RESEARCH PROTOCOL

PROSPER

Prediction and Outcome Study in PTSD and Personality disorders

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsingcommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

PM: See abbreviation of measures in section 5.1.1. and page 23

SUMMARY

Rationale: Evidence-based treatments for posttraumatic stress disorder (PTSD), such as Eye Movement Desensitization and Reprocessing (EMDR) and Imagination and Rescripting Therapy (ImRs), are highly effective treatments in the majority of the PTSD patients. PTSD is highly comorbid with personality disorders (PD), especially borderline personality disorder (BPD), and cluster C - avoidant, dependent, or obsessive-compulsive - personality disorders (CPD). It is not clear yet what treatment is most effective for those who suffer from both PTSD and PD.

There is growing motivation in clinicians to offer PTSD treatments to PTSD with comorbid PD, because these treatments are highly effective, relatively short (weekly sessions, 3-6 months) and there is some evidence that with PTSD treatment, comorbid PD symptoms might resolve as well. PTSD treatments are less time-consuming than PD treatments and - at least in the short term - financially attractive. However, at least 30-44% PTSD patients do not sufficiently respond to these treatments. Moreover, a high number of PTSD patients are excluded from these therapies because of suicidality, self-destructive behaviour or other personality problems. Therefore, it might be more efficient to add a PD treatment at the same time. Evidence-based treatments for personality disorders (PD), such as dialectical behaviour treatment (DBT) for BPD, and schema-focused treatment (SFT) for CPD are well established. These treatments are more intensive (twice a week for at least one year) than PTSD treatments. There is some evidence that integrated PTSD-PD treatment is twice as effective on reducing PTSD symptoms than PD treatment alone, but integrated PTSD-PD treatment is not yet directly compared to PTSD treatment alone. This study will address this knowledge gap, including secondary outcome measures on functioning, quality of life and cost-effectiveness.

The result of this study might be that one or the other treatment works better, depending on the personal profile of the patient. So far, some psychological factors have been found to be associated with worse outcome of PTSD treatment. These are cognitive (educational level, working memory emotion regulation), affective (anger, sleep problems, dissociation), and relational factors (therapeutic alliance, attachment, social support). In addition, neurobiological factors are found to be associated with PTSD treatment outcome, such as increased activity connectivity of the limbic network and decreased activity and connectivity of the cognitive control networks, and disturbed hormonal levels and epigenetic factors (5-HTTLPR, BDNF, cortisol/FKBP5-methylation, oxytocin/OXTR). Because these candidate predictors are found on a group level (in non-responders vs. responders), they cannot directly be used on an individual level. By using machine-learning techniques we might use these candidate predictors on an individual level to guide treatment choices and thereby personalise psychiatry.

We hypothesize that in patients with PTSD with BPD, integrated DBT-EMDR treatment results in a higher effect size and higher response rate than EMDR-only (A1); in patients with PTSD and CPD, integrated SFT- ImRs treatment results in a higher effect size and higher response rate than ImRs - only (A2). Furthermore, we hypothesize that non-response to PTSD-treatment can be individually predicted by a machine-learning model with (B1) psychological factors (cognitive, affective, and relational) and (B2) neurobiological factors (neural factors, and hormonal/ epigenetic factors.

Objective: In the current project, we will firstly study effectiveness of PTSD-treatment compared to integrated PTSD-PD-treatment in treatment-seeking, adult patients with comorbid PTSD and PD in a wide range of severity (minimally 4 criteria of a personality disorder). Secondly, we will investigate psychological (cognitive, affective, and relational) and neurobiological candidate predictors of treatment outcome, and use them in a machine-learning paradigm to come to a clinically useful and individual prediction instrument of treatment outcome.

Study design: Two related randomized controlled trials (A1, A2) with prediction analyses (B1, B2).

Study population: With the assumptions of a small effect size (< 0.5) of PTSD treatment in patients with comorbid PTSD and PD and a double effect size of integrated PTSD-PD-treatment (1.0), the number of persons needed to include is 64 persons per condition to reach for 80% power. Expecting a dropout rate of 25%, we will include 80 persons per arm, for 4 arms a total of 320 adult patients with PTSD and - at least 4 - PD symptoms. Of these patients, 80 next to 40 healthy matched controls will be asked for additional MRI research before and after treatment. In total, 360 persons will be included in this study.

Intervention: In patients with PTSD and BPD: EMDR (3-6 months plus 6-9 months treatment pause) compared to integrated DBT-EMDR (12 months); in patients with PTSD and CPD: ImRs (3-6 months plus 6-9 months treatment pause) compared to integrated ImRs-SFT (12 months).

Main study parameters/endpoints: Primary outcome measure is PTSD symptom severity after 12 months. Secondary outcome measures are PD symptoms (SCID-5-PD), disability (WHODAS), quality of life (EQ-5D-5L) and health costs (Tic-P). At baseline (T0) and after 12 months (T4) clinical interviews (CAPS-5, SCID-5-PD dimensional score) and self-rating scales (PCL-5) will be used. After 3 (T1), 6 (T2), 9 (T3), and 18 months (follow-up), questionnaires only will be used. At baseline, candidate predictors will be measured including above mentioned cognitive, affective, relational

factors, and hormonal and epigenetic factors. In a subgroup, structural and functional MRI, with resting-state and an emotion processing (face recognition) will be performed.

Nature and extent of the burden and risks associated with participation and benefits: The burden and risks associated with participation in this study is reasonable. All patients will receive psychotherapy, which is considered to be the most effective treatment for PTSD and PD. There is evidence that all four conditions are therapeutic in patients with PTSD and PD and no evidence yet what condition is more effective. Total time of the six measurements is approximately 5 hours per patient for interviews and 5 hours for questionnaires (see table 3), which are partly part of the routine outcome measurements (ROM). Questionnaires can be filled in at home. On the one hand, extensive clinical interviews and self-rating scales can be felt as disturbing because of fatigue, taken time and emotional burden. On the other hand, patients may feel well recognized by the time taken by specialized clinicians for them. Assessors will be well-trained and work in close connection with the treatment teams. For predicting treatment response, biological and genetic measures are integrated in the study. These measurements include physical examination, blood samples and hair samples. The burden and risk associated with the baseline blood sample and hair sample is reasonable. For the subgroup of MRI research, participants will twice have a 60-minute MRI session during which they will perform affective-laden tasks during scanning. Functional MRI is a commonly used technique that is considered to be safe if you follow the safety instructions (e.g. no metal objects in the MRI room) and contraindications (e.g. no metal implants, not pregnant, no seriously claustrophobia). Lying in the scanner while performing affective-laden tasks in the scanner can occasionally give patients uncomfortable feelings of anxiety and distress by reliving of their traumatic experiences. During and after the scan procedure a debriefing will be held to cover this by the executor of the scan protocol. The principal investigators of this study have long experience with symptom provocation in the scanner (Thomaes: early traumatized PTSD patients with comorbid personality disorders: only 1 in 33 patients had a panic attack; OA van den Heuvel in patients with panic disorder, PTSD, OCD, Tourette, Parkinson, hypochondriasis: panic attacks were rare and not more frequently than healthy controls). In all, we consider the risk and burden associated with participation to be low.

There are no benefits for individual patients participating in this study. Benefits for PTSD patients as a whole are that this study will provide important information about profiling patients guiding optimal treatment choices base on individual prediction models in patients with both PTSD and personality problems. It will help to know what works for whom and personalize mental health care as short as possible and at the main time most effective. It will help to understand why (working mechanisms) what treatment works best for whom.

1. INTRODUCTION AND RATIONALE

Part A: Treatment outcome in PTSD with comorbid PD

Posttraumatic stress disorder (PTSD) develops in about 9-18% of trauma-exposed persons and involves considerable impairments in functioning (Breslau et al., 1998). This syndrome consists of re-experiencing of traumatic details (e.g. flashbacks and nightmares), avoidance of situations feelings and thoughts linking to the traumatic content, numbing and hyper-arousal, e.g. irritability, over-alertness symptoms (DSM-5). Evidence-based treatments for PTSD are trauma-focused cognitive behaviour therapy (TF-CBT) - including imaginary of prolonged exposure (IE/PE) and cognitive therapy (CT, i.e. without exposure element) - and eye movement desensitization and reprocessing (EMDR) (Balkom van et al., 2013, Bisson et al., 2013, Bisson et al., 2007). More recently, there is growing evidence of effectiveness of Imagination and Rescripting Therapy (ImRs) for PTSD, as a separate PTSD-treatment (Raabe et al., 2015). Effect sizes of TF-CBT compared to waitlist/usual care are generally large (standardised mean difference, SMD -1.62; 95% CI -2.03 to -1.21; 28 studies; n = 1256) (Bisson et al., 2013). Effect sizes of EMDR (SMD -1.17; 95% CI -2.04 to -0.30; 6 studies; n = 183 respectively) are similarly large, and although EMDR is less well studied than TF-CBT (Bisson et al., 2013), it is practised increasingly.

PTSD treatments are highly effective treatments in the majority of PTSD. However, at least 30-44% PTSD patients do not sufficiently respond to these treatments or drop out of treatment prematurely (Bradley et al., 2005, van Rooij et al., 2016). Even more PTSD patients are excluded from these therapies because of suicidality, self-destructive behaviour or other personality problems (Dorrepaal et al., 2014, Ehring et al., 2014). PTSD is highly comorbid with personality disorders (PD), around 60%, especially borderline personality disorder (BPD), and cluster C - avoidant, dependent and obsessive-compulsive - personality disorders (CPD) (Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ, 2008). This comorbidity is associated with more severe symptoms and worse functioning than PTSD or PD alone (Fría & Palma 2015). PDs are associated with significant personal and societal burden and tend to run a chronic course, at least in the first year (Gunderson et al., 2011, Bohus et al., 2013). Longer-term courses are more favourable: 88% of BPD patients achieved remission after 10 years, with the largest remission within 2 years (39.3%) and another part within 4 (22.3%) and 6 years (21.9%). Predictors of later remission were mainly childhood sexual abuse and a CPD (Zanarini et al., 2006).

It is not clear yet what treatment is most effective for those who suffer from both PTSD and PD. There is growing motivation in clinicians to offer PTSD treatments to PTSD patients with comorbid PD, because these treatments are highly effective, relatively short (weekly sessions, 3-6 months), and there is some evidence that with PTSD treatment, comorbid PD symptoms might resolve as

well (Feeny et al., 2002, Hembree et al., 2004, Clarke et al., 2008, Roberts et al., 2017, Kredlow et al., 2017). However, it may be more efficient to add a PD treatment at the same time. PTSD patients with (even mild) BPD symptoms were less likely to achieve good end-state functioning post-treatment (Feeny et al., 2002, Hembree et al., 2004) and dropped out twice as likely as PTSD patients without PD symptoms when receiving PTSD treatment alone (Zayfert et al., 2005). Worse end-state functioning may lead to a higher relapse rate, which is over 20% in anxiety disorders (Penninx et al., 2011). This might be so because emotion dysregulation, interpersonal malfunctioning, attachment or other personality problems are not sufficiently dealt with in PTSD treatments.

Psychotherapy is the most effective treatment for all personality disorders (Leichsenring & Leibing, 2003). In BPD the strongest evidence exists for dialectical behaviour therapy (DBT) with moderate to large effect sizes for affective instability (SMD -1.07 [95% CI -1.61 - -0.52]; n = 59) and anger (SMD -0.83 [95% CI -1.43 - -0.22]; n = 46, 2 RCTs), and moderate effect sizes in terms of impulsivity (SMD -0.61; 95% CI -1.14 to -0.09, n = 59), para-suicidality / self-harm (SMD -0.54, 95% CI -0.92 to -0.16; n = 110, 3 RCTs) and general mental health (SMD 0.65 [95% CI 0.07 - 1.24]; n = 74, 2 RCTs) (Stoffers et al., 2012). For comparisons between different comprehensive psychotherapies in BPD, statistically significant superiority was demonstrated for DBT over client-centered therapy (Kliem et al., 2010), and schema-focused therapy (SFT) over transference-focused therapy (Giesen-Bloo et al., 2006). In CPD (avoidant, dependent, obsessive compulsive PD), no effect differences are found between different theoretical references, such as SFT and psychodynamic therapy (Svartberg et al., 2004). DBT and SFT both have their roots in cognitive behavioral therapy and working mechanisms are based on improving emotion regulation, consisting of strategies aimed at modulating and adjusting unpleasant emotional experiences (John & Gross, 2004; Pedersen et al., 2014). Although DBT and SFT are both improve emotion regulation skills, there are major differences in the explanatory models and techniques used in both methods (Fassbinder et al., 2016): DBT directly focuses on the acquisition of emotion regulation skills (mindfulness, distress tolerance, emotion regulation, interpersonal effectiveness) and patients are encouraged to train these skills on a regular basis; SFT focuses primarily on the avoidance of emotions and dysfunctional meta-cognitive schemas about the meaning of emotions by working with limited re-parenting, empathic confrontation and experiential techniques like chair dialogs. As add-on to SFT, ImRs can be used specifically to focus on traumatic experiences (see above).

For PTSD with comorbid (B)PD an integrated DBT-PTSD-treatment is investigated in 3 RCTs (Steil et al., 2011, Bohus et al., 2013, Harned et al., 2014). The first study showed moderate to large effect sizes of DBT-PTSD compared to waiting list, in terms of overall BPD severity (SMD -0.74 [95%CI -1.47 - -0.01]), depression (SMD -1.06 [95% CI -1.84 - -0.29]), and anxiety (SMD -0.96 [95% CI -1.72 - -0.20])

(Steil et al., 2011). The second study indicated that DBT-PTSD resulted in a greater mean change than waiting list on PTSD symptoms (CAPS 33.16 vs. 2.08), but not on BPD symptoms (Bohus et al., 2013). Integrated DBT-PTSD-treatment was also compared to DBT-alone, and led to larger and more stable improvements in PTSD symptoms, doubled remission rate (80% vs. 40%), and decreased suicide rates (2.4 times less likely) and self-injury (1.5 times less likely), with moderate to large effect sizes for dissociation, trauma-related guilt cognitions, shame, anxiety, depression, and global functioning in completers (Harned et al., 2014). However, integrated PTSD-PD treatment is not yet directly compared to PTSD treatment alone.

In summary, there is growing motivation in clinicians to offer PTSD treatments to PTSD with comorbid disorders, because these treatments are highly effective, relatively short, and there is some evidence that with PTSD treatment, comorbid PD symptoms might resolve as well. However, it may be more efficient to add a PD treatment at the same time. Evidence-based treatments for personality disorders (PD), such as dialectical behaviour treatment (DBT) for BPD, and schema-focused treatment (SFT) for CPD are well established. These treatments are more intensive (twice a week for at least one year) than PTSD treatments. There is some evidence that integrated PTSD-PD treatment works twice as good as PD treatment alone, but integrated PTSD-PD treatment is not yet directly compared to PTSD treatment alone. This study will address this knowledge gap.

Hypotheses A: We hypothesize that in PTSD with comorbid PD it is more effective to provide integrated PTSD-PD-treatment compared to PTSD treatment alone, primarily in terms of response rate in PTSD symptoms. Secondarily, we hypothesize that PD symptoms, disability and quality of life will improve and cost-effectiveness will be better with integrated treatment.

A1. In patients with PTSD with BPD, integrated DBT-EMDR treatment results in a higher response rate than EMDR-only;

A2. In patients with PTSD and CPD, integrated SFT- ImRs treatment results in a higher response rate than ImRs -only.

Part B: Predictors of PTSD treatment

As yet, we cannot predict PTSD treatment outcome to individual patients. Certain candidate psychological predictors of treatment response are identified, at least on a group level. It was found that men with PTSD show worse treatment response than women (Tarrier et al., 2000, Karatzias et al., 2007). Younger age is associated with higher dropout (Rizvi et al., 2009). Type of trauma and severity of depressive symptoms were not found to be predictive of treatment

response (Minnen van et al., 2002, Ehlers et al., 2005, Ford & Kidd 1998, Rizvi et al., 2009, Forbes et al., 2002, Ronconi et al., 2015).

Cognitive candidate predictors of PTSD treatment outcome are: educational level/ intelligence (Ehlers et al., 2005, Rizvi et al., 2009), working memory (Nijdam et al., 2015, Wild et al., 2008) and cognitive control of emotions, i.e. emotion regulation. Emotion regulation problems and an extern locus of control are associated with worse response to PTSD treatment (Cloitre et al., 2004, Arntz et al., 2007, Bardeen et al., 2013, Böttche 2016), including high suicide risk (Tarrier et al., 2000) and alcohol intake (Forbes et al., 2002). Borderline personality symptoms (affective instability and impulsivity) are related to worse end-state functioning (Feeny et al., 2002, Hembree et al., 2004, Barnicot et al., 2011) and higher drop-out from PTSD treatment (Zayfert et al., 2005, McDonagh et al., 2005), but not if symptoms are relatively mild (Clarke et al., 2008, Walter et al., 2012, Thornback et al., 2014).

Affective factors found to be candidate predictors are related to hyper-arousal (anger/irritability, sleep problems/intrusions) or hypo-arousal (avoidance/numbing, dissociation), both key symptoms of PTSD. PTSD treatment is thought to be effective only when the patient's affective state is within a window of tolerance: arousal enough to be able to work with the traumatic material but not too much overwhelmed by emotions (hyper-arousal) or disconnected from it (hypo-arousal). Severity of PTSD – if measured with a clinical interview – is associated with worse treatment response (Karatzias et al., 2007, Taylor et al., 2003). Higher anger scores are related to worse response and higher dropout (Forbes et al., 2003, Rizvi et al., 2009, Lloyd et al., 2014). Severity of dissociative symptoms is associated with worse response to PTSD-treatment (Ford & Kidd 1998, Lanius et al., 2010, Resick et al., 2012, Cloitre et al., 2010, 2012, Wolf et al., 2016, Bae et al., 2016), although this might not be true for mild dissociative symptoms (Hagenaars et al., 2010; Minnen van et al., 2016). Severe dissociation is however <u>not</u> predictive for worse treatment outcome in integrated PTSD-PD treatment (Zlotnick et al., 1997, Chard et al., 2005, Dorrepaal et al., 2012, Cloitre et al., 2012, Kleindienst et al., 2016).

In addition, *relational variables,* such as quality of the therapeutic alliance (Cloitre et al., 2004, Barnicot et al., 2011), credibility of the therapy (Taylor et al., 2003, Alfonsson et al., 2016), attachment problems (Forbes et al., 2010), and especially a lack of social support are predictive of PTSD treatment response (Brewin et al., 2000; Yehuda et al., 2015).

Only few studies focused on *neurobiological predict*ors of treatment response. It is assumed that PSTD treatments mainly rely on extinction and memory re-consolidation processes (Careaga et al., 2016). Extinction, in short, is the attenuation or disappearance of a previously learned response when that response is not reinforced. The amygdala and ventral anterior cingulate cortex (ACC) are associated with extinction processes and there is evidence that these neurobiological correlates

normalize with treatment (Thomaes et al., 2014). Non-responders of TF-CBT showed greater amygdala and greater right ventral ACC activation in response to masked fearful faces before treatment compared to responders (Bryant et al., 2008a, Dickie et al., 2011, Schmidt et al., 2013, Rooij et al., 2016). A smaller ventral ACC volume and a smaller hippocampus volume were associated with poorer treatment response to TF-CBT (Bryant et al., 2008b, Rooij et al., 2015a). During viewing of negative picture before treatment, both decreased (Bryant et al., 2008a) as well as increased activity in the dorsal ACC – a region associated with emotion regulation - was found to be predictive of PTSD treatment response (Rooij et al., 2016), and this inconsistency of findings might point to heterogeneity in PTSD populations. In addition, *non-responders* showed an increased demand on the executive frontostriatal network during a response inhibition task (Falconer et al., 2013, Rooij et al., 2016) and increased left inferior parietal lobe activation, a region associated with attention processes (Rooij et al., 2015b). In research into BPD response inhibition tasks are also used as a paradigm (see Van Zuthphen et al., 2015 for a review), but not yet for predicting treatment outcome.

Recently, research criteria and neurobiological models are set to prioritize factors to study and use them in a personalized precision psychiatry (RDoc-criteria of the National Institute of Mental Health, NIMH https://www.nimh.nih.gov/research-priorities/rdoc/; Heuvel et al., 2016, Williams 2016). These models are close to the above-mentioned psychological candidate predictors of treatment outcome: 1) cognitive factors or 'cognitive' brain networks, 2) affective factors related to the 'limbic' brain networks, and 3) relational factors related to the 'positive affect' and social processing brain networks (see figure 1 below). Using these models will help to build a more dimensional instead of categorical psychiatric model that will be better applicable to treatment choice (Williams 2016).

Preliminary evidence exists on neurohormonal and associated (epi)genetic predictors of treatment outcome. A serotonin transporter gene promoter-region polymorphism (the LL 5HTTLPR genotype) was associated with greater responsiveness of PTSD to pharmacotherapy, while the S allele was associated with treatment non-response (Schmidt et al., 2013). Lower brain derived neurotrophic factor (BDNF) levels predicted a greater response to pharmacotherapy in PTSD (Schmidt et al., 2013). It is not clear yet if these factors might predict psychotherapy outcome as well. Cortisol levels and FKBP-5 predicted PTSD susceptibility and might be useful as a treatment outcome marker too (Schmidt et al., 2013, Galatzer-Levy et al., 2017). The same holds for oxytocin and the oxytocin receptor (OXTR) gene (Bandelow et al., 2016; 2017)

Unfortunately, all those candidate predictors are found on a group comparison level only, and in few studies with small and heterogeneous groups of patients. Therefore, they are not yet applicable on an individual level for treatment choice. Single predictors have not shown a large

explaining variance, in depressed or anxiety patients, while combining clinical with MRI data increased explained variance significantly (Serra-Blasco et al., 2016; Månsson et al., 2015; Ball et al., 2014; Doehrmann et al., 2013), using machine-learning models. Machine learning prediction models have also been made for pediatric obsessive-compulsive disorder (Lenhard et al., 2017) and in depressed patients that received electroconvulsive therapy (Redlich and al., 2016). We will explore if candidate predictors of PTSD treatment outcome can be used in a machine-learning model to predict treatment outcome on an individual basis.

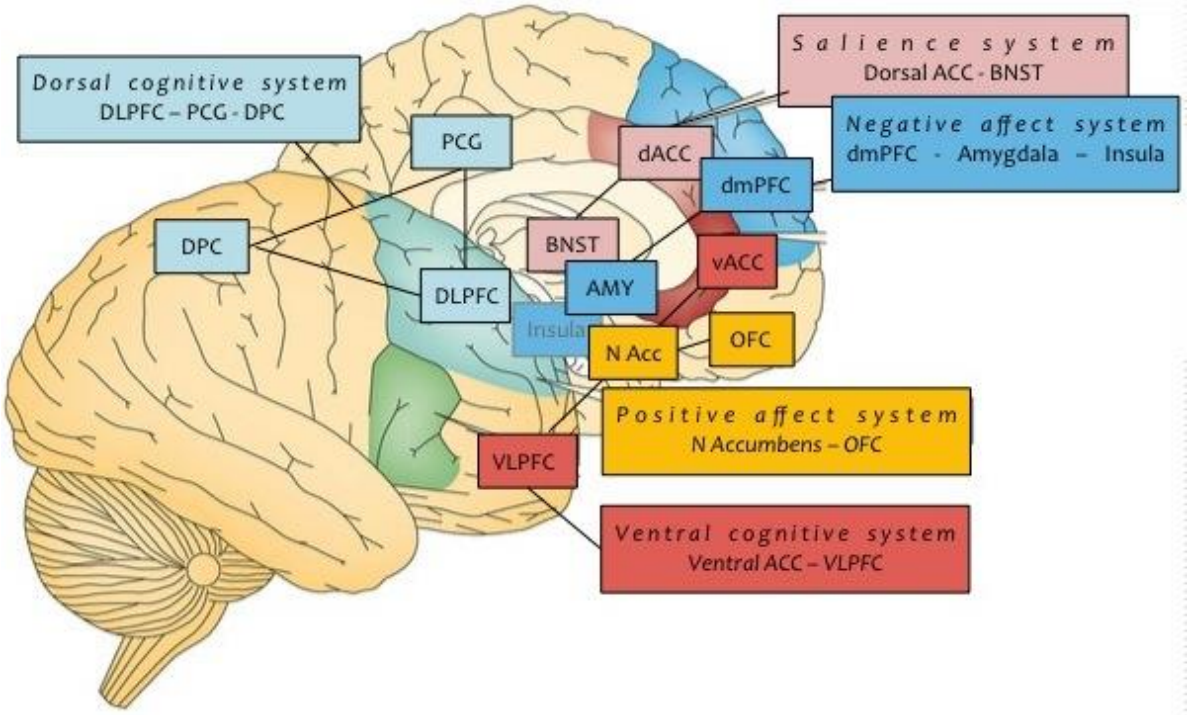

Figure 1. Brain networks as candidate predictors for treatment outcome in PTSD and PD

Hypotheses B: We hypothesize that non-response to PTSD-treatment and to integrated PTSD-PD treatment, can be individually predicted by a machine-learning model with:

B1. Psychological factors: Cognitive factors (educational level/IQ, working memory, emotion regulation), Affective factors (hyper-arousal: anger, sleep; hyper-arousal: dissociation), and Relational factors (therapeutic alliance, attachment, social support).

B2. Neurobiological factors: Neural factors (volumes ACC and hippocampus, activity and connectivity of salience and negative affect network and ventral and cognitive control network)), and Hormonal/ epigenetic factors (5-HTTLPR, BDNF, cortisol/FKBP5-methylation, oxytocin/OXTR).

2. OBJECTIVES

The primary objectives of this study are:

A. To investigate if in adult patients with PTSD and comorbid PD it is more effective to provide integrated PTSD-PD treatment compared to PTSD treatment alone in terms of response rate in PTSD symptoms:

A1. In patients with PTSD with BPD, integrated DBT-EMDR treatment results in a higher effect size and higher response rate than EMDR-only.

A2. In patients with PTSD and CPD, integrated SFT- ImRs treatment results in a higher effect size and higher response rate than ImRs -only.

B. To investigate individually prediction by a machine-learning model of PTSD treatment outcome in adult patients with comorbid PTSD and personality disorders (profiling), in order to improve treatment indication leading to more precise (personalized) and efficient treatments, with candidate predictors:

B1. Psychological factors: cognitive (educational level/IQ, working memory, emotion regulation), affective (hyper-arousal: anger, sleep; hyper-arousal: dissociation), and relational factors (therapeutic alliance, attachment, social support).

B2. Neurobiological factors: Neural factors (smaller ACC and hippocampus volume, increased right amygdala and ventral ACC activity and de/increased dorsal ACC activity), and Hormonal/ epigenetic factors (5-HTTLPR, BDNF, cortisol/FKBP5-methylation, oxytocin/OXTR).

3. STUDY DESIGN

The design of this study consists of two – connected - RCTs comparing PTSD-treatment to integrated PTSD-PD treatment in patients with PTSD and comorbid PD in a specialized treatment setting (figure 2):

A1. EMDR versus integrated DBT-EMDR, and

A2. ImRs versus integrated SFT- ImRs.

Assessment points are: baseline (T0), after 3 months (T1), after trauma treatment has finished, around 6 months (T2), 3 months after T2 (T3), after 12 months (T4) and at 18 months (follow-up, FU).

PTSD treatments specifically address the troubling memories of the traumatic event and the personal meaning of the event and consist of 12 to 18 sessions in maximum 6 months, and are:

- EMDR (Eye Movement Desensitization and Reprocessing)

EMDR was developed in 1987 by Shapiro (De Jongh & Ten Broeke, 1998). In EMDR the therapist induces a bilateral stimulation once the client has focused the attention on a disturbing image or memory related to the traumatic experience. The bilateral stimulation is induced by the movement of the therapist's fingers in front of the patients face from the left to the right with the instruction for the client to follow this movement of the hand with the eyes. Attention is drawn to what traumatic memory and the dysfunctional thoughts about it are currently doing with the patient and not to what the patient was thinking during the traumatic experience.

- ImRs (Imagination and Rescripting Therapy) (Arntz et al., 2007, Raabe et al., 2015).

In ImRs, the patient imagines the (onset of a) traumatic experience and subsequently changes the original course of events by imagining different interventions and outcomes, thereby allowing for the change of original schematic representations and cognitions (Hackmann et al., 2011). ImRs implies changing the traumatic imagery in fantasy, to produce a more favourable outcome (without denying the trauma), imagining having control over the situation and being able to act according to one's needs, to express one's feelings and action tendencies. ImRs was hypothesized to alleviate PTSD symptoms as well as change trauma-related beliefs and schemas (e.g. powerlessness, victimization, and inherent badness). It is suggested that ImRs might be more effective in patients with emotions and cognitions like anger, irrational guilt, shame disgust and/or self-contempt (Arntz et al., 2007).

Integrated PTSD-PD treatment consist of a PTSD treatment interwoven in a PD treatment that takes at least twice sessions per week, for the duration of one year:

- DBT (Dialectical Behavior Treatment), a manualized outpatient cognitive–behavioral treatment with two components: (a) weekly individual therapy and (b) weekly group skills training. Individual

sessions focus on a hierarchy of target behaviors, which the patient tracks on a daily basis with diary cards. Behavioral analyses of the pattern and chain of thoughts, emotions, and events take place routinely to help the patient identify triggers and alternative strategies for coping. Change strategies such as problem solving and reinforcement techniques are used in combination with acceptance and validation of the patient's experience. Group skills' training is used to help patients develop less self-destructive and more adaptive means of coping with intolerable affects. These skills include awareness of emotions and reactions, interpersonal effectiveness, emotion regulation, and distress tolerance. Skills are then integrated into the individual treatment in problem situations, e.g. suicidal urges (Linehan, 1993).

- SFT (schema focused treatment) is a form of psychotherapy integrating cognitive therapy, behavior therapy, object relations, and gestalt therapy into one unified, systematic approach to treatment. The focus in SFT is on changing maladaptive schemes that patients develop early in life and thereby improve emotion regulation skills. Change is achieved through a range of behavioral, cognitive, and experiential techniques that focus on (1) the therapeutic relationship, (2) daily life outside therapy (also through homework assignments), and (3) past (traumatic) experiences (Young et al., 2003). Psychomotor therapy (PMT) is part of the SFT treatment protocol.

In the Sinai Centrum, 2 "Zorgpaden" will be implemented in Fall2017:
"Zorgpad 1" with EMDR or ImRs (3-6 months) and Zorgpad 2" with EMDR-DBT or ImRs -SFT (9-12 months). Therapists need to be "adherent-to-the model", which will be ascertained by regular supervision with audiovisual recordings based on the different theoretical psychotherapeutic principles and therapies are delivered by protocol. At this moment, there is no clear scientific evidence and criteria are not explicitly defined for the one or the other treatment, except that patients with PTSD without comorbid PD have to be indicated for "Zorgpad" 1.

Use of co-intervention: Patients may continue taking medication for PTSD throughout the study. Patients who started with new medication for PTSD within 1 month prior to the initial screening will be excluded from participation. No other psychological or new pharmacological therapy is allowed during treatment. Medication use is monitored during the study.

Escape medication/treatment: Participants might start taking medication or another form of treatment/therapy in case of acute crisis during the study. The use of these medications or crisis intervention during the study as co-intervention will not lead to exclusion from the study, but will be monitored, documented, and reported.

Further treatment: After completion of the EMDR or ImRs a first follow-up assessment will be completed and the therapist will see the patient for an evaluation. If more treatment is acutely needed, a clinical evaluation is done and the indication staff will decide what treatment to offer to the patient. The kind, intensity and frequency of this further treatment will be monitored,

documented and reported. All patients in Zorgpad 1 are allowed to start SFT or DBT after T4 (i.e. 6 months after completing Zorgpad 1).

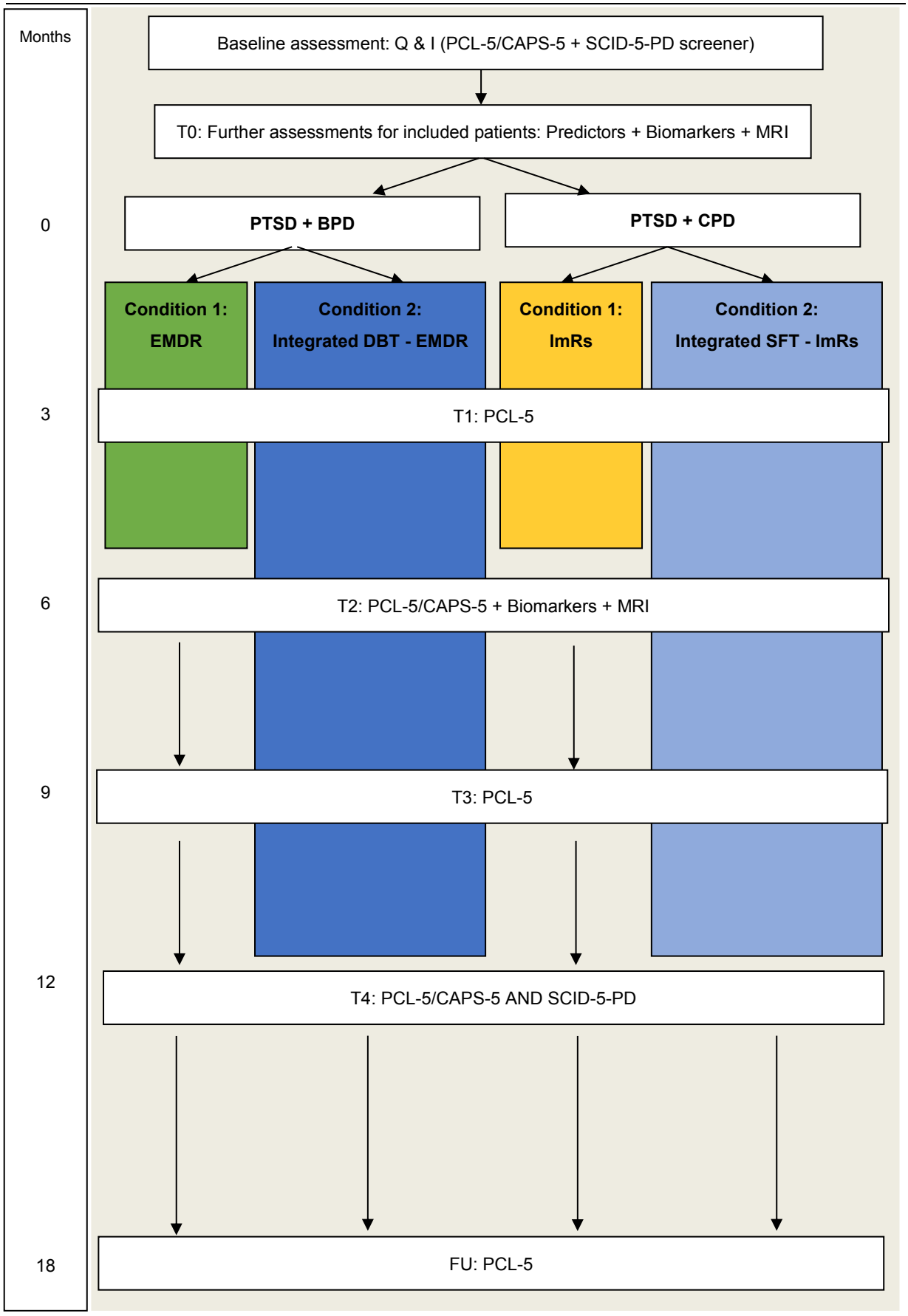

Figure 2. Flow chart for two connected randomized controlled trials (RCTs) for patients with PTSD and borderline personality disorders (BPD) resp. with PTSD and cluster C personality disorders (CPD)

4. STUDY POPULATION

4.1 Population

The study population consists of all patients between 18-65 years old, referred to the SC with comorbid PTSD and PD, who are willing to participate in the study (informed consent); N = 320 patients (see 4.4), of which sub-group of 80 patients (N = 40 Condition 1 + 40 Condition 2) will participate in the MRI study (before and after treatment). For baseline MRI comparison, extra 40 healthy controls, matched on age, gender and educational level, will be recruited also for the MRI study via advertisements in local newspapers and through hersenonderzoek.nl. In total, 360 persons will be included in this study.

A pilot episode will be introduced (September – December 2017) to test the feasibility of the study and inclusion rate. Feasibility is enhanced by the opportunity to build on the established expertise of the academic research group in Arkin – Research and VUmc in conducting effect studies, longitudinal and neurobiological studies.

4.2 Inclusion criteria

In order to be eligible for study participation as a patient, he/she has to be at T0:

- Diagnosed with PTSD (309.81) , and
- Diagnosed with a personality disorder (301.81 borderline, 301.4 obsessive-compulsive, 301.6 dependent, 301.82 avoidant), or at least 4 PD symptoms of those PDs.

To be eligible for the study, both patients and healthy controls have to:

- Be aged between 18 and 65 years
- Give written informed consent
- Speak / understand Dutch sufficiently

4.3 Exclusion criteria

A patient who meets any of following criteria will be excluded from participation in this study:

- Current psychosis
- Comorbidity interfering with treatment or randomisation (severe outward aggression, antisocial PD, treatment interfering addiction or eating disorders, somatic problems)
- Primary diagnosis of paranoid, schizoid, schizotypal, narcissistic, histrionic or antisocial PD
- Mental retardation

For the healthy controls, current psychiatric diagnosis is an exclusion criterion.

For the subgroup of patients and controls that also undergo MRI examination more exclusion criteria are: Pregnancy; Metal implants (such as pacemakers, etc.); Somatic disorders interfering with brain functioning; Claustrophobia; Other psychopharmaca than at-least-3-months stabile dose SSRI or low-dose benzodiazepines

4.4 Sample size calculation

A power calculation was made based on Twisk (2007). We assume that PTSD treatment (EMDR or ImRs) have a small effect size (< 0.5) in the complex patient group with PTSD and comorbid CPD/BPD, while the integrated treatment will show double effect sizes (1.0) (Harned et al., 2014). With a minimal clinical relevant difference of a 0.5SD on the CAPS-5, and the assumptions of a SD of 20.0, an intra-person correlation coefficient of 0.7, 5 follow-up measurements, the needed number to include is 64 persons per condition to reach for 80% power. Expecting a drop-out rate of 25%, we will include 80 persons per arm, or for 4 arms in total 320 persons.

In 2016, approximately 950 new patients were referred to the SC (Amstelveen). From these patients, ca. 450 had PTSD. From these PTSD patients, 168 had a comorbid PD and 188 more were not assessed for personality traits ("Uitgestelde diagnose"). We expect that introducing the assessment of axis II assessments with this study will result in an estimated 300 patients with PTSD and PD per year, and after 33% refusals or exclusions, in an estimated 200 patients possible to include per year. To be sure to include enough patients, we will need to include more patients from another site of the Sinai Center, i.e. Amersfoort (400 patients, from which 216 PTSD patients, from which an estimated 100 PTSD + PD patients), and extend the inclusion period.

From these 320 patients, 80 will be asked for additional MRI, next to 40 healthy controls (Total sample size = 360). An estimated 40 patients will be available for a second MRI after 6 months (total of 160 scan sessions).

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Primary outcome parameters

- Severity of PTSD (DSM-5) as measured with:
  - CAPS-5 (Clinician Administered PTSD Scale, Weathers et al., 2014, Boeschoten et al., 2014). The first psychometric evaluation of the CAPS-5 showed good reliability, convergent and divergent validity (Weathers et al., 2017). Severity of PTSD is measured on a continuous scale on the CAPS-5. All 20 symptoms of PTSD from the DSM-5 are assigned a severity score of 0-4. These 20 scores are then summed to calculate total PTSD symptom severity.

5.1.2 Secondary outcome parameters

- Presence of PTSD (DSM-5) as measured with: CAPS-5 (Clinician Administered PTSD Scale, Weathers et al., 2014, Boeschoten et al., 2014)
- PCL-5 (PTSD Checklist for DSM-5; Weathers et al., 2013; Boeschoten et al., 2014; Bovin et al., 2016).
- Presence and severity of personality disorders as measured with the SCID-5-PD (Structured Interview for DSM-5 Personality Disorders; First et al 2016) to assess presence and severity (dimensional score) of the DSM-5 personality disorders
- Demographic questionnaire
- Outcome Questionnaire -45 (OQ-45), with 25 items on psychiatric symptoms and 20 on interpersonal, occupational and social functioning (de Jong et al., 2008)
- BDI (Beck Depression Inventory, Beck et al., 1988)
- AUDIT (Alcohol Use Disorders Identification Test, Babor et al., 2001) to assess alcohol and drug abuse
- SCID-5-S (American Psychiatric Association, 2017).
- WHODAS 2.0 (World Health Organization Disability Assessment Schedule, Ustun et al 2010)
- EQ-5D-5L (http://www.euroqol.org/eq-5d-products/eq-5d-5l.html) to measure quality-adjusted life year (QALY)

- Tic-P (Trimbos/iMTA questionnaire for costs associated with psychiatric illness) for health care consumption (Hakkaart-van Roijen et al., 2002)
- NSSI screening; Screeningsvragenlijst opzettelijk zelfverwondend gedrag (Baetens & Claes, 2014) to assess selfinjury.

5.1.3 Biological predictors (see table 2):

- Biological parameters
    - Body measures: Weight, height, blood pressure
    - HPA axis (cortisol): Hair sample
    - Biomarkers: Fasting blood sample (BDNF, FKBP-5) & Full blood
- MRI session in subsample (60 min)
    - 3 Tesla-MRI (GE, VUmc): functional MRI with a face recognition , Structural MRI, Resting state MRI, DTI. In between scans a visual analogue scale (VAS) will be applied to assess distress during the scan session.

5.1.4 Psychological predictors

- Trauma exposure as measured with:
    - CTQ (Child Trauma Questionnaire, Bernstein et al., 2003), 28-item questionnaire to check self-reported child trauma experiences, with 5 subscales: physical, emotional and sexual abuse, physical and emotional neglect (5-point Likert scale), and 3-item scale to detect under-reporting
    - LEC-5 (Life Events Questionnaire, Weathers et al., 2013).
- Cognitive factors
    - DERS (Difficulties in Emotion Regulation Scale; Gratz & Roemer, 2004; Lavender et al., 2015) a 36-item self-report measure that assesses state levels of emotion dysregulation across six domains: non-acceptance of negative emotions, difficulties engaging in goal-directed behaviors when distressed, difficulties controlling impulsive behaviors when distressed, limited access to effective emotion regulation strategies, lack of emotional awareness, lack of emotional clarity (5-point Likert scale).
    -
    - PAI-BOR (Personality Assessment Inventory- Borderline features scale, Distel, de Moor & Boomsma, 2009) to measure severity of borderline

personality disorder symptoms. The PAI-BOR consists of 24 items rated on a 4-points Likert scale. It measures four domains of BPS, affective instability, identity problems, negative relations and self harm.

- Stop/signal task as a measure for interference/working memory.

o Affective factors (Hyper-arousal: anger, sleep; hypo-arousal: dissociation)

- STAS (State-Trait Anger Scale, Spielberger et al., 1994) on trait and state anger with 10 items per scale using a 4-points scale.
- PSQI (Pittsburg Sleep Quality Index, Buysse et al., 1989) with 4 items on sleep time and 6 associated items (4-points scale).
- DES-II (Dissociative Experiences Scale; Bernstein & Putnam 1986), 28-items to asses dissociative symptoms.

o Relational factors (therapeutic alliance, attachment, social support) as measured with:

- WAI (Working Alliance Inventory, Horvath & Greenberg, 1992; in Dutch: Werk Alliantie Vragenlijst, WAV, Vertommen & Vervaeke, 1990), 12-items
- RSQ (Relationship Scale Questionnaire, Griffin & Bartholomew, 1994) contains 30 statements on attachment rated on a 5-point scale
- CPI (Close Person Inventory, Stansfeld & Marmot 1992) to assess social support.
- Therapists will be asked to rate to which extent they believe in the effectiveness of the protocol, on a scale of 1 to 10.

Table 1: Overview of measurements: interviews and questionnaires

MEASUREMENTS				**To**	**T1**	**T2**	**T3**	**T4**	**FU**
TIME POINTS (months)				**0**	**3**	**6&**	**9**	**12**	**18**
SCREENING	**ROM Questionnaires**	**Items**							
Psychiatric symptoms	OQ-45.2 (1996)	45	SR	X*	X	X	X	X	X
PTSD symptoms	PCL-5 1.1 (2014)	22	SR	X*	X	X	X	X	X
PD symptoms	SCID-5-PD screener	119	SR	X					
Axis I disorders	SCID-5-S screener	??		X*					
INTERVIEWS DAY 1	**Semi-structured interviews**	**Duration**	**Type**						
PTSD	CAPS-5 1.2 (2015)	45 min	INT	X		X		X	
Axis I-disorders	SCID-5-S	45 min	INT	X*#				X	
Personality disorders	SCID-5-PD	120 min	INT	X#				X	
QUESTIONAIRES DAY1	**Additional questionnaires**	**Items**							
Demographics	Demographic questionnaire PROSPER (2017)	30	INT	X*					
Life events	LEC-5 1.1 (2014)	17	SR	X*					
Child trauma	CTQ (NESDA 2004)	25	SR	X					
Emotion regulation	DERS NL (2004)	36	SR	X		X		X	
Anger	STAS NL (ZAV 1982)	10	SR	X		X		X	
Sleep	PSQI NL (1989)	10	SR	X		X		X	
Dissociation	DES-II (1986)	28	SR	X		X		X	
Depression severity	BDI-II (2002)	21	SR	X		X		X	
Alcohol / drugs	AUDIT (MATE-nl 2.1 2010)	10	SR	X		X		X	
Self harm behaviour	NSSI screening (NL versie 2014)	7	SR	X	X	X	X	X	X
Borderline personality symptoms	PAI-BOR (2009)	24	SR	X		X			X
DAY2	**Additional Questionnaires**								
Therapeutic alliance	WAV (1990)	12	SR		X	X			
Attachment	RSQ (1994)	30	SR	X		X		X	
Social support	CPI (NESDA 2004)	4	SR	X		X		X	
General functioning	WHODAS 2.0 (2014)	12	SR	X		X		X	X
Quality of live	EQ-5D-5L 2 (2010)	9	SR	X		X		X	X
Health care consumption	Tic-P (2012)	32	SR	X		X		X	X

AUDIT = Alcohol Use Disorders Identification Test; BDI = Beck Depression Inventory;; CPI = Close Person Inventory; CTQ = Child Trauma Questionnaire; DES-II = Dissociative Experiences Scale; INT = interview; LEC-5 = Life Events Checklist; SCID-5-S; OQ-45 = Outcome Questionnaire 45; PCL-5 = PTSD Checklist for DSM-5; PSQI = Pittsburg Sleep Quality Index; ROM = Routine Outcome Measurement; RSQ = Relationship Scale Questionnaire; DERS = Difficulties in Emotion Regulation Scale; SR = self-report questionnaire; SCID-5-PD =

Structured Clinical Interview for DSM-5 Personality disorders; STAS = State Trait Anger Scale; Tic-P = Trimbos/iMTA questionnaire for costs associated with psychiatric illness; WAI = Working Alliance Inventory, WHODAS = World Health Organization Disability Assessment Schedule 2.0.; NSSI = Non Suicidal Self-Injury screener; PAI-BOR: Personality Assessment Inventory- Borderline features scale.

***** Healthy controls will only fill out these questionnaires and interviews

[&] Timing of the T2 measurement will be directly after trauma treatment, around 6 months

[#] The SCID-5-P at T0 is part of the regular intake procedure at the Sinai Centre

Table 2: Overview of add-on cognitive task, biological measurements, including MRI

MEASUREMENTS		**DURATION**	T0	T1	T2	T3	T4	FU
in months			**0**	**3**	**6&**	**9***	**12**	18
COGNITIVE TASKS AT DAY 2		**10 min**						
Working memory	N-back	10	X*****					
Interference	Stop/Signal task	15	X*****					
PHYSICAL EXAMINATION AT DAY 2		**30 min**						
Body measures	Weight, height	10	X					
Blood pressure	Systolic and diastolic	5	X					
HPA axis (Hair)	Hair sample (cortisol)	5	X		X			
Biomarkers	Fasting blood sample (5-HTTLPR, BDNF, FKBP5, oxytocin/OXTR) & Full blood	10	X		X			
MRI SESSION IN SUBSAMPLE WITHIN 2 WEEKS		**60 min**						
Functional MRI	Face recognition task	15	X		X			
Structural MRI		7	X		X			
Resting state MRI		10	X		X			
DTI		10	X		X			

DTI = Diffusion Tensor Imaging, MRI = Magnetic Resonance Imaging.

[&] Timing of the T2 measurement will be directly after trauma treatment, around 6 months

[*] Timing of the T3 measurement will be 3 months after T2, around 9 months

Table 3: Overview of duration of measurements (in minutes)

	T0	T1	T2	T3	T4	Follow-up
Interviews	45	-	45	-	195	-
Questionnaires	86	15	83	15	83	27
n-back	10	-	-	-	-	-
TOTAL	**141 (ca. 2.5 hrs)**	**15**	**128 (ca. 2 hrs)**	**15**	**278 (ca. 4,5 hrs)**	**27**
Blood/hair	30	-	30	-	-	-
MRI	90	-	90	-	-	-
TOTAL for subgroup with MRI/blood/hair	**261 (ca. 4 hrs)**	**15**	**218 (ca. 3,5 hrs)**	**15**	**278 (ca. 4,5 hrs)**	**27**

5.2 Randomisation, blinding and treatment allocation

5.2.1 Randomization

An independent central research assistant will randomize participants to condition after checking all in- and exclusion criteria. Randomization will be based on block randomization (n=4 per block) per site, to guarantee a balance between conditions per site and over time. For both RCTs there will be a separate randomization procedure depending on comorbid PD diagnosis:

A1. If PTSD + BPD: EMDR vs. integrated DBT-EMDR

A2. If PTSD + CPD: ImRs vs. integrated SFT- ImRs.

5.2.2 Unblinding Procedure

Blinding of participants and therapists to condition is not possible as it will be clear to both therapists and patients which treatment is given.

5.3 Study procedures

The study will lead to separate although integrated research projects for 3 PhDs.

A1: Is EMDR treatment more effective compared to integrated DBT-EMDR in patients with PTSD with comorbid BPD?

1. Systematic review and meta-analysis: do personality or dissociative symptoms predict effectiveness of PTSD treatment?
2. Do patients in the present study show higher response rate and effect sizes in integrated DBT-EMDR-treatment compared to EMDR-treatment alone after 12 months?
3. Is DBT-EMDR-treatment more effective as compared to EMDR-treatment alone in terms of PD symptoms, general psychiatric symptoms, disability, quality of life and health costs?
4. Do psychological (cognitive, affective, relational) factors predict (integrated DBT-) EMDR-treatment outcome?

A2: Is ImRs more effective compared to integrated SFT- ImRs in patients with PTSD with comorbid CPD?

1. Systematic review and meta-analysis: do personality or dissociative symptoms predict effectiveness of PTSD treatment?

2. Do patients in the present study show higher response rate and effect sizes in integrated SFT- ImRs -treatment compared to ImRs -treatment alone after 6-12-18 months?
3. Is SFT- ImRs -treatment more effective as compared to ImRs -treatment alone in terms of PD symptoms, general psychiatric symptoms, disability, quality of life and health costs?
4. Do psychological (cognitive, affective, relational) factors predict (integrated SFT-) ImRs -treatment outcome?

B: Predictors of PTSD-treatment

1. Literature review: what is known on working mechanisms of PTSD treatment and do neurobiological findings predict PTSD treatment outcome?
2. Are PTSD treatments in this PTSD + PD population mainly working on increasing extinction of fear responses? Is this associated with decreasing salience, negative affect and cognitive control network activity and connectivity?
3. Do biomarkers (ACC volume, amygdala and ventral ACC and dorsal ACC activity, and/or hormonal/epigenetic factors (5-HTTLPR, BDNF, cortisol/FKBP5-methylation, oxytocin/OXTR) individually predict treatment outcome of PTSD treatment?

Timing of assessments

Baseline (To) visit

All patients coming to the Sinai Center are asked to fill in the ROM questionnaires before the intake as part of standard care (OQ-45, LEC-5/PCL-5, SCID-5-PD screener, see Table 1). As part of the standard intake procedure at the Sinai Centre, patients who score positively on the SCID-5-PD screener will be interviewed with the M.I.N.I.-plus and the SCID-5-PD. Patients with potential eligibility based on the in- and exclusion criteria described earlier receive the study information folder from the psychologist who performed the intake with them . If a patient is interested and gives their consent, the intaker informs the researchers to contact the patient. One of the researchers will explain the study to the possible participant and provide the information folders. After a consideration period of at least one week, they will be asked whether they want to take part in the research.

At To/Day 1, the study- intaker will explain the study information once more. If informed consent is obtained, in- and exclusion criteria will again be checked to assess the patient's potential eligibility for participation (Dutch language, , LEC-5/PCL-5, SCID-5-PD screener) and if the patient is included, the CAPS-5 will be performed.

After the interview, the patients receive an online code to fill in additional questionnaires online at the center or at home, if the patient has access to the internet (see Table 1). Total duration of the measurements of To/Day 1 will be ca. two hours (see Table 3).
At To/Day 2, patients are invited for the physical examination (weight and height to calculate Body Mass Index (BMI), blood pressure, hair sample by a research assistant and fasting blood sample as well as questions on cigarette smoking, alcohol and coffee consumption, medication and drug use) and they will be asked to perform a working memory task (N-back-task) outside the scanner and to fill in the last set of questionnaires (see Table 1) either at the Sinai Center or online at home. Total duration of the measurements of To/Day 2 will be ca. 40 minutes (see Table 3).
Blood samples will be collected in 3 x 6ml tubes and the frozen samples will be stored at -80°C for intended future assaying of inflammatory markers (see Coelho et al., 2014), neuropeptides (such as oxytocin, 5HT), and epigenetics (such as FKBP5-methylation, OXTR- & 5HTTLPR-genes). The tubes will be stored without personal data linked to it, and they will only be marked with a subject number as described in section 9.1. below. Cortisol level (HPA-indicator) will be assessed in hair. This sample can be collected non-invasively by cutting a 1-cm distal to the scalp (1 month's exposure) sample of hair (Russell et al., 2012). All samples will be stored for 15 years (according to Archiefwet 1995).

In a subgroup: MRI session

Exclusion criteria for MRI research will be checked (metal implants, pregnancy, somatic disorders interfering with brain functioning, other (psycho-)pharmaca than at-least-3-months stabile dose SSRI or low-dose benzodiazepines, claustrophobia). A separate visit for MR scanning will be planned within 2 weeks of To, before the start of treatment, without causing a delay in treatment start. MRI sessions take at maximum 60 minutes (30-min functional MRI with a face recognition, and a suppression vs. reappraisal task, 5-min structural MRI, 8-min resting state MRI; and 8-min DTI) plus 30 min preparation. Next to patients, 40 healthy control persons, matched for age, gender, and education, will be asked to participate in one MRI session (no repeat MRI). These healthy control persons will be recruited via advertisements in local papers.

T1 , T3 and FU

Patients do not have to come to the study center for T1, T3 and FU and can fill in the questionnaires via a login code at home if they have access to the internet (see Table 1.). Child

trauma and life events questionnaires are only done at baseline (CTQ, LEC-5). Total duration of these measurements (T1, T3 and FU) will be between 15 and 30 minutes (see Table 3).

T2 visit

From all participants whose blood and hair was collected at baseline, blood and hair will be collected at T2 as well (duration 30 minutes). All participants who participated in the fMRI study at baseline will have their second MRI at T2. (duration 90 minutes). At T2, the CAPS-5 will also be conducted and participants will fill out the same questionnaires as at T0, except for the CTQ and LEC-5. Total duration of these measurements of will be ca. 2 hours (see Table 3).

Extra contact moment

For participants in the trauma-treatment only group, there will be an extra moment of contact 3 months after T3, with a short reminder about the following measurements and attention for the wellbeing of the client.

T4 visit

This is the same as T0, except for the informed consent procedure and except for the N-back task and physical examination and trauma questionnaires that will be done at T0 only (CTQ, LEC-5). Total duration of these measurements will be 4,5 hours (see Table 3).

Treatment visits

These will be scheduled as usual. For durations of specific treatments see 3.

5.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so, without any consequences. The principal investigators can decide to withdraw a subject from the study for urgent medical reasons.

Reasons to terminate a patient's participation include:

- The patient withdraws her/his consent
- The nature of the patient's treatment is changed to coercive treatment (based on judicial ruling)

- The investigator considers a patient's continued participation in the study to be unjustifiable on medical or psychiatric grounds (i.e., because of side effects or unusual risks of the treatments).

If an individual patient is discontinued due to one of the above-mentioned reasons, this patient will be treated as usual in normal daily practice. The treating physician remains the primary caregiver during the study and will be contacted at the baseline visit and updated throughout the study. The treating physician will contact the study team in cases of important changes and will be responsible to apply for legal custody if appropriate.

All patients leaving the study early, regardless of the reason, will be requested to return to the site for an "early termination" visit to finalize participation. If the patient is not willing to complete all measures, priority will be given to the PCL-5 and OQ-45.

There are no consequences if a patient also refuses this.

5.5 Replacement of individual subjects after withdrawal

Not applicable.

5.6 Follow-up of subjects withdrawn from treatment

Patients who drop-out out of (part of) the treatment remain in the study and will still be asked to complete the follow-up measures. Priority will be given to the online assessment with the PCL-5 and OQ-45.

5.7 Premature termination of the study

There are no criteria, other than mentioned under section 6, for a premature termination of the study.

6. SAFETY REPORTING

6.1 Section 10 WMO event

This study will be performed according to the Declaration of Helsinki (64th WMA general assembly; October 2013) and the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP). The definitions of adverse events and serious adverse events described in these guidelines will be used for the present study.
In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited Ethical Review Board (ERB) if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited ERB, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.
Subjects are entitled to get information and to ask questions, before, during and after being part of the research to th researchers. Apart from the provided information, there is an independent expert involved. He can provide information for patients, but is not involved in this study himself. In this study the independent expert is a psychiatrist working in one of the companies within Arkin, named Mentrum. He is not involved in the Sinai Center.

6.2 AEs, SAEs and SUSARs

6.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the study. All adverse events reported by the subject or observed by the investigator or his staff will be recorded.

6.2.2. Serious adverse events (SAEs)

We do not expect any serious adverse event (i.e. any untoward medical occurrence or effect that results in death; is life threatening (at the time of the event); requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an

intervention to prevent one of the outcomes listed above). The main reason for this is that all four treatments given in the RCTs are evidence-based for at least one of the disorders the patients suffer from (PTSD and PD) and patients who will be assigned to the PTSD-treatment only can given PD-treatment as well after T4 (after 6-12 months) within the research design.

Suicidality or self-injurious behaviour is very common in the study population included for this study. It is also known that starting a new treatment, such as EMDR or DBT could increase symptoms in the beginning, which can develop into suicidal behaviour. SAE's which will occur during the treatment and for which medical care is needed, will be reported to the accredited METC. To monitor the SAE's, patients will be asked to fill in a self-injury questionnaire (Opzettelijk zelfverwondend gedrag, *Baetens & Claes 2014 based on* The Brief Non-Suicidal Self-Injury Assessment Tool (BNSSI-AT) *van Janis Whitlock en Amanda Purington (2013)*) at the regular assessments. In case of SAE's for which medical care is needed, in between the assessments, therapists will report these incidents to the researchers at the weekly consultations, whom will report these to the accredited METC. The sponsor will report SAEs to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

6.2.3. Suspected unexpected serious adverse reactions (SUSARs)

This part is not applicable to the presented study.

6.3 Annual safety report

Not applicable (no pharmacological or other agents involved in this study).

6.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs will be reported till the end of the study within the Netherlands, as defined in the protocol.

6.5 Data Safety Monitoring Board

It has been decided not to engage a Data Safety Monitoring Board in this study, no pharmacological or other agents are involved in this study. In addition, no interim analyses are planned. In the investigator's opinion, implementation of a DSMB will not have sufficient added value for the current study.

7. STATISTICAL ANALYSIS

Descriptive statistics of continuous outcomes will be presented by disorder category and include sample size, mean, median, standard deviation, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented by disorder category. Statistical analyses will be performed using SPSS for Windows (version 20) or in R (https://www.r-project.org).

7.1 Primary study parameters

For population description, the CAPS-5, M.I.N.I.-plus, SCID-5-PD, will be used in addition to the CTQ, LEC-5, DERS, PAI-BOR, STAS, PSQI, DES-II, WAV, RSQ, CPI, BDI, AUDIT, WHODAS, EQ-5D-5L, and Tic-P will be used (see Table 1). The subgroup of patients that underwent MRI will be compared to the rest of the group to test for pretreatment differences in PTSD severity and type/severity of PD.

The primary analysis in the RCTs will be improvement of PTSD symptoms at 3 time points. This primary analysis will include trauma symptom scores at T0, T2 and T4 (CAPS-5, severity score) in a repeated measurements model, a linear mixed model for repeated measurements including at least time points, treatment group, the interaction between time point and treatment, sex, age and severity as fixed factors, baseline score as covariate and subject as random intercept factor. An cAR(1) structure will be used to model the residual covariance matrix. Responders will be defined as participants with a posttest score at least 1 SD below the pretest score (based on Jacobsen and Truax, 1991).

Secondary analyses will examine whether hormonal and epigenetic factors (5-HTTLPR, BDNF, cortisol/FKBP5-methylation, oxytocin/OXTR) mediate the treatment effects. Mediation analyses will include levels of the aforementioned variables on T0 and T2 to estimate the direct and indirect paths of casual treatment on the primary and secondary study parameters, through the proposed mediators.

For individual prediction analyses, machine learning techniques (in R: supervised and unsupervised techniques, e.g. the random forest model method) will be applied to separate treatment responders from non-responders based on clinical and neurobiological candidate predictors and in order to define the predictors contributing most to classification accuracy, calculating sensitivity, specificity, and positive and negative likelihood ratios from the prediction model (Ball et al., 2014). Candidate predictors that will be used are:

- Psychological factors: Cognitive factors (educational level/IQ, working memory, emotion regulation), Affective factors (hyperarousal: anger, sleep; hyperarousal: dissociation), and Relational factors (therapeutic alliance, attachment, social support);
- Neurobiological factors: Neural factors (smaller ACC and hippocampus volume, increased right amygdala and ventral ACC activity and de/increased dorsal ACC activity), and Hormonal/ epigenetic factors (5-HTTLPR, BDNF, cortisol/FKBP5-methylation, oxytocin/OXTR).

Questions that will be answered with machine learning in this study are:

1. Does brain activity predict treatment outcome for PTSD and PD (all treatment conditions together; N = 80)
2. Does brain activity predict treatment outcome for PTSD (EMDR and ImRs; N = 40)
3. Does brain activity predict treatment outcome for integrated PD/PTSD treatment (EMDR + DBT and ImRs + SFT, N = 40)
4. Data from the MRI at T2 can be used to predict relapse after treatment for all treatments together (N = 80 if all patients return for a second MRI) or for trauma treatment and integrated treatment seperatly (N = 40 for both).

fMRI data will be analysed wit Statistical Parametric Mapping (SPM) software or FMRIB Software Library (FSL) to map connectivity in the brain. Standard group comparisons will be used to analyse structural and task-related (face recognition) fMRI. First, ANOVA analyses will be performed with patients vs. controls for baseline comparison. Second, full factorial analyses will be conducted in patients-only, with time (baseline vs. end of treatment) and condition (type of treatment) as factors to analyse the effect of treatment on (task-related) brain structure, connectivity and activity. Independent component analysis (ICA; FSL MELODIC) and dual regression analyses will be used to study changes in functional connectivity of brain networks (with a focus on the salience network, negative affect network, ventral and cognitive control network). Brain areas that fluctuate simultaneously over time in blood-oxygen level dependent (BOLD; proxy for brain activity) response are automatically assigned to a component per subject. After filtering and preprocessing of the components (e.g. components that are caused by movement or scanning artefacts), these components are averaged across groups. Through non-parametric permutation testing (FSL randomise) we compare functional connectivity of these networks between intervention groups and over time (T0 to T2). For the whole-brain network analyses, the structural MRI will be parcellated into 92 regions of interest (ROIs), based on the Automated Anatomical

Labeling (AAL) atlas. These parcellations will be transformed to resting-state fMRI and time series are extracted for each ROI and correlated to get a whole-brain connectivity matrix per subject. The brain connectivity toolbox (BCT) will be used to calculate network topological indices (e.g. modularity, betweenness centrality, clustering coefficient and efficiency) from these matrices. Network topological indices narrow down the large amount of information from the brain scans to a few neurobiologically meaningful measures (Rubinov & Sporns, 2010). A more detailed description of these topological measures can be found in Bullmore and Sporns (2009). These measures will be calculated for every condition and compared through permutation-testing.

7.2 Secondary study parameters

Secondary study parameters are quality of life with WHODAS, EQ-5D-5L, and health care consumption with Tic-P. The secondary analyses on these continuous measures will be similar to the primary analyses.

7.3 Other study parameters

The analyses on other study parameters, including the AUDIT will also be similar to the primary and secondary analyses. Safety data: Incidences (number and % of subjects with at least one occurrence) of key SAEs and AEs will be presented per group. For exploratory purposes, confidence intervals comparing both groups will be provided.

7.4 Interim analysis (if applicable)

No interim analyses are planned.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted in accordance with this protocol as well as the principles of the Declaration of Helsinki (64th WMA general assembly; October 2013).

8.2 Recruitment and consent

Patients diagnosed with PTSD and/or personality disorders will be informed on the study with oral and written information of the intaker. The participant will be informed about the entire course of the study, potential individual benefits and personal risks. Here it must be emphasized that participation is absolutely voluntary. Patients are given sufficient time to read all the provided information, counsel partners or relatives, and clarify any questions with the investigator (3 days to 2 weeks). Participation requires written consent before any (screening) procedure takes place. This consent can be revoked at any time without citing reasons and without any consequences. A copy of the consent form and patient information will be given to the participant. For healthy controls, an extra screening informed consent will be used to assess their eligibility.

8.3 Benefits and risks assessment, group relatedness

All treatments given in our center are evidence-based and delivered by specialized health care professionals with continuing supervision. The safety and efficacy of the treatments are well established. The number of patient visits will be limited. The additional questionnaires for research purposes require an additional time, which can be completed at home if the patient has access to the Internet.

Potential benefits of this study for the patients is that outcome monitoring will be better implemented and that patients can be better informed on improvements and eventual deteriorations so as to adapt treatment plans. Patients are not withheld any standard treatment. Furthermore, routine care consists of less extensive monitoring of symptom change and functioning compared to the current study, so all patients may benefit from the thorough examinations during study participation.

In the face of the limited additional burden for the patient when participating in the current study as compared to routine treatment, and the possible positive outcome for future treatment, offering participation to selected patients appears to be justified.

8.4 Compensation for injury

The sponsor/investigator has a liability insurance and a trial insurance, which is in accordance with article 7, sub-section 6 of the WMO.

8.5 Incentives

Participants will receive a monetary reward: 10 euro for the assessments for which they have to visit the Sinai centrum. (at T0, T2 and T4). The subgroup that participates in the MRI research will receive 20 euro per scan session plus travel costs. Participants will receive the amount of money in "VVV-bonnen".

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1. Handling and storage of data and documents

Privacy laws and regulations will be adhered to during the complete study. The collection and processing of participants' personal information will be limited to what is necessary to ensure the study's scientific practicability, the evaluation of efficacy and adherence. Information collected about participants during this clinical investigation will be treated confidentially. At inclusion into this study, a unique project number will be allocated to each subject. For the PTSS-BPD RCT numbers will begin with 45 (year of liberation after WW-II), followed by number 001 resulting in 45001, 45002, etc.. For the PTSS-CPD RCT numbers will begin with 46, resulting in 46001, 46002, etc.. Healthy controls will be numbered with 47001, 47002, etc..

The key of these project numbers will only be available to the principal investigators and datamanagers (maximum of 3) of the project. All (paper and digital) questionnaires and data will be stored and handled de-identified using this project number. Study outcomes will be reported anonymously. Storage of data will be supervised by the principal investigator and complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). All the data will be stored for 15 years.

9.2. Monitoring and Quality Assurance

Associated investigators will be carefully selected and comprehensively informed and trained regarding Good Clinical Practice (GCP), all study procedures and the required examinations and documentation.

9.3. Amendments

A 'substantial amendment' is defined as an amendment to the terms of the ERB application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects of the study;
- The scientific value of the study;
- The conduct or management of the study; or
- The quality or safety of any intervention used in the study.

All substantial amendments will be submitted for approval to the ERB and to the competent authority. For non-substantial amendments, only a notification will be send to the accredited ERB, which will be recorded and filed by the sponsor.

9.4. Annual progress report

The sponsor/investigator will submit a summary of the progress of the study to the accredited ERB once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events/ serious adverse reactions, and other problems. The investigators will inform the METC about the start of the study and any amendments.

9.5. End of study report

The sponsor will notify the accredited ERB and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited ERB and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited ERB and the Competent Authority.

9.6. Public disclosure and publication policy

The results of the study will be submitted for publication in an international peer-reviewed journal adhering to applicable privacy laws and regulations. The principal investigator will determine publication strategy. No treatment group information will be made available until after study completion.

10. STRUCTURED RISK ANALYSIS

10.1 Potential issues of concern

No additional concerns.

Pharmacokinetic interactions

Not applicable.

10.2 Synthesis

Not applicable

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