*, 171-189. [https://doi.org/10.1016/0167-6296\(94\)00044-5](https://doi.org/10.1016/0167-6296(94)00044-5)
- Kullberg, M. J., Schoorl, M., Oprel, D. A. C., Hoeboer, C. M., Smit, F., van der Does, W., De Kleine, R. A., Van Minnen, A., & van den Hout, W. (2023). Exposure-based treatments for childhood abuse-related post-traumatic stress disorder in adults: a health-economic evaluation. *European Journal of Psychotraumatology*, *14*(1), 2171752. <https://doi.org/10.1080/20008066.2023.2171752>
- Le, Q. A., Doctor, J. N., Zoellner, L. A., & Feeny, N. C. (2014). Cost-effectiveness of prolonged exposure therapy versus pharmacotherapy and treatment choice in post-traumatic stress disorder (the Optimizing PTSDTreatment Trial): A doubly randomized preference trial. *The Journal of Clinical Psychiatry*, *75*, 222–230. <https://doi.org/10.4088/jcp.13m08719>
- Mavranouzouli, I., Megnin-Viggars, O., Grey, N., Bhutani, G., Leach, J., Daly, C., Dias, S., Welton, N. J., Katona, C., El-Leithy, S., Greenberg, N., Stockton, S., & Pilling, S. (2020). Cost-effectiveness of psychological treatments for post-traumatic stress disorder in adults. *PLoS ONE* *15*(4): e0232245. <https://doi.org/10.1371/journal.pone.0232245>.
- Oostenbrink, J. B., & Ai, M. J. (2005) The analysis of incomplete cost data due to dropout. *Health Economics*, *14*, 763-76. <https://doi.org/10.1002/hec.966>
- Pacella, M. L., Hruska, B., & Delahanty, D. L. (2013). The physical health consequences of PTSD and PTSD symptoms: a meta-analytic review. *Journal of Anxiety Disorders*, *27*(1), 33–46. <https://doi.org/10.1016/j.janxdis.2012.08.004>
- Patrick, D. L., & Erickson, P. (1993). *Health Status and Health Policy*. Oxford University Press.



- Raabe, S., Ehring, T., Marquenie, L., Arntz, A., & Kindt, M. (2021). Imagery Rescripting versus STAIR plus Imagery Rescripting for PTSD related to Childhood Abuse: A randomized controlled trial. *Journal of Behavior Therapy and Experimental Psychiatry*, 77, 101769. <https://doi.org/10.1016/j.jbtep.2022.101769>
- R Core Team (2022). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. <https://www.R-project.org/>
- Rice, D. P. (1994). Cost-of-illness studies: Fact or fiction? *The Lancet*, 344, 1519–1520. [https://doi.org/10.1016/s0140-6736\(94\)90342-5](https://doi.org/10.1016/s0140-6736(94)90342-5)
- Rink, J., & Lipinska, G. (2020). Evidence of distinct profiles of ICD-11 post-traumatic stress disorder (PTSD) and complex PTSD in a South African sample. *European Journal of Psychotraumatology*, 11(1), 1818965. <https://doi.org/10.1080%2F20008198.2020.1818965>
- Shapiro, F. (2018). *Eye movement desensitization and reprocessing (EMDR) therapy: Basic principles protocols, and procedures*. Guilford Press.
- Van Vliet, N. I., Huntjens, R. J. C., Van Dijk, M. K., & De Jongh, A. (2018). Phase-based treatment versus immediate trauma-focused treatment in patients with childhood trauma-related posttraumatic stress disorders: Study protocol for a randomized controlled trial. *Trials*, 19(1), 1-10. <https://doi.org/10.1186/s13063-018-2508-8>
- Van Vliet, N., Huntjens, R., Van Dijk, M., Bachrach, N., Meewisse, M., & De Jongh, A. (2021). Phase-based treatment versus immediate trauma-focused treatment for post-traumatic stress disorder due to childhood abuse: Randomised clinical trial. *BJPsych Open*, 7(6), E211. <https://doi.org/10.1192%2Fbjo.2021.1057>
- Von der Warth, R., Dams, J., Grochtdreis, T., & König H. H. (2020). Economic evaluations

- and cost analyses in posttraumatic stress disorder: a systematic review. *European Journal of Psychotraumatology*, 11(1). <https://doi.org/10.1080/20008198.2020.1753940>
- Weathers, F. W., Blake, D. D., Schnurr, P. P., Kaloupek, D. G., Marx, B. P., & Keane, T. M. (2013). *The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. National Center for Posttraumatic Stress Disorder, 2013 ([www.ptsd.va.gov](http://www.ptsd.va.gov) [2013]).
- Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., Keane, T. M., & Marx, B. P. (2018). The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychological Assessment*, 30(3), 383–395. <https://doi.org/10.1037/pas0000486>
- World Health Organization (2013). *Guidelines for the management of conditions specifically related to stress*. World Health Organization: Geneva.
- Zorginstituut Nederland. *Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Geactualiseerde versie 2015*. Zorginstituut Nederland, editor: Zorginstituut Nederland; 2015a.
- Zorginstituut Nederland. *Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg*. Zorginstituut Nederland, editor: Zorginstituut Nederland; 2015b.



## **Summary and general discussion**

## 8. Summary and general discussion

The introduction of this thesis highlights the need for improvement in the treatment of individuals with (Complex) PTSD stemming from childhood abuse. This is all the more important because adult patients with a history of childhood abuse are more at risk for the development of (Complex) PTSD (Leiva-Bianchi et al., 2023). Aligning with this need, this research project aimed to accomplish several objectives: 1) determining whether a phase-based treatment would be more effective than a trauma-focused treatment in patients with PTSD related to childhood abuse, 2) determining what kind of treatment works best for which patient, 3) identifying predictors for PTSD treatment dropout, and 4) calculating and comparing the cost-effectiveness of a phase-based treatment with that of a trauma-focused treatment.

The study design, as described in Chapter 2, involved a direct comparison of a phase-based treatment and a trauma-focused treatment for patients with PTSD related to childhood abuse. The trauma-focused treatment consisted of 16 sessions of EMDR therapy, whereas the phase-based treatment involved 16 sessions of EMDR therapy, preceded by eight sessions of Skills Training in Affective and Interpersonal Regulation (STAIR). STAIR, a well-studied evidence-based first-phase treatment (Cloitre et al., 2002; Cloitre et al., 2010), focuses on teaching emotion regulation and interpersonal skills. Participants were recruited from two mental health care organizations and were diagnosed with PTSD that was due to childhood abuse experienced before the age of 18 by a caretaker or person in authority. Assessments were conducted before treatment, immediately after treatment, and at three- and six-month follow-ups to evaluate the presence and severity of PTSD, Complex PTSD, general psychopathology, and dissociative symptoms.

In the following paragraphs, the study results are presented and discussed in the context of other studies in the field. Additionally, strengths and limitations are discussed. This

chapter concludes with implications for clinical practice, along with potential directions for future research.

## **8.1 Summary of the findings**

### *8.1.1 Main outcomes*

Our first objective aligns with the suggested research direction from the ISTSS position paper published in 2018 (ISTSS, 2018), which emphasizes studying the effectiveness of therapeutic interventions that directly address the symptoms of Complex PTSD, such as STAIR. Our findings indicated that a phase-based treatment incorporating STAIR as a preparation phase was not more effective than a direct trauma-focused treatment. Both the phase-based treatment and the trauma-focused treatment proved to be effective for a wide variety of symptoms (i.e., those related to PTSD, Complex PTSD, general psychopathology, dissociative symptoms, and separate Complex PTSD/DSO symptoms), as the results showed a significant decline from pre- to post-treatment for all symptom clusters in both conditions. Notably, there was no significant additional symptom reduction in the STAIR-EMDR condition compared to the EMDR-only condition from pre- to posttreatment, despite patients in the former condition receiving eight more treatment sessions. For the variables measured after each of the eight sessions (i.e., emotion regulation difficulties, interpersonal problems, posttraumatic cognitions, and self-reported PTSD symptoms), a significant interaction effect between treatment condition and time was found for the variables interpersonal problems, post-traumatic cognitions, and self-reported PTSD symptoms. These variables exhibited a significantly slower decline in symptoms during the first eight sessions in the STAIR-EMDR condition compared to the EMDR-only condition, suggesting that the addition of STAIR to EMDR therapy has delayed the symptom improvement in these areas. Importantly, the

dropout rates did not differ between the two conditions and in only three (non-study related) adverse events occurred.

### *8.1.2 Predictors and moderators*

To address the call of the ISTSS (2018) for a more personalized treatment approach and the evaluation of multicomponent treatments, it is crucial to develop a better understanding of patient characteristics that may predict or moderate PTSD treatment outcomes in individuals with PTSD related to childhood abuse. This is important as it is plausible that characteristics often observed in these patients (e.g., dissociative experiences) have a negative effect on their treatment. Therefore, common comorbid symptoms in patients with PTSD related to childhood abuse were identified as potential predictors. Our study aimed to determine whether the presence of a borderline personality disorder (BPD), suicidality, self-injurious behavior, and dissociative phenomena could predict treatment outcomes (corrected for PTSD severity) or whether DSO symptoms serve as moderators between treatment conditions and PTSD treatment outcomes, corrected for pre-treatment PTSD severity. The results of these analyses indicated that the severity of PTSD symptoms at pre-treatment was the most reliable predictor of less favorable PTSD treatment results, and that only dissociative symptoms predicted worse PTSD treatment outcomes independent of pre-treatment PTSD severity. However, the latter effect was observed only at the post-treatment assessment and not at the six-month follow-up, and when corrected for false positives the predictive effect posttreatment was absent, which makes that we should interpret these results with caution.

### *8.1.3 Creating a Personalized Advantage Index (PAI)*

The results of our RCT showed that an outpatient treatment with EMDR therapy alone is a viable option to treat PTSD, that preliminary preparation in the form of skills training prior to

EMDR therapy is unnecessary, and that many patients benefit from it. The latter also applies when the PTSD was the result of childhood abuse. To ensure that we did not overlook patient characteristics or combinations of patient characteristics that could potentially serve as predictors or moderators, we conducted a second analysis to determine whether certain patients would benefit more from a phase-based treatment approach (STAIR-EMDR) than of direct trauma-focused treatment by calculating a personalized advantage index (PAI; DeRubeis et al., 2014). This method applies machine learning techniques, allowing for the exploration of a large number of moderators that may, when combined, lead to differential treatment effects in the compared treatment conditions. The procedure identified several moderators. The moderators that were identified were combined to build the PAI and, thereafter, the utility of the PAI was tested by comparing actual post-treatment outcomes of individuals receiving the PAI-indicated treatment with those allocated to the treatment not indicated by the PAI. For the post-treatment PTSD severity scores, no significant differences were found between individuals receiving the PAI-indicated treatment and those receiving the treatment not indicated by the PAI. This means that treatment of patients in their best treatment option did not result in significantly better treatment outcomes than treatment in their less optimal treatment option.

#### *8.1.4 Risk factors for dropout*

We also investigated PTSD treatment dropout among patients with PTSD related to childhood abuse. Predicting treatment dropout may be essential in order to limit attrition in the treatment of patients with Complex PTSD which is important as dropout rates among patients with PTSD are relatively high (ranging from 16 to 20.9% (Lewis et al., 2020; Varker et al., 2021)). Patients were considered dropouts if they prematurely discontinued treatment after the first session, which involved psychoeducation and case conceptualization. Over both



conditions, 19% of the patients dropped out. All dropped-out patients that could still be measured (37 % of the dropouts) at the post-treatment assessment still met the criteria for a PTSD diagnosis. The results indicated that the median number of sessions before dropping out was four. To identify predictive patient characteristics for dropout, we applied machine learning techniques to analyze all pretreatment variables and developed a model using Elastic Net Regularization (ENR, R package ‘glmnet’, Friedman et al., 2010). The ENR model accurately predicted dropout in 81.6 % of all individuals. The model revealed that low education level, presence of suicidal thoughts, and not using benzodiazepine medication during screening were most strongly related to dropout risk.

#### *8.1.5 Calculating cost-effectiveness of a phase-based treatment and a trauma-focused treatment.*

PTSD has been found to exert a significant influence on work disability and quality of life, resulting in substantial economic burden (Von der Warth et al., 2020). While it has been noted that a phase-based treatment does not yield superior treatment outcomes compared to a direct trauma-focused treatment, it is conceivable that STAIR reduces societal costs and increases quality of life by equipping patients with essential daily life skills (Cloitre et al., 2002). Consequently, it is important to not only compare the treatment effects of a phase-based treatment with a direct trauma-focused treatment, but also their impact on costs and quality of life.

To assess these aspects, a cost-effectiveness analysis and a cost-utility analysis were conducted. The primary outcome measure of the cost-effectiveness analysis was the proportion of participants with remitted PTSD. Quality-adjusted life years (QALY) served as the primary outcome measure for the cost-utility analysis. The results indicated that STAIR-EMDR was not more cost-effective compared with EMDR therapy alone and no significant

differences were observed in the outcomes measure of remitted PTSD and QALY's between the two treatment conditions. However, the mean societal costs per patient differed significantly between STAIR-EMDR vs EMDR (€19.599 vs €13.501), with the phase-based treatment incurring higher societal costs compared to the direct trauma-focused treatment.

## 8.2 General discussion

### 8.2.1 *What is the best treatment option for patients with PTSD related to childhood abuse?*

In line with our conclusion that phase-based treatment is not significantly more beneficial than direct trauma-focused treatment, a recent systematic review of phase-based interventions for Complex PTSD showed that the addition of a preparation or stabilization phase to direct trauma-focused treatment does not improve outcomes compared to direct trauma-focused treatment (Darby et al., 2023). It is important to note that, apart from our study, none of the other studies included in the systematic review of Darby et al. (2023) directly compared a trauma-focused treatment with a phase-based treatment. Instead, most of the studies compared a phase-based treatment with treatment as usual, a waiting list condition, or a trauma-focused treatment form other than the one used in the phase-based condition. The variations in effect sizes between phase-based and trauma-focused conditions may therefore mainly be attributed to differences in the effect sizes of the trauma-focused elements compared with or without a preparatory phase.

During our research project, another study compared trauma-focused treatment with a phase-based treatment (Raabe et al., 2022), with the preparation phase as an actual addition to the trauma-focused element and with the same trauma-focused treatment in both conditions. This study was not included in the systematic review by Darby et al. (2023); however, the results are consistent with our findings. This study investigated another evidence-based trauma-focused therapy used for the treatment of PTSD, imaginary rescripting (ImRs; Raabe

et al., 2022). The researchers randomly assigned 61 patients to 16 sessions of ImRs, 16 sessions of ImRs preceded by eight sessions of STAIR, or a waitlist condition lasting eight weeks. Similar to our study results, there were no significant differences in treatment outcomes between the phase-based treatment and trauma-focused treatment, and even revealed a faster reduction in symptoms of guilt, shame, and anger during trauma-focused treatment than during the STAIR phase. Furthermore, the results of the STAIR phase for PTSD symptom improvement were not significantly better than those of the waitlist control condition were. These findings suggest that the STAIR phase of phase-based treatment is likely to delay a decline in PTSD symptoms.

One can also question whether the addition of STAIR to trauma-focused treatment leads to fewer dropouts compared to direct trauma-focused treatment. In our study we found that direct trauma-focused treatment did not lead to significantly higher dropout rates than phase-based treatment which aligns with the study by Raabe et al. (2022). These results were confirmed by another study (Oprel et al., 2021). These researchers compared 16 sessions of prolonged exposure (PE) with eight sessions of prolonged exposure preceded by eight sessions of STAIR, and with 14 sessions of prolonged exposure in an intensified treatment form (i.e. they did not add a preparation phase to a trauma-focused treatment, but replaced a part of the trauma-focused sessions by a preparation program). Similar to our findings and those of Raabe et al. (2022), this study also showed that commencing treatment directly with trauma-focused therapy did not result in significantly higher dropout rates than beginning with STAIR, followed by trauma-focused treatment. These results support the notion that starting trauma-focused treatment does not lead to more dropouts than starting with a preparation phase followed by trauma-focused treatment in patients with PTSD related to childhood abuse.

In addition to treatment effectiveness and dropout, another important issue is patient safety (Cloitre et al., 2012). Including a preparation phase at the beginning of trauma-focused treatment is recommended to enhance patient safety and to avoid adverse events (Cloitre et al., 2002; Cloitre et al., 2010). Our findings, in conjunction with the results of Oprel et al. (2021), affirm that commencing treatment with a trauma-focused approach is safe for patients with PTSD that stems from childhood abuse. This conclusion was drawn from the absence of a significant difference in the occurrence of adverse events between the trauma-focused and phase-based treatments. Although Raabe et al. (2022) and Sele et al. (2023) did not mention the adverse events in their articles, there is no reason to suspect significant differences in adverse events between the compared conditions in these studies. Hence, initiating treatment with either a trauma-focused approach or a preparatory phase seems equally safe for patients with childhood abuse-related PTSD.

Although direct trauma-focused treatment reduces PTSD symptoms, a final argument for the addition of a preparation phase could be that this may tackle the core symptoms that are characteristic of Complex PTSD more directly and effectively (Cloitre et al., 2012). However, the results of Oprel (2021), Raabe (2022), and our data support the notion that direct trauma-focused and phase-based treatment approaches are equally effective in reducing DSO/Complex PTSD symptoms. This is in agreement with the results of a meta-analysis and systematic review showing that various evidence-based trauma-focused therapies have positive effects on Complex PTSD symptoms (Karatzias et al., 2019). Given that these symptoms decline with the application of a direct trauma-focused treatment, the addition of a preparation program specifically targeting Complex PTSD symptoms to a trauma-focused treatment is unnecessary.

None of the aforementioned studies stated the presence of Complex PTSD as an inclusion criterion. A recent randomized controlled trial did precisely that (Sele et al., 2023).

This trial compared 12 sessions STAIR to eight to 16 sessions of prolonged exposure (PE) and to phase-based treatment (i.e., 12 sessions of STAIR followed by eight sessions of narrative therapy). PE demonstrated a significant advantage over a phase-based approach in terms of reducing PTSD symptoms and the loss of PTSD diagnoses. In addition, for depressive symptoms and interpersonal problems PE was superior to phase-based treatment, although STAIR as stand-alone treatment also performed fairly well. No significant differences were observed between the conditions in terms of reducing Complex PTSD symptoms. These findings suggest that PE is superior to phase-based treatment and STAIR, especially in the long term, although this advantage did not extend specifically to Complex PTSD symptoms, for which all conditions were equally effective.

STAIR was officially developed to address Complex PTSD symptoms and enhance patient safety. Although STAIR appears to be effective on Complex PTSD symptoms when used in isolation (Lorbeer et al., 2022; Sele et al., 2023), incorporating STAIR as a preparatory phase in phase-based treatment does not yield superior results in treating PTSD or the Complex PTSD symptoms (Sele et al., 2023; Van Vliet et al., 2021; Raabe et al., 2022). This prompts the question of why STAIR should be added as a preparation to trauma-focused treatments. In the study by Sele et al. (2023), the pre-post effect size of the combination of STAIR with the trauma-focused treatment condition was lower (0.36) than that when the treatment was not combined with trauma-focused treatment (Hedges'  $g$  of the STAIR only = 0.47). This also applied to our own study. The effect sizes of the trauma-focused treatment did not increase, but decreased when STAIR was added to the treatment and combined with EMDR therapy (Cohen's  $d$ s decreased from 1.54 to 0.93). So STAIR as a stand-alone treatment may be more effective than combined with a trauma-focused treatment.

Therefore, one may wonder why the preparation phase of phase-based treatment may have a negative impact on PTSD treatment. Let us discuss some of the potential reasons. The

addition of a preparation phase may inadvertently convey the message that trauma-focused treatment is risky, suggesting that patients may struggle to handle traumatic memories, and should avoid confronting them. Patients may also perceive the therapists as unable to manage traumatic memories, leading them to keep these memories to themselves (Neuner, 2008). Furthermore, incorporating a preparation phase in trauma-focused treatment can create conflicting messages for patients in that they are encouraged to face their traumatic memories but are also told that it may be too risky. These opposing messages could be more confusing than adhering to a single treatment approach, such as acquiring coping skills or directly addressing traumatic memories.

In summary, when comparing phase-based treatment with trauma-focused treatment, the available evidence suggests that the addition of a preparation/stabilization phase to trauma-focused therapy does not lead to significantly better treatment results than direct trauma-focused treatment and that trauma-focused treatment is just as safe as phase-based treatment in patients with PTSD related to childhood abuse. The addition of a preparation phase may only lead to a delay in symptom improvement. Most importantly, trauma-focused treatments also positively affect Complex PTSD symptoms.

#### *8.2.2. Predictors of less favorable PTSD treatment outcomes.*

Of all the predictors investigated in our study, only the severity of pre-treatment PTSD was shown to be a reliable predictor of less favorable PTSD treatment outcomes. Corrected for PTSD severity, dissociative phenomena were found to predict fewer positive treatment effects; however, these findings should be interpreted with caution, considering false positives and the lack of maintenance at 6-month follow-up. The absence of an association between suicidality and worse PTSD outcomes aligns with the results of a meta-analysis comparing clinical trials that included patients with suicidal ideation versus those that excluded such

patients and found no significant differences in PTSD treatment outcomes (Brooks et al., 2021). Similarly, our finding that the presence of a borderline personality disorder was not a predictor of less favorable PTSD treatment outcomes is in line with the results of a meta-analysis showing that psychotherapy is effective for PTSD in patients with a borderline personality disorder (Slotema et al., 2020). However, the above outcomes do not imply that patients with severe PTSD do not profit from trauma treatment at all, they may only need more time to recover from PTSD. In summary, among patients with PTSD related to childhood abuse, only the severity of PTSD has been demonstrated to be a reliable predictor of fewer positive treatment effects.

Research on the role of dissociative symptoms as predictor in the treatment of patients with a PTSD related to childhood abuse is limited. A meta-analysis of patients with various trauma backgrounds showed that the presence of dissociative symptoms pre-treatment does not predict worse PTSD treatment outcomes (Hoeboer et al., 2020). Notably, this meta-analysis included only three studies involving patients with a history of childhood abuse (Cloitre et al., 2012; Kratzer et al., 2018; Lampe et al., 2014), and two of these studies did not use evidence-based trauma-focused treatment (Cloitre et al., 2012; Lampe et al., 2014). Among the studies included, Kratzer et al. (2018) utilized EMDR therapy as an intervention, but treatment was embedded in an inpatient therapy program, covering over 10 additional types of therapy besides EMDR, which makes the influence of EMDR therapy on symptom decline unclear. Therefore, further research on the influence of dissociative phenomena on PTSD treatment outcomes in patients with a history of childhood abuse is required. This research should not only explore trait dissociation but also examine state dissociation during treatment sessions. For instance, Kleindienst et al. (2016) found that state dissociation during PTSD psychotherapy sessions predicted less favorable treatment outcomes. Therefore, future studies investigating the influence of various dissociative phenomena on the treatment

outcomes of patients with a history of childhood abuse and PTSD are essential, as this area remains poorly understood.

In summary, except for the predictive value of PTSD symptom severity for less favourable treatment outcomes and possibly dissociative symptoms being predictive of less positive treatment outcomes, no other predictors for the treatment outcome of PTSD were identified. Until reliable predictive factors for treatment outcomes have been identified, there is no reason to withhold patients from trauma treatment. Patients with severe PTSD can still benefit from treatment; however, they may need more time to achieve the same treatment outcomes as patients with less severe PTSD symptoms. Exploring the predictive value of dissociative phenomena in PTSD treatment outcomes in patients with a history of childhood abuse remains an important focus for future research.

### *8.2.3 Investigating Complex PTSD symptoms as potential treatment moderators*

The most efficient approach is to offer patients direct trauma-focused evidence-based treatment such as EMDR therapy, which has shown long-term effectiveness in patients with PTSD (Yunitri et al., 2023). In light of the question of whether this also holds true in the case of Complex PTSD, it was considered relevant to determine whether Complex PTSD symptoms would moderate between PTSD treatment outcomes and conditions. To this end, when studying the comparison of EMDR only therapy and EMDR preceded by STAIR, it was observed that none of the Complex PTSD symptoms did moderate between the PTSD treatment outcome and both treatment conditions. This finding aligns with the results of Hoeboer, De Kleine et al. (2021) who used data from a large RCT of patients with PTSD related to childhood abuse to determine whether Complex PTSD symptoms predicted PTSD treatment outcomes or moderated between treatment conditions and PTSD treatment outcomes. Patients were randomly assigned to three treatment conditions: 16 sessions of



prolonged exposure, eight sessions of STAIR followed by 8 sessions of prolonged exposure, and 14 sessions of intensified prolonged exposure (Oprel et al., 2021). Similarly, Hoeboer, De Kleine et al. (2021) did not observe any predictive or moderating effects of Complex PTSD symptoms. The fact that our primary study results revealed that symptom reduction concerning interpersonal problems and posttraumatic cognition was delayed during the STAIR phase further underscores the effectiveness of direct trauma-focused treatment for Complex PTSD symptoms. These results suggests that severity of Complex PTSD symptoms, such as emotion regulation problems, interpersonal problems and negative self-esteem should not be decisive factors in determining whether direct trauma-focused treatment should be withheld from patients with childhood abuse-related PTSD.

#### *8.2.4 Identifying the best treatment option for individual patients*

We employed Personalized Advantage Index (PAI) analyses to explore whether certain patients with PTSD related to childhood abuse might benefit more from a phase-based than from a trauma-focused approach. PAI analyses can identify combinations of pre-treatment characteristics that could potentially lead to enhanced treatment outcomes in either form of treatment. We did not find a significant PAI, indicating that patients assigned to their PAI-indicated treatment did not achieve significantly better results than those assigned to their PAI non-indicated treatment.

Our PAI results differed from those obtained by Hoeboer, Oprel et al. (2021; for more details see Chapter 5). By contrast, they found a significant difference between patients receiving PAI-indicated treatment and those receiving non-PAI-indicated treatment. This suggests that certain patients profited significantly more from either direct trauma treatment or phase-based treatment. Specifically, they discovered that more depressive symptoms, less social support, more overall psychopathology, and higher severity of childhood sexual abuse

were predictors of worse treatment outcomes in the trauma-focused condition than in the phase-based condition. Furthermore, their study indicated that more emotion regulation difficulties, experiencing a lower general health status, and higher baseline PTSD symptoms were predictors of better treatment outcomes in the trauma-focused treatment option than in phase-based treatment. This means that patients with these characteristics may benefit more from trauma-focused treatment than from phase-based treatment. The precise reasons for the difference between our results and those of Hoeboer, Oprel et al. (2021) are difficult to determine; however, several potential explanations can be considered.

As mentioned in Chapter 5, a first explanation for the difference between our results and the results of Hoeboer, Oprel et al., (2021) is that they used a larger sample size, which increases the likelihood of detecting significant differences. Another potential explanation is that individuals with Complex PTSD respond differently to treatment with either exposure therapy (as used in the Hoeboer, Oprel et al., 2021 study) or EMDR therapy (as used in our study). Further research in this area with larger sample sizes and external validation is crucial, as limited knowledge is available regarding therapy type-dependent effects, and is vital for establishing treatment guidelines for PTSD. Another explanation for the difference between our PAI analyses and those of Hoeboer, Oprel et al. (2021) might stem from variations in pre-treatment characteristics included in the PAI analyses. While Hoeboer, Oprel et al. (2021) included measures of pre-treatment severity of childhood abuse, general health status, and social support in addition to demographic and psychopathological variables, our study focused primarily on psychopathology and demographic measures. These added pre-treatment measures of Hoeboer, Oprel et al. (2021) were found to be moderators between PTSD treatment outcomes and treatment conditions. Thus, the inclusion of different pre-treatment variables may lead to different PAI results.

Another potential explanation for the different outcomes between Hoeboer, Oprel et al. (2021) and our study may be provided by a theory developed by Hyland et al. (2023). The latter authors developed the Memory and Identity Theory to potentially explain several phenomena that are especially relevant to ICD-11 Complex PTSD and the treatment of people with this diagnosis. This theory posits that the complex interaction between trauma exposure and individual pre-traumatic vulnerability (e.g., adverse childhood experiences), post-traumatic vulnerability (e.g., social support) and general stress (e.g., health problems) may cause negative self-representations and feelings of being unsafe and powerless. These factors may contribute to affect dysregulation, negative self-concept and interpersonal problems. The absence of social support and lower general health status, as included by Hoeboer, Oprel et al. (2021), where we only included psychopathological symptoms, might represent additional stress that enlarges post-trauma vulnerability, whereas the severity of childhood abuse plays a role in the pre-trauma vulnerability. These (or other) potential underlying factors may carry more weight in predictive and moderating analyses than in straightforward psychopathology or complaints, because the latter may be an outcome of a combination of vulnerability and traumatic experiences. Although the Memory and Identity Theory has not yet been established and needs further research, it may be valuable to keep this theory in mind for future research on moderators and predictors of treatment outcomes in patients with PTSD related to childhood abuse.

In conclusion, we identified some predictors and moderators using machine learning, PAI analysis yielded non-significant results. However, because these findings are not consistent with the findings of Hoeboer, Oprel et al.'s study (2021), it is important that these findings are replicated in larger samples and externally validated before drawing conclusions about their clinical implications. In conclusion, given the fact that evidence supporting the notion that some patients with a PTSD related to childhood abuse may profit more from

phase-based treatment rather than from trauma-focused treatment is inconsistent, patients should be offered the most efficient treatment which is, in the case of this dissertation, EMDR therapy.

#### *8.2.5 Who is at risk of dropping out of treatment?*

Based on the results of their meta-analysis, and as there is a scarcity of literature on this subject, Hoppen et al. (2022) emphasized the importance of routinely and thoroughly assessing and reporting the incidence of dropout, deterioration, and their causes. More knowledge of causes of deterioration and dropout during treatment may result in more knowledge to prevent dropout. Preventing dropout in PTSD treatments is important as untreated PTSD compared to treated PTSD may lead to worse prognoses and diverse societal consequences (Usman et al., 2015). In our study the dropout rate was 19%, a percentage which aligns with the mean dropout rates for PTSD treatments among patients with various trauma backgrounds ranging from 16% (Lewis et al., 2020) to 20.9% (Varker et al., 2021). Prior to our study, most studies that addressed dropout focused on therapy type as potential predictor of dropout; however, in our study, we attempted to find a combination of patient characteristics.

We found a strong association between the combination of low education level, presence of suicidal thoughts, and absence of benzodiazepine medication use during screening on the one hand, and the risk of dropout on the other hand. Although our findings warrant replication, these prompt the question of whether an underlying factor may explain the combination of these characteristics as predictive of dropout risk. To this end, an interesting theory describing potential underlying factors is the Memory and Identity Theory as described above (Hyland et al., 2023). It posits that the interaction between trauma exposure and individual vulnerability pre-trauma (e.g., previous psychopathology, other adverse childhood experiences) and post-trauma (e.g. absence of social support, and unhelpful coping strategies)

may cause negative self-representations and unsafe and powerless feelings. According to the authors of the model, these variables may affect emotional dysregulation, negative self-concept and interpersonal problems (i.e., Complex PTSD symptoms). In a similar vein, if an individual exhibits a tendency towards suicidal thoughts, a potential reliance on unhelpful coping mechanisms like benzodiazepine use (without having access to it), and has lower levels of education, it may suggest the presence of pre-existing vulnerability prior to experiencing trauma. If the patient develops PTSD symptoms and then seeks treatment simultaneously, there could be an increased risk of dropping out of therapy or experiencing less favourable treatment outcomes. However, it's important to note that this theory still requires validation and further research to confirm its validity and our results need to be replicated in larger samples.

Although our study provides insight into patient characteristics that pose a risk of dropping out of PTSD treatment, variables other than patient characteristics may contribute to the risk of dropout from PTSD treatment. To gain a comprehensive perspective on dropout, it may be interesting to consider other factors such as the number of delivered sessions. Varker et al. (2021) revealed a positive correlation between the number of sessions and the dropout rate in that the more treatment sessions were offered, the higher the proportion of dropout. This suggests that shorter PTSD treatments with fewer treatment sessions may be preferable for reducing dropout rates. Another approach to reduce dropout rates could be to intensify PTSD treatment in terms of more frequent scheduling of treatment sessions. Three meta-analysis (Hoppen, Kip et al., 2023; Sciarrino et al., 2020; Wachen et al., 2019) demonstrated that intensive PTSD treatment programs are efficient and are associated with significantly lower dropout rates.

In conclusion, we found a reliable model to predict treatment dropout in patients with PTSD related to childhood abuse. In this model, we found that a combination of low

education level, suicidal thoughts, and absence of benzodiazepine medication was a risk factor for dropout. However, the mechanism underlying the dropout risk of PTSD treatment in patients with PTSD related to childhood abuse remains unclear. When the risk of dropout can be predicted based on patient characteristics, specialized interventions can be developed to prevent dropout. The results of the present study may require replication in larger samples to determine whether the predictive value is sufficiently stable for the adaptation or development of programs targeting these characteristics.

#### *8.2.6 Let's talk money*

In our study, we found that STAIR-EMDR was not cost-effective compared to EMDR-only therapy in the treatment of patients with a PTSD related to childhood abuse, as no statistically significant differences in cost-effectiveness between the two treatment conditions were found. These findings align with the results of Kullberg et al.'s (2023) study, that also found that STAIR-PE is not cost-effective compared to PE-only. Kullberg et al., (2023) compared the costs of three forms of prolonged exposure in patients with a PTSD related to childhood abuse; 16 sessions PE, eight sessions STAIR followed by eight sessions PE, and 14 sessions of intensified PE. Therefore, even when the number of treatment sessions is comparable among the conditions, phase-based treatment proved not cost-effective compared to direct trauma-focused treatment. In our study, we observed a significant difference in mean societal costs per patient between STAIR-EMDR and EMDR therapies (€19,599 vs. €13,501;  $M$  cost-differences = €6,098,  $CI$  (95%) = [€117 ; €12,644]), with STAIR-EMDR bringing more societal costs than EMDR per patient. Kullberg et al. (2023) found no significant differences in societal costs per patient between PE and STAIR-PE. This difference may be explained by the fact that our treatment conditions differed in duration, while in the study of Kullberg et al. (2023) the treatment duration was the same in the conditions. The outcome measures of

remitted PTSD and QALY's yielded no significant differences between the two treatment conditions in our study, with the QALY's for both STAIR-EMDR and EMDR therapy alone being comparable to those for EMDR therapy calculated by Mavranouzouli et al. (2020). However, the QALY outcomes in the study by Mavranouzouli et al. (2020) were measured over a different period (three years) than those in our study (nine months). Thus, several assumptions were made when comparing outcomes, resulting in considerable uncertainty.

For policymakers and decision-makers it may be crucial not only to understand that phase-based treatment is not cost-effective compared to direct trauma-focused treatment, but also that trauma-focused treatment seems to be the most cost-effective option for patients with PTSD related to childhood abuse. Our study revealed that the direct costs of EMDR therapy in our study (€ 2436) were much lower than the costs of prolonged exposure (another evidence-based first-choice PTSD treatment form; APA, 2017) in a comparable study (€ 4479; Kullberg et al., 2023). This finding aligns with that of a large study comparing the costs of 10 PTSD treatment interventions, which found EMDR therapy to be the most cost-effective treatment approach (Mavranouzouli, 2020). However, the only way to know exactly whether EMDR or PE therapy is the most cost-effective treatment for patients with PTSD related to childhood abuse will be to compare them directly in a large RCT.

In addition to clarifying the costs associated with treatment types for patients with PTSD related to childhood abuse, it may be interesting to examine other factors that may contribute to the treatment costs of this patient group. One subject for future research may be further reduction of EMDR treatment costs. One suggestion worth further study is whether the costs will be reduced by maximizing the working memory load during EMDR (i.e., EMDR 2.0; Matthijssen et al., 2021) based on the working memory theory. One well studied theory about the effectiveness of EMDR therapy is the working memory theory, which posits that traumatic memories become unstable during recall and that their reconsolidation is affected

by experiences during recall (Baddeley, 1998). Recalling an episode depends on limited working memory resources. If a secondary task is executed (by making eye movements), fewer resources will be available for recalling a traumatic episode and the memory will become less vivid and emotional (Van der Hout & Engelhard, 2012). There is evidence that the degree of working memory taxation correlates with the reduction of emotional intensity and vividness (Little & van Schie, 2019; Van Veen et al., 2015). Another strategy to enhance cost-effective EMDR treatment may be to intensify the treatment, which may lead to lower societal costs and improved quality of life, as this could limit the loss of societal roles and functions associated with prolonged untreated PTSD. In addition, meta-analyses have shown that intensified PTSD treatments are efficient and lead to fewer dropouts (Hoppen, Kip et al., 2023; Sciarrino et al., 2020; Wachen et al., 2019). Furthermore, it is important to keep in mind that treatment fidelity may be an important factor in the effectiveness of EMDR therapy (Lee & Cuijpers, 2012, 2013), meaning that staying on track during treatment is important for keeping costs as low as possible.

Another important factor in reducing PTSD treatment costs may be early detection of PTSD. The average age of our study population was nearly 37 years, suggesting that their childhood abuse-related PTSD either went unrecognized by the therapists, or that these patients did not dare to tell about their childhood abuse, or the PTSD was inadequately treated prior to study participation. The literature indicates that PTSD often goes unnoticed (e.g., Zammit et al., 2018), which is problematic because untreated PTSD compared to treated PTSD can lead to worse prognosis and numerous societal consequences (Usman et al., 2015). Hence, apart from optimizing the efficiency of EMDR therapy or other PTSD treatments, the most significant benefits may be achieved by recognizing PTSD diagnoses on time and providing effective treatments even during childhood. EMDR has been shown to be effective



in children (Rodenbrug et al., 2009). However, further research is required to treat children with trauma related to abuse.

In summary, although phase-based treatment does not yield better PTSD treatment outcomes or quality of life than trauma-focused treatment does, it incurs higher societal costs. Thus, from a cost perspective, phase-based treatment does not prove to be superior to trauma-focused treatment. Since trauma-focused treatment is less time consuming than phase-based treatment, phase-based treatment does not seem to be a viable alternative for the treatment of PTSD due to adverse childhood events.

### *8.3 Strengths and limitations*

#### *8.3.1 General methodological considerations*

One notable strength of the studies that are part of this dissertation lies in the design, where STAIR was used as an additional phase to trauma-focused treatment in one condition, in line with the ISTSS expert consensus treatment guidelines for Complex PTSD (Cloitre et al., 2012). This study was designed to compare the addition of STAIR to trauma-focused treatment in a purest manner with direct trauma-focused treatment, without the interference of other treatment forms. This approach also answers the call from the ISTSS to study the addition of treatment programs that directly address symptoms of Complex PTSD (ISTSS, 2018).

A possible limitation was the bi-weekly delivery of STAIR sessions in our study instead of once a week (e.g., as in Raabe et al. 's study). Biweekly sessions may have resulted in less time to practice new skills between sessions, potentially affecting the effectiveness of STAIR treatment, although Raabe et al. (2022) found no effect between conditions with one condition consisting of weekly STAIR. On the other hand, a possible strength of biweekly

sessions as used in the present study, is that intensifying treatments may lead to fewer dropouts (Hoppen, Kip et al., 2023; Sciarrino et al., 2020; Wachen et al., 2019).

Another limitation is that, after eight sessions, only emotion regulation difficulties, interpersonal problems, posttraumatic cognitions and the self-report of PTSD were assessed, thus comparing eight sessions of EMDR therapy with eight sessions of STAIR. Measuring a broader range of variables after every eight sessions to compare treatment programs might have provided valuable information. For certain variables, the maximum number of sessions would still have been beneficial, regardless of the specific treatment modality, whereas other variables would have shown a faster decline in one treatment modality than in the other.

A strength of this study is its natural setting. The participants were regular patients seeking treatment from two different mental health institutions (Dimence GGZ and GGZ Oost-Brabant), who were treated by regular therapists within the context of routine clinical care. While studies are inevitably influenced by the characteristics of patients who consent to participate, our sample mirrors the complexity of problems encountered by clinicians in routine care practice. Moreover, we did not have a lot of exclusion criteria, which also resulted in a representative treatment sample. Although suicidality was an exclusion criterion, exclusion from the study was only applied in cases of acute suicidality requiring immediate crisis intervention. Patients hoping that the treatment might aid them were included, even in the presence of suicidal ideation. Another exclusion criterion was the presence of an intellectual disability at registration at the institution. For future research, we recommend considering the inclusion of patients with intellectual disabilities to enhance generalizability and the addition of other diagnostic instruments (e.g., Adapted ADIS-C PTSD-adults; Mevisen et al., 2020). Furthermore, future studies will have to reveal whether the inclusion of patients with severe substance abuse issues is advisable or not (Lortye et al., 2021).

### *8.3.2 Considerations about publications*

While we consider it a strength that we conducted analyses based on empiric studies as well as analyses using machine learning on the dataset, there is a potential risk of exhaustively using the same dataset. This phenomenon is commonly referred to as Salami Publication, which involves deriving multiple publications from a single dataset (Abraham, 2000; Broad, 1981). However, in some cases, Salami Publications are considered possible (Smolčić, 2013). In the context of our RCT, it would have been difficult to present all results in a single manuscript (e.g., due to the word limit adhered to by journals). In addition, although some results in published articles overlap, these are presented from different perspectives, with different goals or subjected to entirely distinct analyses (e.g., Mixed Linear Models, regression analysis, and machine learning) and reported different outcome values (e.g., PTSD symptoms, dropout rate and cost-effectiveness). Finally, each subsequent publication following the main article explicitly indicated that the presented findings were analyzed based on the same RCT dataset.

### *8.4 Implications for future research*

Although our study yielded valuable results, it raises new questions and recommendations for future research. The main article of this thesis that pertains to the comparison of phase-based treatment with trauma-focused treatment (Chapter 3) raises the question of which patients might not benefit from evidence-based treatment, such as EMDR therapy. For example, among patients who were still diagnosed with PTSD post-treatment, 16.7% did not exhibit a decline in PTSD complaints from pre- to post-intervention. Investigating the commonalities among these non-responsive patients could offer valuable insights. In line with the recommendations put forth by Hoppen et al. (2022), there is a need to routinely and thoroughly assess and report the incidence of harm and deterioration, along with their underlying causes, as the literature on this subject is scarce. Researchers should carefully

monitor harm and deterioration of PTSD symptoms during treatment, and the potential causes of adverse events. If patient characteristics associated with non-response, or even symptom deterioration, can be determined special treatment programs may be developed to address these issues.

In addition, based on the findings of this thesis, it is recommended to minimize the exclusion of certain patient groups in future studies on the treatment of patients with PTSD related to childhood abuse. Even patients with intellectual disabilities and high suicidal ideation should not be excluded from trauma-focused therapies, because knowledge about the response to treatment of these patient groups is needed and evidence suggests that trauma-focused interventions do not lead to worse treatment outcomes in these patient groups (Brooks et al., 2022; Tapp et al., 2023).

In an article on predictors and moderators (Chapter 4) it was found that more severe pre-treatment PTSD symptoms predicted worse treatment outcomes. This raises the question of whether the presence of more severe PTSD symptoms requires a longer duration of trauma-focused treatment, or another form of treatment. A possible idea for future studies is to conduct two-stage research. In such study, patients who still meet a PTSD diagnosis after trauma-focused treatment (i.e., in the present study, approximately 25% of the participants) would be randomly assigned to a condition in which trauma-focused treatment would be continued or to an alternative form of treatment. The latter could consist of another evidence-based therapy or a relatively new treatment for PTSD (i.e., Interpersonal Therapy [IPT], Markowitz et al., 2015).

Furthermore, our study on predictors and moderators (Chapter 4) raises questions regarding the influence of dissociative experiences on PTSD treatment outcomes in patients with PTSD related to childhood abuse. We recommend not only studying the influence of pre-

treatment dissociative symptoms (trait dissociation), but also the influence of dissociative symptoms during treatment sessions (state dissociation).

The fact that our PAI analyses resulted in non-significant results (Chapter 5) while finding moderators between PTSD treatment outcomes and treatment conditions requires studies that generate extensive datasets (Luedtke et al., 2019). This need is emphasized by the differences found between our study and that of Hoeboer et al. (2021) concerning the PAI. These differences call for a comparison of EMDR therapy with Prolonged Exposure, to determine whether some patient characteristics predict better treatment outcomes in EMDR therapy than in PE or the other way around.

The findings of our dropout article (Chapter 6) require replication studies on this subject and the investigation of a combination of factors related to dropout and their potential underlying mechanisms. In addition to studying patient characteristics that may predict dropout, understanding the treatment mechanisms that lead to symptom change is crucial for comprehending the treatment mechanisms responsible for PTSD treatment dropout. One way to understand the mechanisms of therapeutic change is to identify variables that may precede and predict symptom changes (Kazdin et al., 2007; Kraemer et al., 2002). To establish a mediator of PTSD treatment, study designs must be longitudinal and measure the potential mediator frequently enough to show that treatment influences a change in the mediator, followed by change in the mediator influencing change in the outcome (Kazdin, 2007; Kraemer et al., 2002). Another important future research topic may be the exploration and identification of factors other than patient characteristics that potentially influence treatment dropout, such as the way treatments are delivered (e.g. intensity) and the number of sessions provided.

Concerning costs in relation to effectiveness (Chapter 7), more economic analyses of PTSD treatments in patients with PTSD related to childhood abuse are needed. Economic

analyses are scarce and not always complete (i.e., they did not always include cost-utility and cost-effectiveness evaluations; Von de Warth et al., 2020). These economic analyses may target cost-effectiveness in the comparison of different treatment forms or the cost-effectiveness of an intensified PTSD treatment with regular PTSD treatments.

### *8.5 To prepare or not? Future directions for the treatment of patients with childhood abuse related PTSD*

The findings of this thesis suggest that patients with PTSD related to childhood abuse, should be, offered direct trauma-focused treatment without stabilization. This is because both phase-based treatment and trauma-focused treatment lead to equal results, whereas trauma-focused treatment requires less time. Second, the decision to provide trauma-focused treatment should not depend on the presence of Complex PTSD symptoms (e.g. emotion regulation difficulties, interpersonal problems and problems with self-esteem), as Complex PTSD symptoms did not appear to moderate PTSD treatment outcomes and treatment conditions. In addition, a PAI analysis showed patients assigned to their PAI indicated treatment did not show significant better PTSD treatment outcomes than patients assigned to their non-PAI indicated treatment form. Third, the immediate use of trauma-focused treatments in patients with PTSD related to childhood abuse is likely to contribute to reducing societal costs associated with PTSD, because the societal costs of phase-based treatment turned out to be higher.

The results of the present study therefore raise the question of the utility of distinguishing between Complex PTSD and “regular” PTSD in clinical practice, as both diagnoses necessitate the same treatment approach thus far. These results agree with a previous study indicating lack of empirical evidence for the distinction between PTSD and Complex PTSD (Achterhof et al., 2019). The ISTSS guidelines position paper on Complex PTSD (2018) suggests to apply “personalized medicine”, interventions or series of interventions tailored to individual patients based on symptoms that are clinically significant (e.g., are severe or

associated with functional impairment). Clearly, it is necessary to establish that these symptoms are significant predictors of treatment outcome first. The results of the present and other recent studies indicate that patient characteristics that predict PTSD treatment outcomes have not yet been identified, making it unclear which symptoms require extra attention during treatment or call for different treatment interventions. The same holds true for moderators of PTSD treatment, making it unclear who should receive which treatment. Until predictive symptoms or moderators are identified, regardless of the complexity of PTSD symptoms, trauma-focused treatment should be the standard approach, as described in several guidelines for PTSD (e.g., Department of Veterans Affairs and the Department of Defense, 2023; ISTSS, 2018). According to the results of our study and those of Oprel et al. (2021) and Raabe et al. (2022), the ISTSS guidelines on Complex PTSD in 2018 should be updated by stating that trauma-focused treatments are the preferred treatment forms in patients with PTSD related to childhood abuse, as these treatments are effective, efficient and safe.

To underscore the safety of trauma-focused treatments in this patient group, it is worth noting that, contrary to the standard EMDR treatment guidelines proposed by Shapiro (2018), in our study there were no emotion regulation techniques in the EMDR-only condition such as the safe place or Resource Development and Installation (RDI) procedures. Instead, we directly targeted the traumatic memories. The main reason for deviating from this standard procedure is to ensure that we do not apply any form of stabilization in trauma-focused conditions. Despite the absence of emotion regulation techniques, EMDR therapy did not result in higher dropout rates or adverse events compared with the phase-based condition. This raises the question of whether a safe place and RDI are necessary elements within standard EMDR therapy. This subject requires further research.

In our study, we were not able to identify convincing patient characteristics that could potentially predict treatment outcomes or moderate between treatment outcomes and

treatment conditions. Therefore, in clinical practice it might not only be valuable to look at patient characteristics if trauma-focused treatment does not yield positive results in a specific case, it may also be relevant to investigate whether the therapist delivered the treatment correctly, rather than solely focusing on potential patient characteristics that might complicate trauma treatment. The importance of treatment fidelity in the effectiveness of EMDR therapy is well established (Lee & Cuijpers, 2012, 2013). If it is ineffective, supervision and peer consultation might help ameliorate treatment execution, in addition to monitoring patient characteristics.

### *8.6 Conclusions*

The results of our research project suggest that: 1) direct trauma-focused treatment is a safe and effective treatment even for patients with PTSD related to childhood abuse. Patient should thus not be denied trauma-focused treatment, 2) phase-based treatment does not lead to better treatment results than direct trauma-focused treatment and is less efficient.

Accordingly, trauma-focused treatment is probably the best treatment option for patients with PTSD related to childhood abuse, 3) phase-based treatment does not lead to less dropout or less adverse events compared to trauma-focused treatment, 4) as so far, there are no clear predictors or moderators for treatment outcome, it seems logical to use the most efficient treatment form, which in this case is direct trauma-focused treatment on a standard basis in this patient-group, 5) phase-based approach is not cost-effective compared to a trauma-focused treatment.



## References

- Abraham, P. (2000). Duplicate and salami publications. *Journal of Postgraduate Medicine*, *46*, 67-69.
- Achterhof, R., Huntjens, R. J. C., Meewisse, M. L., & Kiers, H. A. L. (2019). Assessing the application of latent class and latent profile analysis for evaluating the construct validity of complex posttraumatic stress disorder: cautions and limitations. *European Journal of Psychotraumatology*, *10*(1), 1698223. <https://doi.org/10.1080/20008198.2019.1698223>
- American Psychiatric Association (2017). *Clinical practice guideline for the treatment of PTSD*. Retrieved from <https://www.apa.org/ptsd-guideline/ptsd.pdf>
- Baddeley, A., (1998). Working memory. *Comptes rendus de l'académie des sciences - series III - sciences de la vie*, *321*(2-3). [https://doi.org/10.1016/S0764-4469\(97\)89817-4](https://doi.org/10.1016/S0764-4469(97)89817-4)
- Broad, W. J. (1981). The publication game: getting more for less. *Science*, *211*, 1137-1139. <http://dx.doi.org/10.1126/science.7008199>
- Brooks, E., Spokas, M. & Goldschmidt, D. (2021), Exclusion of Suicidal Participants From Randomized Controlled Trials for Posttraumatic Stress Disorder: A Meta-Analysis. *Journal of Traumatic Stress*, *34*, 1209-1218. <https://doi.org/10.1002/jts.22610>
- Cloitre, M., Courtois, C. A., Ford, J. D., Green, B. L., Alexander, P., Briere, J., Herman, J. L., Lanius, R., Stolbach, B. C., Spinazolla, J., Van der Kolk, B. A., & Van der Hart, O. (2012). *The ISTSS expert consensus treatment guidelines for complex PTSD in adults*. <https://terrorvictimresponse.ca/wp-content/uploads/ISTSS-Expert-Concesnsus-Guidelines-for-Complex-PTSD-Updated-060315.pdf>
- Cloitre, M., Koenen, K. C., Cohen, L. R., & Han, H. (2002). Skills training in affective and

- interpersonal regulation followed by exposure: A phase-based treatment for PTSD related to childhood abuse. *Journal of Consulting and Clinical Psychology*, 70(5), 1067–1074. <https://doi.org/10.1037//0022-006x.70.5.1067>
- Cloitre, M., Petkova, E., Wang, J., & Lu Lassell, F. (2012). An examination of the influence of a sequential treatment on the course and impact of dissociation among women with PTSD related to childhood abuse. *Depression and Anxiety*, 29(8), 709–717. <https://doi.org/10.1002/da.21920>
- Cloitre, M., Stovall-McClough, K. C., Noonan, K., Zorbas, P., Cherry, S., Jackson, C. L., Gan, W., & Petkova, E. (2010). Treatment for PTSD related to childhood abuse: a randomized controlled trial. *The American Journal of Psychiatry*, 167(8), 915–924. <https://doi.org/10.1176/appi.ajp.2010.09081247>
- Darby, R. J., Taylor, E. P., & Segovia Cadavid, M. (2023). Phase-based psychological interventions for complex post-traumatic stress disorder: A systematic review. *Journal of Affective Disorders Reports*, 14, 100628, 1-11. <https://doi.org/10.1016/j.jadr.2023.100628>
- Department of Veterans Affairs and the Department of Defense (2023). *Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder*. Retrieved from: <https://www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPG.pdf>
- DeRubeis, R. J., Cohen, Z. D., Forand, N. R., Fournier, J. C., Gelfand, L. A., & Lorenzo-Luaces, L. (2014) The Personalized Advantage Index: translating research on prediction into individualized treatment recommendations. A demonstration. *PLoS one*, 9(1), e83875. <https://doi.org/10.1371/journal.pone.0083875>

- Friedman, J., Hastie, T., & Tibshirani, R. (2010). Regularization paths for generalized linear models via coordinate descent. *Journal of Statistical Software*, *33*(1), 1. <https://doi.org/10.18637/jss.v033.i01>
- Hoeboer, C. M., De Kleine, R. A., Molendijk, M. L., Schoorl, M., Oprel, D. A. C., Mouthaan, Van der Does, W., & Van Minnen, A. (2020). Impact of dissociation on the effectiveness of psychotherapy for post-traumatic stress disorder: meta-analysis. *British Journal of Psychiatry Open*, *6*(3), 1–8. <https://doi.org/10.1192/bjo.2020.30>
- Hoeboer, C. M., De Kleine, R. A., Oprel, D. A. C., Schoorl, M., Van der Does, W., & Van Minnen, A. (2021). Does complex PTSD predict or moderate treatment outcomes of three variants of exposure therapy? *Journal of Anxiety Disorders*, *80*, 102388. <https://doi.org/10.1016/j.janxdis.2021.102388>
- Hoeboer, C. M., Oprel, D. A. C., Kleine, R. A. De, Schwartz, B., Deisenhofer, A., Schoorl, M., Does, W. A. J. Van Der, & Minnen, A. Van. (2021). Personalization of treatment for patients with childhood-abuse-related Posttraumatic Stress Disorder. *Journal of Clinical Medicine*, *10*(19), 1–15. <https://doi.org/10.3390%2Fjcm10194522>
- Hoppen, T., Lindemann, A., & Morina, N. (2022). Safety of psychological interventions for adult post-traumatic stress disorder: Meta-analysis on the incidence and relative risk of deterioration, adverse events, and serious adverse events. *The British Journal of Psychiatry*, *221*(5), 658–667. <https://doi.org/10.1192/bjp.2022.111>
- Hoppen, T. H., Jehn, M., Holling, H., Mutz, J., Kip, A., & Morina, N. (2023). The efficacy and acceptability of psychological interventions for adult PTSD: A network and pairwise meta-analysis of randomized controlled trials. *Journal of Consulting and Clinical Psychology*, *91*(8), 445–461. <https://doi.org/10.1037/ccp0000809>
- Hoppen, T. H., Kip, A., & Morina, N. (2023). Are psychological interventions for adult

- PTSD more efficacious and acceptable when treatment is delivered in higher frequency?  
A meta-analysis of randomized controlled trials. *Journal of Anxiety Disorders*, 95, 102684. <https://doi.org/10.1016/j.janxdis.2023.102684>
- Hyland, P., Shevlin, M., & Brewin, C. R. (2023). The memory and identity theory of ICD-11 complex posttraumatic stress disorder. *Psychological Review*, 130(4), 1044–1065. <https://doi.org/10.1037/rev0000418>
- International Society for Traumatic Stress (2018). ISTSS Guidelines Position Paper on Complex PTSD in Adults. [http://www.istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS\\_CPTSD-Position-Paper-\(Adults\)\\_FNL.pdf.aspx](http://www.istss.org/getattachment/Treating-Trauma/New-ISTSS-Prevention-and-Treatment-Guidelines/ISTSS_CPTSD-Position-Paper-(Adults)_FNL.pdf.aspx)
- Karatzias, T., Murphy, P., Cloitre, M., Bisson, J., Roberts, N., Shevlin, M., Hyland, P., Maercker, A., Ben-Ezra, M., Coventry, P., Mason-Roberts, S., Bradley, A., & Hutton, P. (2019). Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. *Psychological Medicine*, 49(11), 1761–1775. <https://doi.org/10.1017/S0033291719000436>
- Kazdin, A. E. (2007). Mediators and mechanisms of change in Psychotherapy Research. *Annual Review of Clinical Psychology*, 3, 1–27. <https://doi.org/10.1146/annurev.clinpsy.3.022806.091432>
- Kleindienst, N., Priebe, K., Görg, N., Dyer, A., Steil, R., Lyssenko, L., Winter, D., Schmahl, C., & Bohus, M. (2016). State dissociation moderates response to dialectical Behavior Therapy for posttraumatic stress disorder in women with and without borderline personality disorder. *European Journal of Psychotraumatology*, 6(7), 30375. <https://doi.org/10.3402%2Fejpt.v7.30375>
- Kraemer, H. C., Wilson, G. T., Fairburn, C. G., & Agras, W. S. (2002). Mediators and

- moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry*, 59(10), 877–883. <https://doi.org/10.1001/archpsyc.59.10.877>
- Kratzer, L., Heinz, P., Schennach, R., Schiepek, G. K., Padberg, F., & Jobst, A. (2018). Stationäre Therapie der komplexen PTBS in Folge körperlicher oder sexualisierter Gewalt in der Kindheit: Wirksamkeit und Prädiktoren des Behandlungsverlaufs [Inpatient Treatment of Complex PTSD Following Childhood Abuse: Effectiveness and Predictors of Treatment Outcome]. *Psychotherapie, Psychosomatik, Medizinische Psychologie*, 69(3-04), 114–122. <https://doi.org/10.1055/a-0591-3962>
- Kullberg, M. J., Schoorl, M., Oprel, D. A. C., Hoeboer, C. M., Smit, F., van der Does, W., de Kleine, R. A., van Minnen, A., & van den Hout, W. (2023). Exposure-based treatments for childhood abuse-related post-traumatic stress disorder in adults: a health-economic evaluation. *European Journal of Psychotraumatology*, 14(1), 2171752. <https://doi.org/10.1080/20008066.2023.2171752>
- Lampe, A., Hofmann, P., Gast, U., Reddemann, L., & Schübler, G. (2014). Long-term course in female survivors of childhood abuse after psychodynamically oriented, trauma-specific inpatient treatment: a naturalistic two-year follow-up. *Zeitschrift für Psychosomatische Medizin und Psychotherapie*, 60(3), 267–282. <https://doi.org/10.13109/zptm.2014.60.3.267>
- Lee, C. W., & Cuijpers, P. (2012, 2013). A meta-analysis of the contribution of eye movements in processing emotional memories. *Journal of Behavior Therapy and Experimental Psychiatry*, 44(2), 231-239. <https://doi.org/10.1016/j.jbtep.2012.11.001>
- Leiva-Bianchi, M., Nvo-Fernandez, M., Villacura-Herrera, C., Miño-Reyes, V., Parra Varela, N. (2023). What are the predictive variables that increase the risk of developing a complex trauma? A meta-analysis. *Journal of Affective Disorders*, 343, 153-165. <https://doi.org/10.1016/j.jad.2023.10.002>

- Lewis, C., Roberts, N. P., Gibson, S., & Bisson, J. I. (2020). Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: Systematic review and meta-analysis. *European Journal of Psychotraumatology*, *11*(1), 1709709. <https://doi.org/10.1080%2F20008198.2019.1709709>
- Little, M. & van Schie, K. (2019). No evidence for the inverted U-Curve: More demanding dual tasks cause stronger aversive memory degradation. *Journal of Behavior Therapy and Experimental Psychiatry* *65*, 101484. <https://doi.org/10.1016/j.jbtep.2019.101484>
- Lorbeer, N., Knaevelsrud, C., & Niemeyer, H. (2023). STAIR and STAIR/NT as a Treatment for Posttraumatic Stress: A Systematic review. *Verhaltenstherapie*, 1-11 <https://doi.org/10.1159/000526592>
- Lortye, S.A., Will, J.P., Marquenie, L.A., Goudriaan, A. E., Arntz, A., & De Waal (2021). Treating posttraumatic stress disorder in substance use disorder patients with co-occurring posttraumatic stress disorder: study protocol for a randomized controlled trial to compare the effectiveness of different types and timings of treatment. *BMC Psychiatry*, *21*(1), 442. <https://doi.org/10.1186/s12888-021-03366-0>
- Luedtke, A., Sadikova, E., & Kessler, R. C. (2019). Sample Size Requirements for Multivariate Models to Predict Between-Patient Differences in Best Treatments of Major Depressive Disorder. *Clinical Psychological Science*, *7*(3), 445–461. <https://doi.org/10.1177/2167702618815466>
- Markowitz, J. C., Petkova, E., Neria, Y., Van Meter, P. E., Zhao, Y., Hembree, E., Lovell, K., Biyanova, T., & Marshall, R. D. (2015). Is Exposure Necessary? A Randomized Clinical Trial of Interpersonal Psychotherapy for PTSD. *The American Journal of Psychiatry*, *172*(5), 430–440. <https://doi.org/10.1176/appi.ajp.2014.14070908>
- Matthijssen, J. M. A., Brouwers, T., Van Roozendaal, C., Vuister, T., & De Jongh, A. (2021). The effect of EMDR versus EMDR 2.0 on emotionality and vividness of aversive

- memories in a non-clinical sample. *European Journal of Psychotraumatology*, *12*(1), 1956793. <https://doi.org/10.1080/20008198.2021.1956793>
- Mavranzouli, I., Megnin-Viggars, O., Grey, N., Bhutani, G., Leach, J., Daly, C., Dias, S., Welton, N. J., Katona, C., El-Leithy, S., Greenberg, N., Stockton, S., & Pilling, S. (2020). Cost-effectiveness of psychological treatments for post-traumatic stress disorder in adults. *PLoS One*, *15*(4), e0232245. <https://doi.org/10.1371/journal.pone.0232245>
- Mevisen, L., Didden, R., De Jongh, A., & Korzilius, H. (2020) Assessing Posttraumatic Stress Disorder in Adults with Mild Intellectual Disabilities or Borderline Intellectual Functioning. *Journal of Mental Health Research in Intellectual Disabilities*, *13*(2), 110-126. <https://doi.org/10.1080/19315864.2020.1753267>
- Neuner, F. (2008). Stabilisierung vor konfrontation in der traumatherapie—Grundregel oder mythos? [Stabilization before confrontation in trauma treatment—Elementary rule or myth?]. *Verhaltenstherapie*, *18*(2), 109–118. <https://doi.org/10.1159/000134006>
- Oprel, D. A. C., Hoeboer, C. M., Schoorl, M., de Kleine, R. A., Cloitre, M., Wigard, I. G., van Minnen, A., & van der Does, W. (2021). Effect of Prolonged Exposure, intensified Prolonged Exposure and STAIR+Prolonged Exposure in patients with PTSD related to childhood abuse: a randomized controlled trial. *European Journal of Psychotraumatology*, *12*(1), 1851511. <https://doi.org/10.1080/20008198.2020.1851511>
- Raabe, S., Ehring, T., Marquenie, L., Arntz, A., & Kindt, M. (2022). Imagery Rescripting versus STAIR plus Imagery Rescripting for PTSD related to Childhood Abuse: A randomized controlled trial. *Journal of Behavior Therapy and Experimental Psychiatry*, *77*. <https://doi.org/10.1016/j.jbtep.2022.101769>
- Rodenburg, R., Benjamin, A., De Roos, C., Meijer, A. M., & Stams, G. J., (2009). Efficacy of

- EMDR in children: A meta-analysis. *Clinical Psychology Review*, 29(7), 599-606.  
<https://doi.org/10.1016/j.cpr.2009.06.008>.
- Sciarrino, N. A., Warnecke, A. J., & Teng, E. J. (2020). A Systematic Review of Intensive Empirically Supported Treatments for Posttraumatic Stress Disorder. *Journal of Traumatic Stress*, 1–12. <https://doi.org/10.1002/jts.22556>
- Sele, P., Hoffart, A., Cloitre, M., Hembree, E., & Øktedalen, T. (2023). Comparing phase-based treatment, prolonged exposure, and skills-training for Complex Posttraumatic Stress Disorder: A randomized controlled trial. *Journal of Anxiety Disorders*, 100, 102786. Advance online publication. <https://doi.org/10.1016/j.janxdis.2023.102786>
- Shapiro F. (2018). *Eye movement desensitization and reprocessing (EMDR): Basic principles, protocols and procedures*. 3rd ed. Guilford Press.
- Slotema, C. W., Wilhelmus, B., Arends, L. R., & Franken, I. H. A. (2020) Psychotherapy for posttraumatic stress disorder in patients with borderline personality disorder: a systematic review and meta-analysis of its efficacy and safety. *European Journal of Psychotraumatology*, 11(1). <https://doi.org/10.1080%2F20008198.2020.1796188>
- Supak Smolčić V. (2013). Salami publication: definitions and examples. *Biochemia medica*, 23(3), 237-41. <https://doi.org/10.11613/bm.2013.030>
- Tapp, K., Vereenoohe, L., Hewitt, O., Scripps, E., Gray, K. M., & Langdon, P. E. (2023). Psychological therapies for people with intellectual disabilities: An updated systematic review and meta-analysis. *Comprehensive psychiatry*, 122. <https://doi.org/10.1016/j.comppsy.2023.152372>.
- Usman, M., Rehman, A., Bakhtawar N., & Bhatti, A. B. H. (2015). Prognosis of PTSD in treated vs. non-treated groups. *Journal of Pakistan Psychiatric Society*, 12(1).
- Van den Hout, M. A. & Engelhard, I. M. (2012). How does EMDR work? *Journal of Experimental Psychopathology*, 3(5), 724-738. <https://doi.org/10.5127/jep.028212>



- Van Veen, S.C., Van Schie, K., Wijngaards-De Meij, L.D.N.V., Littel, M., Engelhard, I.M., & Van den Hout, M.A. (2015). Speed matters: Relationship between speed of eye movements and modification of aversive autobiographical memories. *Frontiers in psychiatry*, 6, 2-9. <https://doi.org/10.3389/fpsyt.2015.00045>
- Varker, T., Jones, K. A., Arjmand, H. A., Hinton, M., Hiles, S. A., Freijah, I., Forbes, D., Kartal, D., Phelps, A., Bryant, R. A., MacFarlane, A., Hopwood, M., & O'Donnell, M. (2021). Dropout from guideline-recommended psychological treatments for posttraumatic stress disorder: A systematic review and meta-analysis. *Journal of Affective Disorders Reports*, 4, 100093-100093. <https://www.doi.org/10.1016/j.jadr.2021.100093>
- Von der Warth, R., Dams, J., Grochtdreis, T., & König H. H. (2020). Economic evaluations and cost analyses in posttraumatic stress disorder: a systematic review. *European Journal of Psychotraumatology*, 11(1). <https://doi.org/10.1080/20008198.2020.1753940>
- Wachen, J. S., Dondanville, K. A., Evans, W. R., Morris, K., & Cole, A. (2019). Adjusting the Timeframe of Evidence-Based Therapies for PTSD-Massed Treatments. *Current Treatment Options in Psychiatry*, 6(2), 107–118. <https://doi.org/10.1007/s40501-019-00169-9>
- Yunitri, N., Chu, H., Kang, X. L., Wiratama, B. S., Lee, T. Y., Chang, L. F., Liu, D., Kustanti, C. Y., Chiang, K. J., Chen, R., Tseng, P., & Chou, K. R. (2023). Comparative effectiveness of psychotherapies in adults with posttraumatic stress disorder: a network meta-analysis of randomised controlled trials. *Psychological Medicine*, 1–13. <https://doi.org/10.1017/S0033291722003737>
- Zammit, S., Lewis, C., Dawson, S., Colley, H., McCann, H., Piekarski, A., Rockliff, H., &

Bisson, J. (2018). Undetected post-traumatic stress disorder in secondary-care mental health services: Systematic review. *The British Journal of Psychiatry: The journal of mental science*, 212(1), 11–18. <https://doi.org/10.1192/bjp.2017.8>



## Samenvatting

**Nederlandse samenvatting en algemene conclusies**

Het doel van deze studie was om te onderzoeken of volwassen patiënten met een PTSS gerelateerd aan kindermishandeling meer baat kunnen hebben bij een gefaseerde behandeling (een traumagerichte behandeling voorafgegaan door een voorbereidingsfase) dan een directe, traumagerichte behandeling.

**Hoofdstuk 1** is een inleiding op het onderzoeksonderwerp. Eén van de uitgangspunten voor dit promotieonderzoek zijn de in 2012 gepubliceerde expert consensus richtlijnen voor de behandeling van Complexe PTSS door de International Society for Traumatic Stress Studies (ISTSS, 2012). De ISTSS richtlijnen stelden dat seksueel misbruik en/of mishandeling typen trauma zijn die het risico vergroten op het ontwikkelen van Complexe PTSS. Hoewel destijds Complexe PTSS nog geen vaststaande classificatie was, waren de richtlijnen die werden voorgeschreven om patiënten met een Complexe PTSS en/of een voorgeschiedenis van mishandeling en/of misbruik in de kindertijd een andere behandeling aan te bieden dan patiënten met een reguliere PTSS. Vanwege de bijkomende symptomen die deze patiënten kunnen tonen, hadden ze volgens de richtlijnen een gefaseerde behandeling nodig in plaats van een directe, traumagerichte behandeling. Een gefaseerde behandeling bestaat uit een voorbereidingsfase voorafgaand aan de eigenlijke traumabehandeling. In die voorbereidingsfase wordt de patiënt vaardigheden geleerd voor het omgaan met emotieregulatieproblemen en interpersoonlijke problemen en om de traumagerichte behandeling beter aan te kunnen. Hoewel de adviezen in de richtlijnen gebaseerd zijn op verschillende onderzoeken, was tot voor kort het bewijs voor de toegevoegde waarde van een gefaseerde behandeling boven een direct traumagerichte behandeling nog erg mager. Het hoofddoel van deze studie was om een directe traumagerichte behandeling te vergelijken met een gefaseerde behandeling bij patiënten met een PTSS gerelateerd aan herhaalde

mishandeling en/of seksueel misbruik in de kindertijd en de volgende vragen te beantwoorden:

- Heeft een gefaseerde behandeling meerwaarde boven een directe traumagerichte behandeling bij patiënten met een PTSS gerelateerd aan herhaalde mishandeling en/of misbruik in de kindertijd?
- Zijn er patiëntkenmerken die slechtere behandeluitkomsten voor PTSS voorspellen of die modereren tussen PTSS behandeluitkomsten en de behandelconditie bij patiënten met een PTSS gerelateerd aan mishandeling en/of misbruik in de kindertijd?
- Zijn er (combinaties van) patiënt-kenmerken die de drop-out voor een PTSS behandeling kunnen voorspellen bij patiënten met een PTSS gerelateerd aan mishandeling en/of misbruik in de kindertijd?
- Is een gefaseerde behandeling kosteneffectief in vergelijking met een directe traumagerichte behandeling?

**Hoofdstuk 2** is het onderzoeksprotocol voor dit onderzoeksproject. Het beschrijft de achtergrond van het onderzoek en benadrukt de relevantie. We concluderen daarin dat het bewijs voor de stellingname van de ISTSS expert consensus richtlijnen om patiënten met een (complexe) PTSS en een voorgeschiedenis van mishandeling en/of misbruik te behandelen met een gefaseerde behandeling, zeer zwak is. Voorafgaande aan dit promotie-onderzoek was er nog maar één studie verschenen waarbij de resultaten van een gefaseerde behandeling met die van een traumagerichte behandeling waren vergeleken. In deze studie werd de werkzaamheid van een gefaseerde behandeling (STAIR/Exposure) versus een ondersteunende counseling, gevolgd door Exposure (support/Exposure), versus STAIR, gevolgd door ondersteunende counseling (STAIR/support), geëvalueerd bij vrouwen met een PTSS gerelateerd aan misbruik en/of mishandeling in de kindertijd. STAIR is de enige bewezen

effectieve voorbereidingsfase in een gefaseerde behandeling waarbij patiënten vaardigheden voor emotieregulatie en interpersoonlijke problemen krijgen aangeleerd en ze worden voorbereid op een traumagerichte behandeling. Er werden geen significante verschillen gevonden tussen de behandelingen direct na de behandeling. Alleen bij de follow-up meting bleek de STAIR/Exposure conditie het beter te doen dan de support/exposure conditie wat betreft de ernst van de PTSS symptomen, de interpersoonlijke problemen en de emotieregulatie. Er ontbrak echter een behandelconditie waarbij patiënten direct werden blootgesteld aan de traumatische herinneringen, waardoor het onmogelijk is om ferme conclusies te trekken over de voordelen van gefaseerde behandeling boven een directe traumagerichte behandeling bij patiënten met een PTSS gerelateerd aan misbruik en/of mishandeling in de kindertijd.

**Hoofdstuk 3** beantwoordt de kernvraag van dit onderzoeksproject, namelijk of een gefaseerde behandeling effectiever is dan een directe traumagerichte behandeling voor patiënten met een PTSS gerelateerd aan seksueel misbruik en/of mishandeling in de kindertijd. Voor dit onderzoek werden patiënten geworven uit twee GGZ-instellingen. De inclusiecriteria waren volwassenen met een PTSS diagnose in verband met herhaald seksueel misbruik en/of mishandeling in de kindertijd door een autoriteitspersoon. De exclusiecriteria waren a) onvoldoende beheersing van de Nederlandse taal, b) een hoog risico op suïcidaliteit, c) behandeling voor PTSS in het afgelopen jaar met minimaal acht zittingen van een goed geëvalueerde behandeling, d) alcohol- of drugsverslaving volgens de DSM-IV-TR, e) slachtoffer zijn van aanhoudend seksueel misbruik en/of mishandeling en, f) een verstandelijke beperking. Zodra patiënten in aanmerking kwamen voor deelname aan dit onderzoek, werden ze ad random toegewezen aan één van de twee behandelcondities.

In de traumagerichte behandelconditie kregen patiënten alleen 16 sessies EMDR therapie als directe traumabehandeling. In de gefaseerde behandelcondities werden 16 sessies EMDR therapie voorafgegaan aan acht sessies van Skills Training in Affective and Interpersonal Regulation (STAIR). Verschillende symptomen en diagnoses werden gemeten en vastgesteld, voor en na de behandeling, en drie en zes maanden na de behandeling. Dit gold voor PTSS (diagnose en ernst), complexe PTSS (diagnose en ernst), dissociatieve symptomen en algemene psychopathologie. Andere symptomen werden gemeten voor de behandeling, na elke acht sessies en na de behandeling. Dat wil zeggen in de EMDR-therapie conditie na acht EMDR sessies en 16 EMDR sessies (na de behandeling) en in de STAIR-EMDR conditie na acht sessies STAIR, na acht sessies EMDR en na zestien sessies EMDR (na behandeling). Dit gold voor zelfrapportage van PTSS symptomen, emotieregulatieproblemen, interpersoonlijke problemen en posttraumatische cognities.

Zowel de gefaseerde behandeling als de directe traumagerichte behandeling bleken effectief te zijn ten aanzien van alle symptomen (PTSS, Complexe PTSS, algemene psychopathologie, dissociatieve symptomen), met een significante afname van voor de behandeling tot na de behandeling in beide condities. Vanaf de voormeting tot de nameting werden geen significante verschillen in symptoomafname waargenomen tussen de twee behandelcondities, hoewel patiënten acht sessies meer hadden gekregen in de STAIR-EMDR conditie dan in de EMDR conditie. De symptomen namen tijdens de follow-up in geen van beide condities significant af. Voor de variabelen die om de acht sessies gemeten werden, werd een significant interactie-effect tussen behandelconditie en tijd gevonden voor interpersoonlijke problemen, posttraumatische cognities en de PTSS zelfrapportage. Deze variabelen vertoonden een significant langzamere afname van symptomen tijdens de eerste acht sessies in de STAIR-EMDR conditie dan in de EMDR conditie. Dit geeft aan dat de toevoeging van STAIR aan EMDR de afname van symptomen kan vertragen. Het aantal



dropouts (STAIR-EMDR conditie 22.8 %, en EMDR conditie 17.2%) en *early completers* (STAIR-EMDR conditie 50.9%, en EMDR conditie 45.3%) verschilde niet significant tussen de twee behandelcondities. Deze uitkomsten laten zien dat een directe traumagerichte behandeling veilig is voor de patiënten met een PTSS gerelateerd aan misbruik en/of mishandeling in de kindertijd en dat een voorbereidingsfase bij de behandeling van deze patiënten de afname van sommige symptomen kan vertragen vergeleken met directe traumagerichte behandeling.

**Hoofdstuk 4** beantwoordt de vraag of bepaalde variabelen op de voormeting een slechtere PTSS behandeluitkomst voorspellen of dat ze modereren tussen PTSS behandeluitkomsten en de behandelconditie. In 2018 pleitte de ISTSS voor een meer gepersonaliseerde behandeling van patiënten met een (complexe) PTSS gerelateerd aan mishandeling en/of misbruik in de kindertijd. Voor het personaliseren van een behandeling is het noodzakelijk om te verduidelijken welke symptomen behandeluitkomsten voorspellen of welke symptomen modereren tussen PTSS behandeluitkomsten en behandelconditie. Als potentiële predictoren bestudeerden we de dissociatieve symptomen en de aanwezigheid van een borderline persoonlijkheidsstoornis met zelfbeschadiging of suïcidaliteit. Als potentiële moderatoren bestudeerden we de afzonderlijke complexe PTSS symptomenclusters: interpersoonlijke problemen, emotieregulatie problemen en problemen in het zelfbeeld. De analyses werden gecorrigeerd voor de ernst van de PTSS bij aanvang van de behandeling, waarvan de ernst een voorspeller bleek voor slechtere behandeluitkomsten. Er werd vastgesteld dat, gecorrigeerd voor de ernst van de PTSS voor de behandeling, de ernst van de dissociatieve symptomen een significante voorspeller was van minder goede PTSS behandelresultaten, maar alleen direct na de behandeling en niet bij follow-up en dit effect was niet meer zichtbaar na correctie voor vals positieve uitkomsten. Complexe PTSS symptomen modereerden niet tussen de

behandelconditie en de PTSS behandeluitkomsten. Bovenstaande resultaten suggereren dat patiënten met complexe PTSS symptomen niet méér baat hebben bij een gefaseerde behandeling dan bij een directe traumagerichte behandeling. De invloed van dissociatieve verschijnselen behoeft verder onderzoek. Daarnaast voorspellen ernstigere PTSS symptomen bij aanvang van de behandeling een slechtere behandeluitkomst. De dissociatieve symptomen lijken echter geen reden om PTSS behandeling uit te stellen aangezien ze na zes maanden follow-up geen slechtere PTSS behandelresultaten voorspellen.

**Hoofdstuk 5** beschrijft het gebruik van *machine learning* om te onderzoeken voor wie welke behandeling het beste werkt. Met de gegevens van onze studie hebben we onderzoek gedaan door een *Personalized Advantage Index* (PAI) te ontwikkelen en het potentiële voordeel berekend dat behaald zou kunnen worden door de meest geschikte behandeling aan te bieden volgens deze index aan patiënten met een PTSS gerelateerd aan misbruik en/of mishandeling in de kindertijd. De moderators die geïdentificeerd werden, waren de aanwezigheid van een borderline persoonlijkheidsstoornis, suïcidale gedachten, burgerlijke staat, de subschalen zelfopoffering, wraakzucht/egocentrisme en koud/afstandelijk van de IIP, de BSI subschaal vijandigheid en de score op de DES. We vonden geen significante verschillen voor de ernstscore van PTSS na de behandeling tussen individuen die de PAI-geïndiceerde behandeling kregen en de individuen die de behandeling kregen die niet door de PAI geïndiceerd werd. Deze resultaten ondersteunen niet de idee dat sommige patiënten meer baat zouden kunnen hebben bij een gefaseerde behandeling of een traumagerichte behandeling. Om deze resultaten te bevestigen zijn replicatiestudies met grotere steekproeven en met externe validatie nodig.

In **Hoofdstuk 6** had als doel om door middel van *machine learning* (een combinatie van) patiëntkenmerken te vinden die de drop-out uit PTSS-behandelingen kunnen voorspellen. In de huidige studie was het percentage drop-outs 19% en hadden alle drop-out patiënten, die de nameting nog ingevuld hadden, nog steeds een PTSS diagnose. De mediaan van het aantal sessies voor drop-out was vier. Om patiëntkenmerken te identificeren die drop-out voorspellen, pasten we *machine learning* technieken toe. We ontwikkelden een model met behulp van *Elastic Net Regularization* (ENR), dat 81,6% van de drop-out correct voorspelde. Het bleek dat de combinatie van het behoren tot het mannelijk geslacht, een lagere opleiding hebben, suïcidale gedachten hebben, meer problemen hebben met emotieregulatie, meer algemene psychopathologie en het niet gebruiken van benzodiazepines bij screening een belangrijke voorspeller is voor drop-out bij PTSS behandelingen. Van deze variabelen waren suïcidaliteit, opleiding en het gebruik van benzodiazepinen bij screening de belangrijkste variabelen in het model. Een uitdagende taak voor toekomstig onderzoek is om te onderzoeken of deze resultaten gerepliceerd kunnen worden met behulp van een grotere steekproef van patiënten.

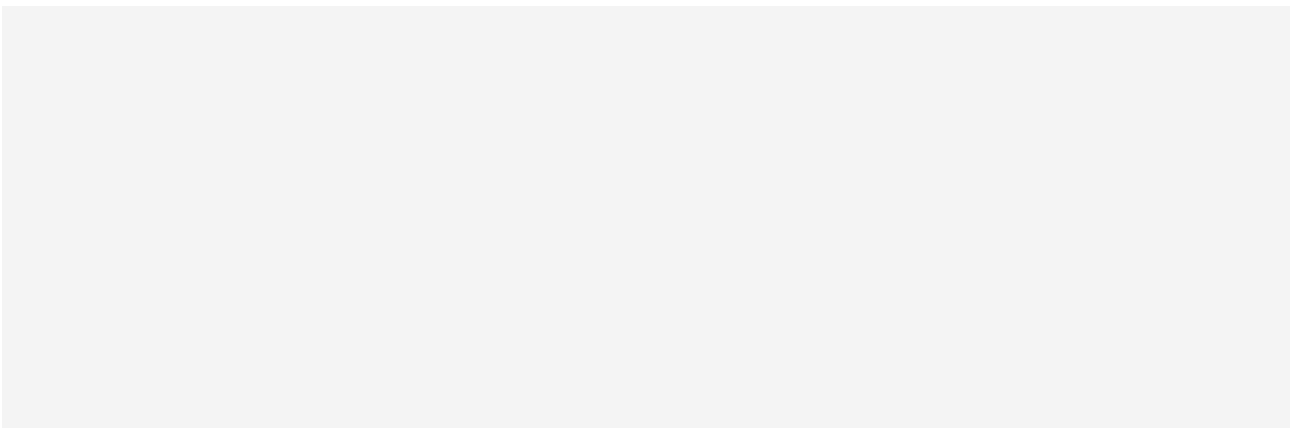
In **Hoofdstuk 7** wordt het kosteneffectiviteitsonderzoek van een gefaseerde behandeling versus een directe traumagerichte behandeling beschreven bij patiënten met een PTSS gerelateerd aan mishandeling en/of seksueel misbruik in de kindertijd. We hebben zowel een kosteneffectiviteitsanalyse uitgevoerd als een kostenutiliteitsanalyse. De primaire uitkomstmaat van de kosteneffectiviteitsanalyses was het percentage deelnemers waarvan de PTSS in remissie was. De primaire maat voor de kostenutiliteitsanalyse waren de *Quality of Life Years* (Qaly's). Uit de resultaten kwam naar voren dat STAIR-EMDR niet kosteneffectief is vergeleken met alleen EMDR. De uitkomstmaten lieten geen significante verschillen zien

tussen de twee behandelcondities, terwijl de gemiddelde maatschappelijke kosten per patiënt significant verschilden tussen STAIR-EMDR en EMDR (respectievelijk €19,599 vs €13,501).

### **Algemene conclusies**

De resultaten van ons onderzoeksproject suggereren dat: 1) directe traumabehandeling veilig en effectief is voor mensen met een PTSS gerelateerd aan mishandeling en/of misbruik in de kindertijd, 2) gefaseerde behandeling niet leidt tot betere behandelresultaten dan directe traumagerichte behandeling en minder efficiënt is, 3) gefaseerde behandeling niet leidt tot minder uitval of incidenten tijdens de behandeling, 4) er geen duidelijke predictoren of moderatoren zijn voor behandeluitkomsten in de vergelijking van een gefaseerde behandeling met een directe trauma-gerichte behandeling, 5) gefaseerde behandeling niet kosteneffectief is vergeleken met een directe traumagerichte behandeling.





List of authors and contributions

List of Publications

Additional publication, awards and presentations

Appendices

Curriculum Vitae

Dankwoord (Acknowledgements)

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6. Dr. Mark Huisman
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### Authors' contributions

## **Chapter 2: Phase-Based Treatment versus Immediate Trauma-Focused Treatment in Patients with Childhood Trauma-Related Posttraumatic Stress Disorder: Study Protocol for a randomized controlled trial**

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5. *Agreed to the final version of the manuscript:* Noortje van Vliet, Rafaele Huntjens, Maarten van Dijk, and Ad de Jongh

**Chapter 3: Phase-Based Treatment versus Immediate Trauma-Focused Treatment in Patients with PTSD due to childhood abuse: A randomized clinical trial**

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**Chapter 4: Predictors and moderators of treatment outcomes in phase-based treatment and trauma-focused treatments in patients with childhood abuse-related post-traumatic stress disorder**

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**Chapter 5: Predicting optimal treatment outcomes in phase-based treatment and direct trauma-focused treatment among patients with PTSD due to childhood abuse**

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7. *Agreed to the final version of the manuscript*: Susanne Bremer, Noortje van Vliet, Suzanne van Bronswijk, Rafaele Huntjens, Ad de Jongh, and Maarten van Dijk

**Chapter 6: Predictors of treatment dropout in patients with PTSD due to childhood abuse**

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**Chapter 7: Cost-effectiveness analysis of the treatment of posttraumatic stress disorder related to childhood abuse. Comparing a phase-based treatment and a direct trauma-focused treatment.**

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7. *Agreed to the final version of the manuscript:* Noortje van Vliet, Dennis Stant, Rafaele Huntjens, Maarten van Dijk, and Ad de Jongh

**Additional publications**

Germann, J., Boeschoten, M., Nijdam, M. J., van der Aa, N., Eidhof, M. B., Hoeboer, C. M., de Jongh, A., Olf, M., Schoorl, M., van Vliet, N. I., Vermetten, E., & Ter Heide, F. J. J. (2023). Psychometric evaluation of the Dutch International Trauma Questionnaire for the 11th revision of the International Classification of Diseases posttraumatic stress disorder and complex posttraumatic stress disorder. *Psychological trauma : theory, research, practice and policy*, 10.1037/tra0001576. Advance online publication. <https://doi.org/10.1037/tra0001576>

**List of awards during PhD**

April 2021: research award of the Dutch EMDR Association

**List of invited talks during PhD**

03-21-2017 Presentation congress Committee Scientific Research Dimence  
 09-17-2017 Presentation congress Bipolar disorders and trauma Dimence  
 09-25-2018 Presentation congress Committee Scientific Research Dimence  
 01-25-2020 Presentations KOP festival Deventer  
 04-01-2021 Presentation congress psychiatrists Dimence  
 04-10-2021 Presentation congress of the Dutch EMDR Association  
 05-20-2021 Presentation congress Altrecht academic Center  
 09-24-2021 Presentation Dutch Network for Mood and Anxiety  
 11-04-2021 Presentation congress Dutch Association for Cognitive Behavioral Therapy (VGCT)  
 01-27-2022 Presentation congress Dutch Psychotrauma Association  
 09-08-2022 Presentation European Association for Behavioral and Cognitive Therapy Barcelona  
 09-30-2022 Presentation congress Dutch Psychotrauma Association  
 11-03-2022 Presentation Dutch Association for Cognitive Behavioral Therapy

**Appendices**

Chapter 3 Supplemental Table 1: Demographic characteristics at baseline

Characteristic	STAIR-EMDR (n=57) % of total population	EMDR (n=64) % of total population	Total sample (n=121)	$\chi^2$	df	<i>p</i>
Gender				0.03	1	.88
Male	14.0% (n = 17)	17.4% (n = 21)	31.4% (n = 38)			
Female	33.1% (n = 40)	35.5% (n = 43)	68.6% (n = 83)			
Education				2.94	2	.23
Low	25.9% (n = 30)	19.8% (n = 23)	45.7% (n = 53)			
Middle	16.4% (n = 19)	25,0% (n = 29)	41,4% (n = 48)			
High	6.0% (n = 7)	6.9% (n = 8)	12.9% (n = 15)			
Employment				0.04	2	.98
Unemployed	28.6% (n = 34)	31.9% (n = 38)	60.5% (n = 72)			
Employed	13,4% (n = 16)	14,3% (n = 17)	27,7% (n = 33)			
Student	5.9% (n = 7)	5.9% (n = 7)	11.8% (n = 14)			
Living Condition				8.40	3	.04
Married or cohabitating	14.4% (n = 17)	30.5% (n = 36)	44.9% (n = 53)			
Alone	23.7% (n = 28)	16.9% (n = 20)	40.7% (n = 48)			
With relatives or friends	5.1% (n = 6)	4.2% (n = 5)	9.3% (n = 11)			
Sheltered house	3.4% (n = 4)	1.7% (n = 2)	5.1% (n = 6)			
Sexual abuse (% per condition)	37.2% (n = 45)	37.2% (n = 45)	74.4% (n = 90)	0.77	1	.38
Physical abuse (% per condition)	37.2% (n = 45)	41.3% (n = 50)	78.5% (n = 95)	0.00	1	1.00
Dissociative subtype (% per condition)	14.0% (n = 17)	20.7% (n = 25)	34.7% (n = 42)	0.76	1	.38
Suicidality				0.81	2	.67
No suicidal thoughts	10.7% (n = 13)	14% (n = 17)	24.8% (n = 30)			
Suicidal thoughts, no intention	28.1% (n = 34)	27.3% (n = 33)	55.4% (n = 67)			
Preferring to cause suicide	8.3% (n = 10)	11.6% (n = 14)	19.8% (n = 24)			

Chapter 3 Supplemental Table 2a  
 Results of the Linear Mixed Model (LMM) of the primary and secondary outcome variables measured at pre-treatment, after eight sessions and at post-treatment.

	Treatment						Time						Treatment time interaction								
	Pre-treatment vs. post-treatment			Pre-treatment vs. after eight sessions			After eight sessions vs. post-treatment			Pre-treatment vs. post-treatment			Pre-treatment vs. after eight sessions			After eight sessions vs. post-treatment					
	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI			
<b>PSS-SR</b>	3.87	1.96	-0.01	-11.78***	1.60	-14.94	-0.52	1.68	-3.83	-11.27***	1.82	-14.87	-2.84	2.18	-7.15	-6.67**	2.40	-11.40	3.83	2.51	-11.13
			7.74			-8.63		2.79		-7.67					1.47		-1.94				8.79
<b>IIP</b>	0.16	0.12	-0.07	-0.31***	0.78	-0.46	0.16*	0.08	0.00	-0.47**	0.89	-0.65	-0.10	0.11	-0.31	-0.36**	0.12	-0.59	0.26*	0.12	0.02
			0.40			-0.16		0.33		0.30					0.11		-0.13				0.50
<b>DERS</b>	7.21	4.74	-2.15	-15.49***	3.25	-21.91	-1.90	3.42	-8.66	-13.59***	3.72	-20.94	-3.31	4.52	-12.24	-5.40	4.92	-15.11	2.09	5.13	-8.04
			16.57			9.08		4.85		-6.24					5.63		4.32				12.22
<b>PTCI</b>	12.58	8.18	-3.55	-32.50***	5.84	-44.03	6.11	6.29	-6.32	-38.61***	6.75	-51.95	-5.67	8.06	-21.59	-25.16**	8.85	-42.63	19.49*	9.21	1.31
			28.72			-20.97		18.54		-25.27					10.25		-7.69				37.67

Est = Estimated effect, SE = Standard Error, CI = Confidence Interval, PSS-SR = PTSD Symptoms Scale-self report, IIP = Inventory of Interpersonal Problems, DERS = Difficulties in Emotion Regulation Scale, PTCI = Posttraumatic Cognitions Inventory

Note. \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$

Chapter 3, Supplemental Table 2b  
 Results of the Linear Mixed Model (LMM) for all outcome variables at pre-treatment, post-treatment and at three-month's follow-up.

	Treatment			Time			Treatment-time interaction											
	Est	SE	95% CI	Est	SE	95% CI	Pre- vs. post-treatment	Post-treatment vs. three month Follow-Up	Pre- vs. post-treatment	Post-treatment vs. three month Follow-Up	Pre- vs. post-treatment	Post-treatment vs. three month Follow-Up						
<b>CAPS-5</b>	1.05	2.36	-3.61 5.71	-20.12***	1.62	-23.30 -16.94	-1.99	1.74	-5.42	1.44	-0.68	2.22	-5.05	3.69	0.47	2.42	-4.28	5.23
<b>SIDES-R</b>	1.63	2.53	-6.62 3.35	-11.14***	1.68	-14.45 -7.82	-0.69	1.80	-4.23	2.85	-2.32	2.30	-6.85	2.20	-2.10	2.48	-6.99	2.79
<b>BSI</b>	0.16	0.16	-0.15 0.47	-0.53***	0.99	-0.72 -0.33	-0.06	0.11	-0.27	0.15	-0.18	0.14	-0.45	0.09	-0.08	0.15	-0.37	0.20
<b>DES</b>	3.45	3.02	-2.51 9.41	-8.13***	1.95	-11.96 -4.29	1.39	2.11	-2.77	5.55	-3.44	2.69	-8.73	1.85	-3.17	2.84	-8.75	2.42

Est = Estimated effect, SE = Standard Error, CI = Confidence Interval, CAPS-5 = Clinician Administered PTSD Scale for DSM-5, SIDES = Structured Interview for Disorders of Extreme Stress-Revised, BSI = Brief Symptom Inventory, DES = Dissociative Experiences Scale.

Note. \* $p < .05$ , \*\*  $p < .01$ , \*\*\* $p < .001$

Chapter 3 Supplemental Table 3a  
 Results of the Linear Mixed Model (LMM) for the primary and secondary outcome variables measured at pre-treatment, after eight sessions and at post-treatment, with the pre-treatment measurement as covariate.

	Treatment				Time				Treatment-time interaction			
					After eight sessions				After eight sessions			
	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI
PSS-SR	-2.27	2.25	-6.72 2.19	11.35***	2.00	7.37 15.34	-4.20	2.80	-9.78 -1.39			
IIP	-0.94	0.11	-0.30 0.12	0.47***	0.10	0.28 0.66	-0.23	0.13	-0.50 0.04			
PTCI	-0.96	7.92	-16.63 14.71	39.56***	6.77	26.07 53.05	-21.47*	9.33	-40.09 -2.86			
DERS	-0.25	4.54	-9.24 8.75	13.83***	3.34	7.15 20.51	-3.15	4.71	-12.57 6.27			

Est = Estimated effect, SE = Standard Error, CI = Confidence Interval, PSS-SR = PTSD Symptoms Scale-self report, IIP = Inventory of Interpersonal Problems, DERS = Difficulties in Emotion Regulation Scale, PTCI = Posttraumatic Cognitions Inventor  
 Note: \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$



Chapter 3, Supplemental Table 3b  
 Results of the Linear Mixed Model (LMM) for the outcome variables measured at pre-treatment, post-treatment and at three- and six month's follow-up, with the pre-treatment measurement as covariate.

	Treatment						Time						Treatment-time interaction					
	Treatment		Three month FU		Six month FU		Three month FU		Six month FU		Three month FU		Six month FU		Three month FU		Six month FU	
	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI	Est	SE	95% CI
CAPS-5	-0.25	2.40	-4.99 4.49	-1.39	1.58	-4.52 1.74	-2.03	1.54	-5.06 1.01	0.19	2.21	-4.17 4.54	0.59	2.18	-3.72 4.90			
SIDES	-1.97	2.27	-6.45 2.52	-0.67	1.54	-3.72 2.38	-2.97*	1.49	-5.91 - 0.02	-1.94	2.15	-6.18 2.30	.81	2.11	-3.36 4.99			
BSI	-0.10	0.15	-0.27 0.50	-0.05	0.09	-0.22 0.12	-0.16	0.83	-0.33 0.00	-0.06	0.12	-0.29 0.18	0.53	0.12	-0.18 0.29			
DES	-0.02	2.67	-5.30 5.26	1.45	1.67	-1.86 4.75	-1.17	1.61	-4.35 2.01	-3.03	2.30	-7.57 1.51	-1.76	2.30	-6.31 2.78			

Est = Estimated effect, SE = Standard Error, CI = Confidence Interval, CAPS-5 = Clinician Administered PTSD Scale for DSM-5, SIDES = Structured Interview for Disorders of Extreme Stress-Revised, BSI = Brief Symptom Inventory, DES = Dissociative Experiences Scale. For all variables the effect of the covariate was significant.  
 Note. \* $p < .05$ , \*\*  $p < .01$ , \*\*\*  $p < .001$

Chapter 5, Supplemental Table 1 Continuous baseline variables per treatment group and comparison of the means

Variables pre-treatment	EMDR (n = 51) Mean (Std)	STAIR-EMDR (n = 54) Mean (Std)	t	df	p	Cronbach's $\alpha$
Age	37.19 (11.91)	38.08 (13.15)	-0.37	103	.72	NA
NA	39.94 (9.70)	37.11 (8.10)	1.63	103	.11	NA
SIDES total score	33.24 (13.49)	30.46 (10.51)	1.18	103	.24	NA
DERS total score	117.08 (26.16)	110.09 (21.80)	1.49	103	.14	.92
DES total score	27.22 (15.91)	21.24 (13.03)	2.11	103	.04*	.93
PSS-SR total score	31.23 (8.67)	27.37 (7.99)	2.37	103	.02*	.83
BSI Cognitive Problems	2.45 (0.92)	1.96 (0.86)	2.82	103	.01**	.81
BSI Interpersonal Sensitivity	2.31 (1.02)	1.99 (1.00)	1.60	103	.11	.76
BSI Depression	2.31 (0.93)	2.17 (0.99)	0.78	103	.44	.86
BSI Anxiety	2.32 (0.84)	1.88 (0.97)	2.48	102.19	.02*	.81
BSI Hostility	1.08 (0.71)	0.87 (0.63)	1.64	103	.10	.82
BSI Phobic Anxiety	2.04 (1.11)	1.66 (1.02)	1.83	103	.07	.81
BSI Paranoid Symptoms	1.94 (1.23)	1.73 (0.89)	1.06	103	.29	.76
BSI Psychoticism	1.89 (0.93)	1.54 (0.79)	2.10	103	.04*	.69

BSI Positive Symptoms Total	42.15 (7.42)	38.45 (7.88)	2.47	103	.02*	NA
PTCI Self-Blame	3.47 (1.67)	3.02 (1.44)	1.49	103	.14	.86
PTCI Self-Esteem	4.22 (1.35)	3.84 (1.32)	1.46	103	.15	.94
PTCI Negative Cognitions About the World	5.27 (1.12)	5.12 (1.07)	0.74	103	.46	.89
IIP Domineering	0.60 (0.55)	0.65 (0.63)	-0.38	103	.70	.42
IIP Self-Sacrificing	2.22 (0.96)	2.27 (1.05)	-0.24	103	.81	.72
IIP Cold/Distant	1.84 (1.00)	1.59 (1.01)	1.30	103	.20	.75
IIP Intrusive/Needy	0.91 (0.74)	0.81 (0.66)	0.71	103	.48	.64
IIP Non-assertive	2.28 (1.00)	1.94 (0.98)	1.77	103	.08	.75
IIP Overly accommodating	2.45 (0.90)	2.13 (0.99)	1.76	103	.08	.68
IIP Socially inhibited	2.24 (0.98)	1.93 (0.97)	1.62	103	.11	.68
IIP Vindictive/self centered	1.11 (1.07)	1.15 (1.11)	-0.16	103	.87	.83

CAPS-5 = Clinician Administered PTSD Scale for DSM-5, SIDES = Structured Interview for Disorders of Extreme Stress-Revised, DERS = Difficulties in Emotion Regulation Scale, DES = Dissociative Experiences Scale, PSS-SR = PTSD Symptoms Scale-self report, BSI = Brief Symptom Inventory, PTCI = Posttraumatic Cognitions Inventory, IIP = Inventory of Interpersonal Problems

Note. \*p < .05, \*\*p < .02

Chapter 5, Supplemental Table 2 Categorical baseline variables per treatment group and comparison of the amounts

Variable	EMDR (n = 51)	STAIR-EMDR (n = 54)	$\chi^2$	Df	P
Sex			0.00	1	1.00
Woman	35	37			
Man	16	17			
Education			.78	2	.68
low	23	29			
middle	20	18			
high	8	7			
Employment			.23	2	.89
unemployed	32	32			
employed	13	16			
student	6	6			
Married	28	17	4.96	1	0.03*
Sexual Abuse	37	42	0.16	1	0.69
Physical Abuse	38	42	0.03	1	0.87
Dissociative subtype	20	15	1.07	1	0.30
Complex PTSD	16	13	0.38	1	0.54
Borderline personality disorder	8	11	0.14	1	0.71
Self-injury			1.64	2	0.44
no self-injury	29	32			
doubtful	6	10			
self-injury	16	12			
Suicidal thoughts	37	41	0.03	1	0.86
Psychoactive medication use at screening	29	27	0.26	1	.61
Benzodiazepine medication use at screening	12	10	0.15	1	.70

\*p<0.05

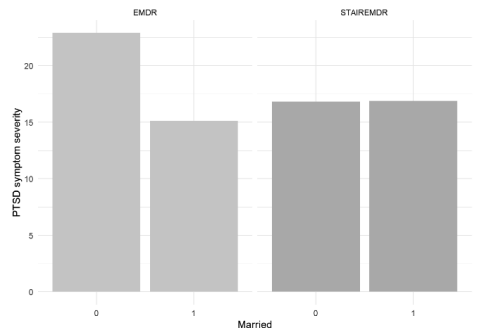
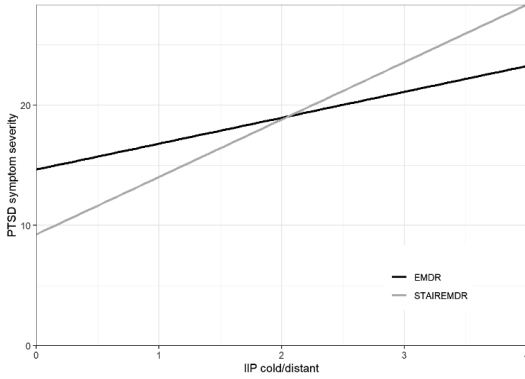
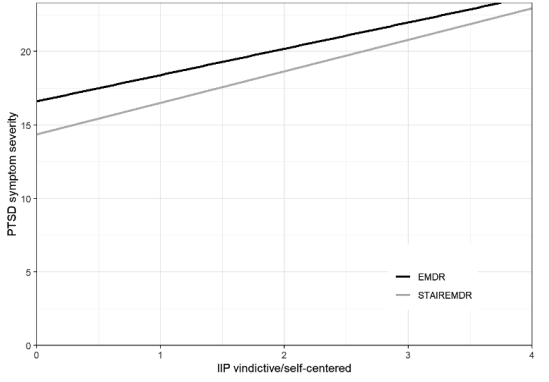
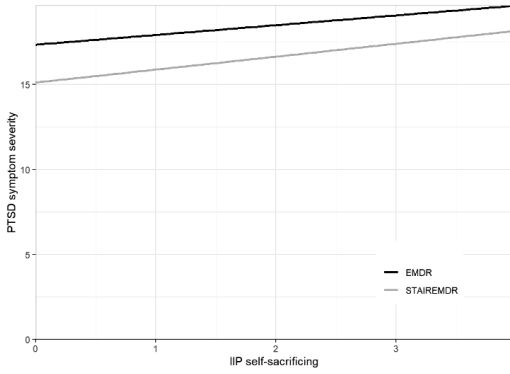
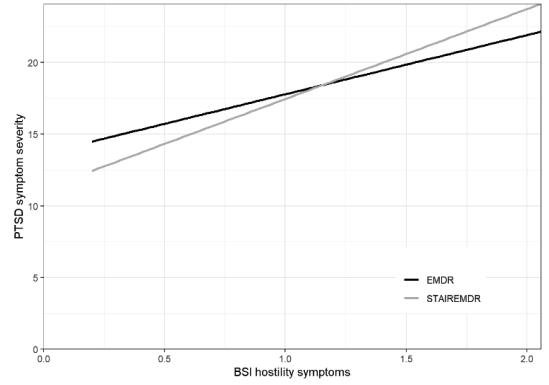
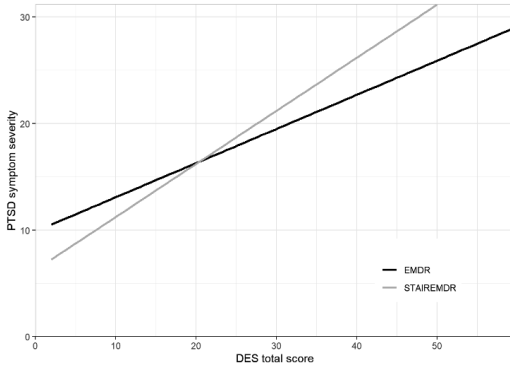
Chapter5, Supplemental Table 3 Variable selection results

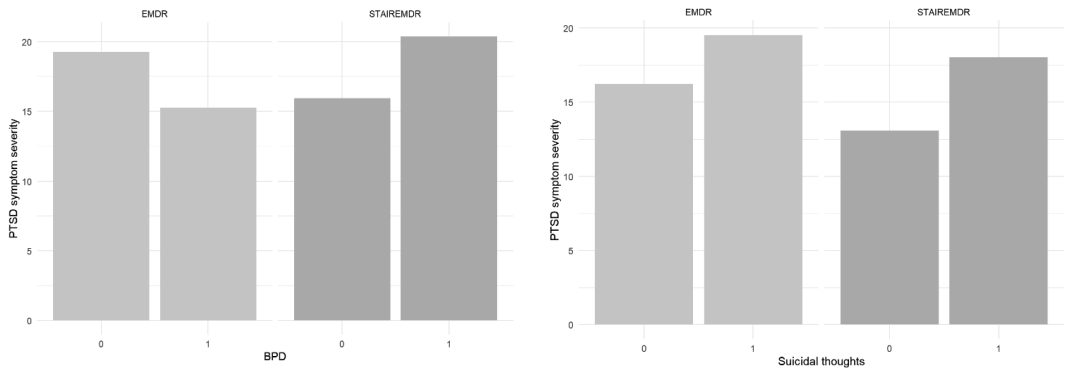
Variable	Random Forest	Elastic Net	Included in BootStepAIC	Result BootstepAIC
Sex		X	X	X*
Education		X	X	X*
Employment		X	X	
Age		X	X	
Married		X	X	X
Dissociative subtype	X	X	X	X
BDI-II item 9 Suicidal thoughts		X	X	X
Complex posttraumatic stress disorder (PTSD)		X	X	X
SCID-II item 97 and 98 Borderline personality disorder (BPD)		X	X	X
Self-injury		X	X	X*
Psychoactive medication use at screening		X	X	X*
Benzodiazepine medication use at screening		X	X	X*
SIDES total score		X	X	
DES total score	X	X	X	X
BSI Cognitive Problems		X	X	
BSI Interpersonal Sensitivity		X	X	
BSI Depression		X	X	X
BSI Anxiety		X	X	
BSI Hostility		X	X	X
BSI Paranoid Symptoms		X	X	X
BSI Psychoticism		X	X	X*
BSI Positive Symptom Total		X	X	X*
PTCI Self-Esteem		X	X	
PTCI Negative Cognitions About the World		X	X	X*
IIP Domineering/controlling		X	X	X*
IIP Self-sacrificing		X	X	X
IIP Cold/distant	X	X	X	X
IIP Intrusive/needy		X	X	X
IIP Overly accommodating		X	X	
IIP Socially inhibited		X	X	
IIP Vindictive/self-centered		X	X	X

\* these variables were selected by the BootStepAIC, however the p-values of these variables were above 0.05 in the final model. As noted by Kuhn and Johnson (2013) to favor simpler models, these variables were excluded in the final PAI model.

BDI-II, Beck Depression Inventory; BSI, Brief Symptom Inventory; DES-II, Dissociative Experiences Scale; IIP, Inventory of Interpersonal Problems; PTCI, Posttraumatic Cognitions Inventory; SCID-II, Structured Clinical Interview for DSM-IV Axis II; SIDES, Structured Interview for Disorders of Extreme Stress.

Chapter 5, Supplemental Figure 1 Moderator Relationships





Graphs of the relationship between the moderator and the mean post-treatment PTSD symptom severity score. BSI = Brief Symptom Inventory, BPD = Borderline personality disorder, DES-II = Dissociative Experiences Scale, EMDR = Eye Movement Desensitization and Reprocessing, IIP = Inventory of Interpersonal Problems, PTSD = Post Traumatic Stress Disorder, STAIR = Skills Training in Affect and Interpersonal regulation.

**Figure 1.** Individuals with more BSI hostility symptoms have lower post-treatment PTSD symptom severity scores when treated with EMDR (trauma-focused treatment) compared to STAIR-EMDR (phase-based treatment). The same effect was visible for IIP subscale cold/distant and for the total score on the DES.

Individuals with BPD reported lower post-treatment PTSD symptom severity scores in EMDR in comparison with STAIR-EMDR. For suicidal thoughts, the individuals with no suicidal thoughts were estimated to have lower post-treatment PTSD symptom severity scores in STAIR-EMDR. Further, married individuals reported lower post-treatment PTSD symptom severity scores in EMDR.

The moderators IIP subscale self-sacrificing and IIP subscale vindictive/self-centered were so-called ordinal moderators, indicating that all scores are linked to different levels of a superior effect of one treatment above the other. In these cases, STAIR-EMDR was superior, meaning lower post-treatment PTSD symptom severity scores, and the degree of superiority was more pronounced when the scores on the IIP subscales were lower.

The moderators IIP subscale cold/distant, BSI subscale hostility symptoms and score on the DES are so-called dis-ordinal moderators, indicating that a low score is associated with superiority of one treatment, and a high score is associated with the superiority of the other treatment.

## Chapter 5, Supplemental Variable Selection

RF is a recursive partitioning method based on the construction of so-called “trees” of variables. At each split in the tree, a subset of variables is considered (James et al., 2013). This is an effective way of improving predictive performance (James et al., 2013; Strobl et al., 2008). In order to adjust RF for the purpose of identifying moderators, the model function that determines a split can be extended with treatment ( $y = x \times \text{treatment}$ ). To identify moderator variables, the following parameters were used: *mtry* (number of variables to consider at each split), 10; number of trees, 10 000; minimum  $\alpha$  level, 0.10; and minimum number of observations in a node, 10. Results of the RF procedure is an overall summary of the predictive importance of each variable which is determined through permutation tests (Garge et al., 2013; James et al., 2013). Variables were selected on the basis of surpassing the permutation threshold.

ENR is a penalized regression that combines lasso and ridge regression. ENR is particularly useful in datasets with many and highly correlated variables (Kuhn & Johnson, 2013). It shrinks some coefficients of variables towards zero (ridge regression) and some coefficients of variables to exactly zero resulting in exclusion of those variables (lasso regression) (Kuhn & Johnson, 2013). The amount of shrinkage is determined by the tuning parameter lambda. The other tuning parameter is alpha where zero corresponds to ridge and one to lasso. These parameters are determined with a 10-fold cross validation (CV; James et al., 2013). ENR is particularly useful for identifying prognostic variables and not for identifying moderators. To determine moderators, a prognostic model was created for each treatment condition. Then, the coefficients of the variables of these models were explored. Variables were selected as possible moderators on the basis of existence in only one model, or in both models with different coefficient values (Cohen et al., 2019).



Chapter 6, Supplemental Table 1, variable importance

Reasons for dropout given by patients	Dropout n = 23
Unknown	10
Severe physical complains	3
Problems in living condition or family	3
Exacerbation of psychiatric complains	2
Quitting medication	1
Too fast decline of the PTSD symptoms	1
Drug abuse (not able to stop during treatment)	1
Unsatisfied about the treatment	1
Treatment is too difficult	1

## Chapter 6, Supplemental R code

## R code Elastic Net Regularization

```

# Convert dataset to a matrix
dataset_x <- dataset %>% dplyr::select(-dropout)
dataset_y <- dataset %>% dplyr::select(dropout)
dataset_y2 <- dataset_y
X_dataset <- data.matrix(dataset_x)
Y_dataset <- data.matrix(dataset_y)

# ENR
set.seed(2)
allAlpha <- NULL
nAlphaIterations <- 25
nLambaIterations <- 1000
a <- seq(0, 1, 0.05)
ptm <- proc.time()

##### Tuning the alpha #####
for(j in 1:length(a)){
  for(i in 1:nAlphaIterations){
    set.seed(i)
    cv <- cv.glmnet(X_dataset, Y_dataset, nfold = 10, family = "binomial", type.measure =
"class", par = F, alpha = a[j])
    currAlpha <- data.frame(
      MSE = cv$cvm[cv$lambda == cv$lambda.1se],
      lambda.1se = cv$lambda.1se,
      alpha = a[j],
      seed = i)
    allAlpha <- rbind(allAlpha, currAlpha) # all current alphas combined
  }
  print(j)
}
proc.time() - ptm
aggregate(MSE~ alpha, allAlpha, mean)
plot(aggregate(MSE~ alpha, allAlpha, mean))
alphaMin <- aggregate(MSE~ alpha, allAlpha, mean)[aggregate(MSE~ alpha, allAlpha,
mean)$MSE == min(aggregate(MSE~ alpha, allAlpha, mean)$MSE), "alpha"]

##### Tuning the lambda #####
currentLambda <- NULL
allLambdaIteration <- NULL
nLambaIterations <- 1000
ptm <- proc.time()
for(i in 1:nLambaIterations){
  currentLambda <- cv.glmnet(data.matrix(X_dataset), Y_dataset, nfold = 10, type.measure =
"class", alpha = alphaMin)
}

```

```
allLambdaIteration <-  
  rbind(allLambdaIteration,  
        data.frame(lambdaMin = currentLambda$lambda.min,  
                  lambda1SE = currentLambda$lambda.1se))  
  print(i)  
}  
proc.time() - ptm  
LambdaMin <- mean(allLambdaIteration$lambdaMin)  
  
set.seed(2)  
md3 <- glmnet(X_dataset, Y_dataset, family = "binomial", lambda = LambdaMin, alpha =  
alphaMin)
```

## Chapter 6, Supplemental Table 1. Types of costs included in the analyses

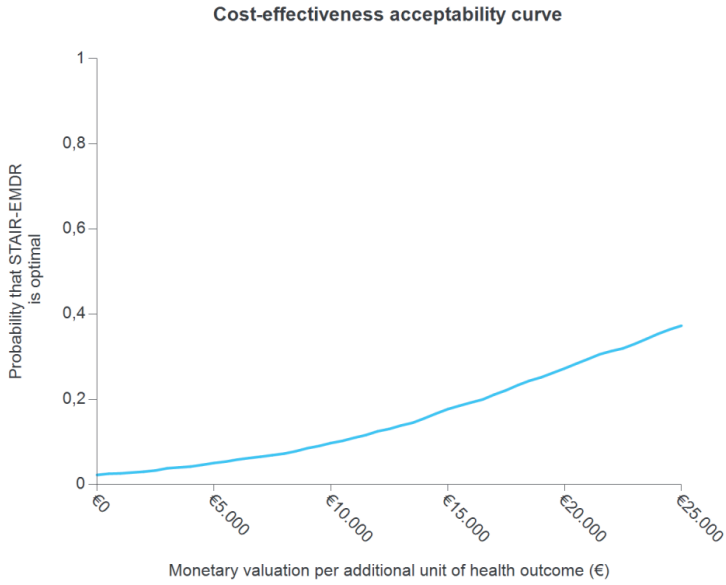
Costs within the healthcare sector	Costs outside the healthcare sector
Interventions (including STAIR and EMDR contacts, supervision, housing)	Informal care
Inpatient and semi-inpatient care	Productivity losses
Outpatient and community care	
General healthcare	
Medication use	

Chapter 6, Supplemental Table 2. Costs (€) in and outside the healthcare sector during 9 months

<i>Selected cost types</i>	STAIR-EMDR (n=45)		EMDR (n=49)	
	Mean costs (SD)	% <sup>1</sup>	Mean costs (SD)	% <sup>1</sup>
<i>Interventions</i>				
STAIR-EMDR, EMDR	€2,436 (€874)	100	€1,686 (€507)	100
<i>(Semi-)inpatient care</i>				
Hospital admissions	€405 (€1,903)	11	€1,187 (€4,625)	16
Day treatment	€7 (€44)	2	€171 (€1,025)	8
Outpatient clinic	€190 (€384)	38	€168 (€297)	35
Sheltered living	€2,071 (€8,540)	7	€142 (€460)	10
<i>Outpatient/community care</i>				
Psychiatrist	€423 (€2,065)	29	€204 (€745)	39
Psychologist	€1,256 (€1,581)	56	€2,086 (€1,797)	73
Psychotherapist	€929 (€1,726)	27	€882 (€1,802)	22
Social worker	€101 (€353)	18	€299 (€1,260)	16
Physiotherapist	€204 (€464)	38	€162 (€344)	29
<i>Medication use</i>				
Prescribed medication	€92 (€150)	64	€155 (€302)	65
<i>Outside healthcare sector</i>				
Informal care	€2,402 (€3,574)	58	€1,849 (€2,871)	55
Out-of-pocket costs	€150 (€639)	13	€188 (€1,271)	4
Productivity losses paid work	€4,256 (€8,515)	29	€1,710 (€4,662)	20

<sup>1</sup> Percentage of participants using the cost types concerned

Chapter 6, Supplemental Figure 1. Cost-effectiveness acceptability curve (with remitted PTSD as primary outcome)



**Curriculum Vitae**

Noortje Inez van Vliet, born in Dedemsvaart in 1977, completed her secondary education in 1996 at the Thomas à Kempis College In Zwolle. While pursuing her degree in Psychology at the University of Groningen, she spent six months abroad studying psychology at the Université Paul Valéry in Montpellier (2000, France). After successfully graduating in Psychology from the University of Groningen (2001), she furthered her studies by spending half a year in Poland focusing on the Polish language (2001/2002). After these studies she acquired registrations as a Cognitive Behavioral Therapist, Health Care Psychologist and EMDR Practitioner. Currently, she is engaged in studies to become a Clinical Psychologist (post-doctorate) at the University of Nijmegen.

Since 2002 she has worked in various Mental Health Care Organization, providing care and therapy to diverse patient groups with a range of disorders, including psychotic disorders, developmental disorders, personality disorders, anxiety and depression. Since 2015 she has developed a particular interest in treating patients with severe trauma backgrounds, especially those with a history of childhood abuse. Intrigued by the resilience of these patients, she decided to contribute to the advancement of treatments for this specific patient group by initiating research in this area.

At the Dimencegroup she served as the chairwoman of the Network Traumarelated Treatment. The aim of this Network is to enhance therapists' knowledge about trauma treatments, aiming to improve trauma treatment at Dimence. She organized several presentation afternoons to disseminate knowledge about this subject.

## Dankwoord

De reden dat ik een wat gammele hangbrug als voorkant heb gekozen, is omdat ik denk dat het lopen over zo'n brug bij benadering voelt zoals het voor mijn patiënten soms voelt om traumabehandeling te ondergaan. Ik heb daarom altijd ook al veel respect en bewondering gehad voor alle patiënten die hulp zoeken om hun vroegkinderlijke trauma's te verwerken. Immers, waar moet je het vertrouwen om dit aan te gaan vandaan halen, als je een groot deel van je leven hebt moeten leren wantrouwen om jezelf veilig te stellen? Juist deze groep mensen is voor mij aanleiding geweest om het onderzoek te starten, waarbij één patiënte in het bijzonder. Ik raakte tijdens haar behandeling zo verstrikt in een web van meningen over stabiliseren of niet stabiliseren, dat ik besloot dit zelf te gaan onderzoeken. Ik ben daarbij ook enorm dankbaar voor alle patiënten die uiteindelijk de bereidheid hadden om aan dit onderzoek mee te werken. Zonder deze bereidheid was dit onderzoek er niet geweest en waren we over dit onderwerp niet zoveel wijzer geworden.

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