EMDR Treatment in PTSD Following Cardiac Events

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A according to ClinO, Art. 61
Study Registration:	The study will be registered at the ClinicalTrials.gov Protocol Registration System The study will be registered at the SNCTP (Swill National Clinical Trial Portal) upon approval of the study protocol by the KEK.
Sponsor:	PD. Dr. med. Christoph Mueller-Pfeiffer
Principal Investigator	PD. Dr. med. Christoph Mueller-Pfeiffer Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine, University Hospital Zurich Culmannstrasse 8, 8091 Zurich +41 44 255 52 80 christoph.mueller-pfeiffer@access.uzh.ch
Investigated Intervention:	Randomized controlled trial to investigate the efficacy of eye movement desensitization and reprocessing (EMDR) therapy in treating posttraumatic stress disorder (PTSD) following cardiac events
Protocol ID	NCT04672551
Version and Date:	Version 8 (dated 17.05.2022)

CONFIDENTIALITY STATEMENT

The information contained in this document is confidential and the property of the sponsor-investigator. The information may not - in full or in part - be transmitted, reproduced, published, or disclosed to others than the applicable Competent Ethics Committee(s) and Regulatory Authority(ies) without prior written authorisation from the sponsor-investigator except to the extent necessary to obtain informed consent from those who will participate in the study.

Protocol Signature Form

Study Title	EMDR Treatment in PTSD Following Cardiac Events
Study ID	2019-00817

The Sponsor-Investigator has approved the protocol version 8 (dated 17.05.2022) and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and the principles of Good Clinical Practice.

Sponsor-Investigator:

Name: PD Dr. med. Christoph Mueller-Pfeiffer

Date: 17.05.2022 Signature:

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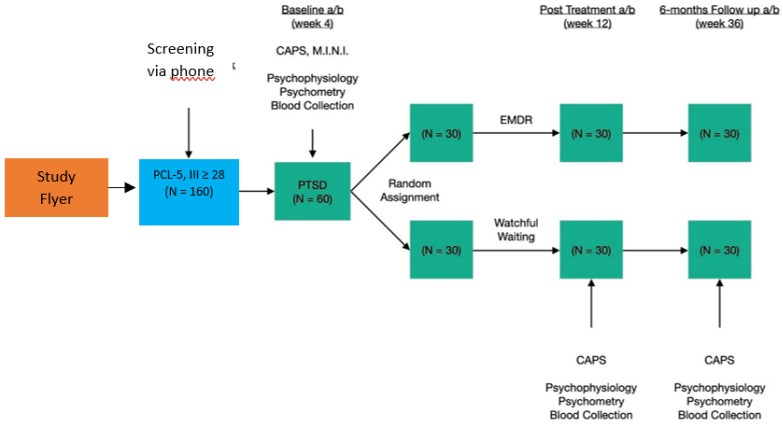
GLOSSARY OF ABBREVATIONS

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees
BLS	Bilateral Stimulation
CHD	Coronary Heart Disease
ClinO	Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)
CVD	Cardiovascular Disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EMDR	Eye Movement Desensitization and Reprocessing
FADP	Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
HR	Heart Rate
HRA	Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)
HRV	Heart Rate Variability
Hs-CRP	High-sensitivity C-reactive protein
ICAM-1	Intercellular adhesion molecule-1
ICD-11	International Classification of Diseases, 11th edition
ICH	International Conference on Harmonisation
IL	Interleukin
KISIM	Klinikinformationssystem
LC-NE	Locus Coeruleus-Norepinephrine
PTSD	Posttraumatic Stress Disorder
RDI	Resource Development and Installation
SAE	Serious Adverse Event
STEMI	ST-elevation myocardial infarction
SC	Skin Conductance
TNF- α	Tumor Necrosis Factor- α
USZ	University Hospital Zurich
VWF	von Willebrand factor
BIPQ	Brief Illness Perception Questionnaire
CAPS-5	Clinical Administered PTSD Scale for DSM-5
DS14	Distress Scale 14
EQ-5D	EuroQol -5 Dimensions
ESSI	Enriched Social Support Instrument
GAD-7	General Anxiety Disorder – 7
IIEF	International Index of Erectile Function (IIEF)
LEC-5	Life Events Checklist – DSM-5
M.I.N.I.	Mini International Neuropsychiatric Interview
MQ	Maastricht Questionnaire
PAS	Posttraumatic Adjustment Scale
PHQ-9	Patient Health Questionnaire – 9
PSQI	Pittsburgh Sleep Quality Index
PTSD	Posttraumatic Stress Disorder
PTSS	Posttraumatic Stress Symptoms
RS	Resilience Scale
TAS-20	Toronto Alexithymia Scale-20

1 STUDY SYNOPSIS

Sponsor-Investigator	PD Dr. med. Christoph Mueller-Pfeiffer
Study Title	EMDR Treatment in PTSD Following Cardiac Events
Short Title / Study ID	EMDR in Cardiac PTSD
Protocol Version and Date	Version 8 (dated 17.05.2022)
Study Registration	NCT04672551
Study Category and Rationale	Risk category A: The here planned eye movement desensitization and reprocessing (EMDR) psychotherapy intervention is effective and well established in patients with posttraumatic stress disorder (PTSD) and acknowledged by the WHO as treatment of choice in PTSD. There are no known complications and the emotional distress arising from the confrontation with traumatic memories, which is part of the EMDR treatment, has been shown to be tolerable and only transient. The collection of biological samples (saliva, blood) and health-related personal data (psychophysiological and psychometric data) involves no risks for the participants. Therefore, the project is assigned to category A.
Background and Rationale	Background: Coronary heart disease (CHD) remains a leading cause of death in Western societies, including Switzerland, where every sixth person dies from CHD each year. About 70% of patients experience psychological responses including moderate to intense fear of dying and distress during cardiac events. The psychological consequences of cardiac events are substantial and 4-16% of all cardiac patients develop full or subsyndromal PTSD after the cardiac event. In addition to poor quality of life and impaired mental health, cardiac-induced PTSD is associated with a negative disease prognosis (e.g., twofold increased risk of adverse clinical outcomes including major adverse cardiac events, CHD-related hospital readmissions, and all-cause mortality). However, research on how to treat PTSD after cardiac events is lacking. Therefore, the here proposed project aims at investigating the effectiveness of EMDR therapy, which is one of the psychotherapies of choice in traditional PTSD. EMDR is very promising in treating cardiac-induced PTSD, which shows a different symptom cluster than traditional PTSD. In cardiac-induced PTSD, there is a positive feedback loop between anxiety and cardiovascular activity (e.g., normal cardiovascular sensations are experienced as threat, which in turn leads to stronger sensations). EMDR includes reprocessing of body sensations associated with the target event and may therefore disrupt the positive feedback loop proposed by the somatic threat model and reduce PTSD symptoms.
Risk / Benefit Assessment	Earlier studies have shown that EMDR was well accepted by patients, emotional arousal was tolerable, and no cardiac complications occurred during EMDR confrontation. The reactivation of traumatic memories can cause a transient burden for patients with PTSD. The collection of psychometric, psychophysiological and biological samples (saliva, blood) according to international standardized procedures are associated with no more than minimal risks and burdens. Moreover, patients participating in this study may benefit from the EMDR therapy in terms of PTSD symptom relief and CHD prognosis. Hence, we see a favourable risk-to-benefit ratio for the here proposed study.
Objective(s)	The here proposed study aims at testing EMDR therapy in cardiac-induced PTSD in a randomized controlled trial. More specifically, the efficacy of the standardized trauma-focused procedure in terms of a reduced PTSD symptom level will be tested against a passive waitlist control group. Primary hypothesis: 1) Posttraumatic stress levels as assessed by the Clinician-Administered PTSD Scale at 3- and 6-months follow-up will be lower in the intervention group (standardized EMDR treatment) than in the control group (waitlist control). Secondary hypotheses:

	2a) Compared to the control group, the intervention group will show reduced psychophysiological responses to sudden noise bursts at 3- and 6-months follow up. 2b) Compared to the control group, the intervention group will show a lower risk of cardiovascular disease evidenced by a more favourable level of inflammation markers, metabolic factors, circulating biomarkers of haemostatic and endothelial function, and stress hormones at 3- and 6-months follow up.
Endpoint(s)	Primary endpoint: Interviewer-rated posttraumatic stress level at baseline, three- and nine-months follow-up (by means of the clinician-administered PTSD scale, CAPS-5). Secondary endpoints: • Psychophysiological responses (e.g., heart rate, skin conductance) • Cardiometabolic biomarkers (e.g. inflammation markers, metabolic factors) • Stress hormones
Study Design	Randomized controlled trial, two arms 1) PTSD patients receiving EMDR on traumatic event 2) PTSD patients in the wait-list
Statistical Considerations	Linear mixed models with three time points (assessments 1-3) as within-subject factors and the two groups (intervention vs. waitlist control) as between-subject factors will be applied to test for differences in primary and secondary outcomes between assessments and groups, probably taking sociodemographic, medical and psychometric covariates into account. The interaction effect between time and group is relevant to evaluate for different development depending on group membership.
Inclusion- / Exclusion Criteria	Inclusion criteria: • Age between 18-80 years • Men or women • Cardiac event (e.g. myocardial infarction, cardiac arrest, resuscitation) • Diagnosis of PTSD caused by the cardiac event Exclusion-criteria: • Current psychotic disorder, bipolar disorder, substance abuse as measured with the Mini International Neuropsychiatric Interview (M.I.N.I) • Acute suicidal ideation as assessed with the M.I.N.I. • Non-selective beta blockers (e.g., propranolol) and or benzodiazepine during the study period • Ongoing trauma-related treatment outside of the trial during the study period • Visionary problems, e.g. strabismus, which does not allow adequate eye movements • Insufficient knowledge of the German language • Expected inability or willingness to follow the study protocol
Number of Participants with Rationale	Based on previous studies, including our own work performed in Switzerland, about 10% will develop PTSD after an acute cardiac event. In our experience, about half of the patients will participate in the initial screenings, whereby only a few will not consent to participate once they are informed about probably having PTSD. Therefore, over a 4 -year period we assume that we will enroll the target sample size of 60 cardiac-induced PTSD at our hospital. According to meta-analyses, compared to waitlist controls a large effect size of EMDR treatment on PTSD symptom level can be expected (Cohen's d = 0.8). Power analysis (α = 0.05, *1-*β = 0.8, two-sided) revealed that a sample size of 25 patients per group is needed to provide a significant interaction effect between group and time. Expecting 15% of participants to drop out after informed consent, recruiting of 60 patients in total will be necessary (30 patients per group).
Study Intervention	EMDR focusing on the trauma: Eight individual EMDR sessions will be provided over eight weeks by licensed EMDR therapists. The first two sessions will be used for establishing a therapeutic alliance, explaining the EMDR process, obtaining a medical history, and initiating relaxation and safety procedures. The next sessions will be used for assessment of the cardiac event and desensitization and installation procedures according to the standard three-pronged EMDR therapy protocol. In the last session, closing and debriefing will take place. Treatment adherence will be controlled by independent reviewing of 10 percent of the sessions using recordings of the sessions and the therapist's protocols.
Control Intervention	1. Watchful waiting group: no treatment takes place.
Study procedures	

	
Study Duration and Schedule	Study duration for each participant: 36 weeks First-Participant-In: 11/2020 Last-Participant-Out: 11/2024
Investigator	PD Dr. med. Christoph Mueller-Pfeiffer, Senior Psychiatrist ("Leitender Arzt"), Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine, University Hospital Zurich, Culmannstrasse 8, 8091 Zurich, +41 44 255 52 80, christoph.mueller-pfeiffer@access.uzh.ch
Study Center(s)	Study Center (s): Monocentric study which will take place exclusively at the University Hospital Zurich.
Data privacy	Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. Biological material in this project is not identified by participants' name but by a unique participant number. Biological material is appropriately stored in a restricted area and only accessible to authorized personnel. Health-related personal data and biological material will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. Data and biological material will be stored according to HRO, art. 5, at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine of the USZ. To ensure confidentiality, personal data and biological material will be coded. Participants are only identified by a unique participant number. The assignment of the number to the participant is safely stored according to HRO, art. 5, at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine and protected against unauthorized access. Personal data and biological material will only be disclosed in case of an emergency, if disclosure is necessary for the protection of the physical and psychological integrity of the participant, or if there is a legal basis.
Ethical consideration	Social / scientific value: If our randomized-controlled trial proves EMDR to be an effective treatment for the reduction of PTSD symptoms in patients with cardiac events, EMDR could be implemented as a first-line treatment. This knowledge might inform larger trials to test whether poor prognosis following major adverse cardiovascular events can be improved through EMDR in patients with types of cardiac-induced PTSD. Justification of the inclusion of vulnerable participants: Patients suffering from PTSD can be considered vulnerable and should be treated carefully. As EMDR is already well established and the therapy of choice for the treatment of PTSD, no harm is to be expected. Moreover, it has already been implemented in patients with PTSD resulting from other cardiac events, where EMDR was accepted by patients, emotional arousal was tolerable, and no cardiac complications occurred during EMDR confrontation.

	Justification of the study design: In order to investigate the efficacy of EMDR, it is inevitable to include subjects with PTSD and assign them to a control group. Hence, participants in the control group may be at a disadvantage. However, this disadvantage is only temporary, as they are offered EMDR therapy upon completion of the study in week 36.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

2.1 PTSD and Cardiovascular Disease

Several risk factors for the development of posttraumatic stress disorder symptoms after myocardial infarction have been identified. These factors can be categorized into demographics (e.g., young age, female sex), personality characteristics (e.g., alexithymia, type D-personality), mental and cardiac history (e.g., previous traumatization, recurring cardiac symptoms), negative affect, poor coping strategies, low social support, subjective experience of the myocardial infarction, and acute stress disorder [1]. There is an intriguing recent line of research suggesting that it is much less objective markers of myocardial infarction severity such as cardiac enzyme levels and left ventricular ejection fraction that predict posttraumatic stress after myocardial infarction, but rather the subjective perception of severity [1].

Available evidence suggests that cardiac-induced PTSD symptoms may differ from those observed in traditional PTSD. First, traditional PTSD includes foremost event-related intrusive thoughts (i.e., “flash-backs” of the traumatic event) [2, 3]. Cardiac patients do exhibit intrusion symptoms not necessarily related to the traumatic event itself, as they also respond to unspecific myocardial infarction stimuli such as ambulance sirens during clinical interviews [4]. Second, as cardiac events are manifestations of an internal, chronic disease, patients are often exposed to enduring internal somatic threats such as palpitation or dyspnoea, which may sustain fears of recurring cardiac events in the future. These phenomena are termed “flash-forward” intrusions [4] and can be explained by the somatic threat model [2]. This model proposes a positive feedback loop between anxiety and sympathetic cardiovascular activity. Survivors of a cardiac event experience cardiovascular physical sensations, e.g., heart beating, as threat cues. The threat-related increase in sympathetic activity, in turn, further increases anxiety. Third, other than in PTSD resulting from external causes, avoidance can have severe health consequences, for example if patients with PTSD avoid doctors’ visits and intake of cardiac medications after cardiac events [5]. Fourth, hyperarousal symptoms such as a fast heart beat and palpitations can become somatic cues of cardiac threats that can be misinterpreted as life-threating cardiovascular symptoms [2].

2.2 Consequences of Posttraumatic Stress Disorder after Acute Cardiac Events

Available evidence suggests that PTSD is predictive for incident cardiovascular disease morbidity and mortality and may thus additionally worsen cardiovascular prognosis in patients with PTSD [2, 3, 5-10]. In addition to poor quality of life and impaired mental health [4], Cardiac-induced PTSD is associated with a twofold increased risk of adverse clinical outcomes assessed 1-3.5 years later, including major adverse cardiac events, cardiovascular-related hospital readmissions, and all-cause mortality [10]. While intrusion, avoidance, and hyperarousal symptoms have all been shown to affect cardiac prognosis [5], studies suggest that prominent intrusion symptoms are most deleterious [8]. PTSD associated unhealthy life styles, low adherence with cardiac therapy, and direct pathophysiological changes related to neuroendocrine and autonomic dysfunction, along with inflammatory and prothrombotic states, both facilitating atherosclerosis progression, are plausible mechanisms to explain poor cardiac prognosis in patients with PTSD [3].

As cardiac events area very prevalent which may result in PTSD and as PTSD severely worsens cardiovascular disease prognosis, effective PTSD treatments are needed. These treatment approaches need to be specific for PTSD after cardiac events, because cardiac-induced PTSD symptoms differ from traditional PTSD.

2.3 Eye Movement Desensitization and Reprocessing (EMDR) Therapy for PTSD

Eye Movement Desensitization and Reprocessing (EMDR) is a psychotherapy treatment to reduce PTSD symptoms [11]. A meta-analysis comparing EMDR against waitlist controls, cognitive behaviour therapy involving exposure, and other treatment modalities found an “overall superiority of EMDR compared to the other active treatment conditions” [12]. The efficacy of EMDR as PTSD treatment has now been established in several meta-analyses [13-15] and approximately 20 randomized controlled trials in both civilian [13-15] and combat veteran populations [16]. These findings led to the acknowledgment of EMDR as one of the psychotherapies of choice in the treatment of PTSD in adults by the World Health Organization (2013) [17].

2.4 Eye Movement Desensitization and Reprocessing (EMDR) Therapy

Eye Movement Desensitization and Reprocessing (EMDR) is a psychotherapy treatment to reduce PTSD symptoms such as disturbing memories and hyperarousal by means of reprocessing a traumatic memory. The main component is the alternate bilateral stimulation (BLS, i.e., saccadic eye movements, tapping, or ear tones) inducing a dual focus

of attention (i.e., on the bilateral stimulation) during memory reactivation and thereby ameliorates traumatic reactions [14, 18, 19].

2.5 EMDR for PTSD after cardiac events

To our knowledge, EMDR has only in one study been tested against other evidence-based PTSD treatments in cardiac patients. In that study, 42 patients undergoing cardiac rehabilitation after cardiac surgery, many in the wake of a cardiac event and scoring high on PTSD symptoms, were randomly assigned to either EMDR (all eight phases) or prolonged imaginary exposure therapy for 4 weeks [19]. In agreement with meta-analytic data suggesting that EMDR treatment may be slightly more effective than cognitive behavioural therapy for the treatment of PTSD [20], EMDR was associated with a significantly higher reduction of PTSD, anxiety, and depressive symptoms in cardiac surgery patients than Imaginary Exposure [19]. In a study testing EMDR therapy in 16 patients with implantable cardioverter defibrillator shock-induced PTSD, a reduction of PTSD, anxiety, and depressive symptoms was found 1 year after treatment. EMDR was accepted by patients, emotional arousal was tolerable, and no cardiac complications occurred during EMDR confrontation [21].

However, there is a lack of research on the efficacy of psychotherapy and especially EMDR in cardiac-induced PTSD [4, 7]. In the light of cardiac-induced PTSD having different symptoms than traditional PTSD, this lack of research is highly problematic. Specifically, the unique symptom profile in cardiac-induced PTSD related to the enduring somatic threat model [2] was not addressed in any of the studies targeting PTSD in cardiac patients. In this regard, EMDR might be most promising: The EMDR protocol includes the assessment of body sensations associated with the target event, which is followed by reprocessing. The bilateral eye movements during reprocessing seem to have de-arousing effects [22] and may thereby interrupt the positive feedback loop between cardiovascular sensations and anxiety-induced arousal [19] as explained by the enduring somatic threat model. Hence, EMDR might be more suitable in cardiac PTSD patients compared to treatment protocols that motivates patients to keep focusing on the traumatic event such as Prolonged Exposure, where higher emotional involvement seems to be related to a better outcome [23]. Therefore, the here proposed study aims at testing EMDR therapy in cardiac-induced PTSD in a randomized controlled trial.

11 STUDY OBJECTIVES AND DESIGN

3.1 Hypotheses and objectives

The here proposed study aims at testing EMDR therapy in cardiac-induced PTSD in a randomized controlled trial. More specifically, the efficacy of the standardized trauma-focused procedure in terms of a reduced PTSD symptom level will be tested against a passive waitlist control group.

Primary hypothesis:
1) Posttraumatic stress levels as assessed by the Clinician-Administered PTSD Scale at 3- and 6-months follow-up will be lower in the intervention group (standardized EMDR treatment) than in the control group (waitlist control).

Secondary hypotheses:
2a) Compared to the control groups, the intervention group will show reduced psychophysiological responses to sudden noise bursts at 3- and 6-months follow up.
2c) In terms of cardiovascular disease risk, the intervention group will show a more favourable level of inflammation markers, metabolic factors, circulating biomarkers of hemostatic and endothelial function, and stress hormones than the control groups at 3- and 6-months follow up.

In order to examine changes from before to after treatment, variables will be measured before the treatment) and after the treatment (week 12 and 36).

3.2 Primary and secondary endpoints

Primary endpoint
The primary endpoint is the interviewer-rated posttraumatic stress level at three- and six-months follow-up (by means of the Clinician-Administered PTSD Scale, CAPS-5).

Secondary endpoints
- Noise-related psychophysiological responses
    - Heart rate (HR) and skin conductance (SC) responses
    - Heart rate variability (HRV): Total power, high frequency power, low frequency power, low-to-high frequency power ratio
- Stress hormones:
    - Plasma norepinephrine and epinephrine, salivary cortisol
- Cardiometabolic biomarkers
    - Metabolic Factors: total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides, glucose
    - Inflammation markers: high-sensitivity C-reactive protein(hs-CRP), interleukin (IL)-6, tumor necrosis factor (TNF)-α

Circulating biomarkers of hemostatic and endothelial function: Fibrinogen, cardiac troponin T (cTNT). It is a national, monocentric, prospective, randomized-controlled two-arm trial to test the effectiveness of EMDR therapy in cardiac-induced PTSD. Participants will be randomly assigned to the intervention group (receiving EMDR) or to the control

group (watchful waiting). It will be examined whether the intervention group (n = 25) receiving EMDR differs from the control group (n = 25) in terms of primary and secondary outcomes. To that end, the subjects in both groups will undergo a baseline clinical interview to measure PTSD symptom severity and peripheral physiological reactivity to a stressor (i.e., white noise burst), and blood and saliva sampling to collect stress hormones and cardiovascular biomarkers (week 4). After EMDR treatment (week 12 and 36), participants will return, and the procedure will be repeated.

3.4. Study intervention

3.4.1 Study Therapists
Recruitment, physiological assessments, and blood sampling will be performed by research assistants at the University Hospital of Zurich. CAPS-5 interviews will be administered by licensed psychiatrists or psychotherapists. Study therapists are certified EMDR therapists. They will perform the EMDR therapy under supervision of an experienced EMDR therapist (Dr. Michael Hase, Lüneburger Zentrum für Stressmedizin, Lüneburg, Germany). Dr. Michael Hase will offer a supervision once a month. He will be part of our study team and is listed as a co-author. The supervisions for the EMDR-therapy (30 patients) will be organized per “Click Meeting”.

3.4.2. Intervention group
The intervention group consists of 25 patients diagnosed with full PTSD induced by cardiac events. Eight individual EMDR sessions lasting for 1 hours will be provided over 8 weeks by licensed EMDR therapists from the German-speaking part of Switzerland. Each EMDR session follows a standardized 8-phase protocol. As Shapiro [24] posits that it is necessary to adapt the standard procedures to the unique needs and characteristics of the patient and to apply different EMDR protocols for different pathologies [25], the therapy for cardiac event patients was adapted from the standard protocol [26]. After each session, the EMDR therapist records the date of the session, the number of the session (from 1-8), the duration of the session (in minutes), if the session was audiotaped and any comments (if necessary).

3.4.3. Waiting control group
Other than the assessments described in section 4.3 (Study Procedure), no intervention or any other procedure will be conducted during the study period of 36 weeks. Afterwards these subjects will be offered an EMDR therapy as provided in the intervention.

12 STUDY POPULATIOIN AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Approximately 800 patients/year are referred to the cardiac care unit of the University Hospital Zurich. Based on previous studies, including our own work performed in Switzerland, about 10% will develop PTSD after the acute cardiac event. In our experience, about half of the patients will participate in the initial screenings, whereby only a few will not consent to participate once they are informed about probably having PTSD. Therefore, over a 4-year period we assume that we will enroll the target sample size of 60 cardiac-induced PTSD at our hospital. According to meta-analyses, compared to waitlist controls a large the mean effect size of EMDR treatment on PTSD symptom level can be expected (Cohen’s d = 0.8) [14]. Power analysis (alpha = 0.05, power = 0.8, two-sided) revealed that a sample size of 25 patients per group is needed to provide a significant interaction effect between group and time. Expecting 15% of participants to drop out after informed consent, recruiting of 60 patients in total will be necessary (30 patients per group). Inclusion criteria will be: 1) Age between 18-80 years, 2) Men or women; 3) cardiac event (e.g. cardiac arrest, myocardial infarction, resuscitation, shock delivery) 4) Diagnosis of PTSD caused by the cardiac event. Exclusion criteria will be: 1) Current psychotic disorder, bipolar disorder, substance abuse as measured with the Mini International Neuropsychiatric Interview; 2) Acute suicidal ideation as assessed with the M.I.N.I.; 3) Non-selective beta blockers (e.g., propranolol) during the study period; 4) Ongoing trauma-related treatment outside of the trial during the study period; 5) Visionary problems, e.g. strabismus, which does not allow adequate eye movements; 7) Insufficient knowledge of the German language, 6) Expected inability or willingness to follow the study protocol; 8) Regular medication with benzodiazepine

4.2 Recruitment and informed consent procedure

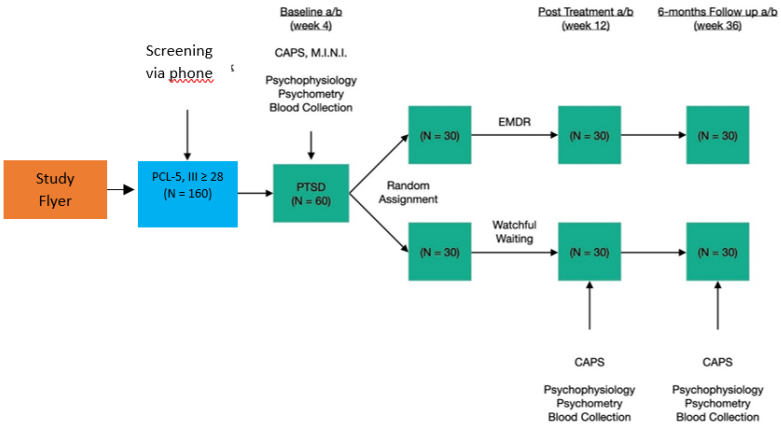
4.2.1 Recruitment: Cardiology Intensive Care Unit
Patients will be enrolled via flyer and advertisement within 4 years (November 2020 and November 2024). We will send the flyers to all hospitals, cardiac rehabilitations, cardiology practices, general practitioner practices and psychological and psychiatric practices in Switzerland. The advertisement will be made in newspapers, magazines and online platforms. All interested patients will be screened for potential PTSD via telephone screening (about 20 minutes).

4.2.2. Informed consent procedure

We will conduct a pre-screening procedure by phone/e-mail where we get implicit informed consent. Subjects who will screen positive for study inclusion, will be invited for a first assessment, where we get written informed consent. To each participant, we will explain the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may

entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment. The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating therapist. All participants will be provided a participant information sheet and a consent form describing the study and providing adequate information for participants to make an informed decision about their participation in the study. Potential participants can decide in their own time if they want to participate in the study. The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure. The consent form will be signed and dated by the study assessor at the same time as the participant signs. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records. The informed consent process will be documented in the patient file and any discrepancy to the process described in the protocol must be explained. Participants from the intervention group will be handed out an additional informed consent to record the therapeutic sessions on a tape recorder. This informed consent is given by the EMDR therapist.

4.3 Study procedures



4.3.1 Screening: Screening for inclusion and exclusion criteria prior to study inclusion
The Screening will be conducted by phone and/or e-mail. Eligible participants will be screened for inclusion and exclusion criteria. Screening for a probable PTSD diagnosis will be conducted using Part III of the PCL-5 for DSM-5 [27, 28]. Subjects who meet a total sum score of 28 or more, will be invited for Baseline a.

4.3.2 Baseline: Definitive inclusion, baseline measurements
Assessment 1 consists of two appointments (a, b) taking place at the University Hospital Zurich. During the first appointment (a), the CAPS-5 and the M.I.N.I will be administered in order to ascertain a PTSD and other psychiatric diagnoses. By means of the CAPS-5, it will be determined whether the participants have full PTSD (inclusion criterion and baseline assessment of primary outcome). The assessment of the traumatic event during the interview can cause distress (although only minimal and transient), which affects biomarkers [30, 31], the assessment of cardiovascular biomarkers and stress sensitization by means of the loud-tone procedure will be carried out at a separate appointment. The second appointment (b) will be scheduled as close as possible to the first appointment to assess the baseline of all secondary endpoints: 1) saliva and blood samples will be collected to obtain, stress hormones, and cardiovascular biomarkers, including blood pressure; 2) the loud-tone procedure will be administered; 3) patient's medication will be documented. Moreover, the following information will be obtained from the potential participants or from hospital charts [32]: Demographic factors, established cardiovascular risk factors and life style behavior, heart diseases in the past objective indices of myocardial damage and severity, related blood parameters measured in hospital, variables related to patient referral to the cardiac care unit, complications/surgeries during the hospital stay, number of days at the hospital/intensive care unit/intermediate care unit recurrent cardiac symptoms,

recurrent hospitalizations, hospital (if patients were referred to another hospital), cardiac rehabilitation, doctor visits, pharmacological treatment, adherence to medication, medical comorbidities.
4) psychometric data will be collected by means of questionnaires. These questionnaires will be completed during the second appointment or from home via eCRF (Red Cap).

4.3.3 Randomization and Intervention
Participants will be randomized into either the intervention group (EMDR treatment) or the wait-list control group. Assessors who ascertain the primary outcome variable, i.e. CAPS scores, will be blind to the subject's treatment condition. Randomization will be conducted by a person of the study team. After randomization, the intervention (EMDR therapy) will be carried out according to section 3.4.

4.3.4 Post Treatment and 6-months Follow-up (a/b): Post-intervention measurements
After the intervention (week 12), procedures of assessment 2 related to primary and secondary endpoints (i.e., CAPS, psychophysiological reactivity, psychometry, blood and saliva sampling) will be repeated as well as life style behavior will be reassessed. In order to test whether the effects of EMDR-treatment are long-lasting, measurements will be repeated at 6-months follow-up. Assessors who ascertain the primary outcome variable, i.e. CAPS scores, will be blind to the subject's treatment condition. Participants from the control group will receive an information letter stating that they can undergo an EMDR- treatment after the follow-up and that they can register in advance for registration.

Reimbursement
After the fasting blood collection, a light /standardized breakfast containing of two rolls and an apple and water/non-caffeinated tea or coffee will be served. Compensation of CHF 150 will be provided for complete study participation. Drop-outs will not be compensated.

Covid-19 plan
As long as there is a risk of a COVID-19 infection, all assessments with physical contact, including EMDR therapy, are carried out according to the detailed COVID-19 action plan (for further information see appendix cover letter).

4.4 Measurement procedures and instruments

4.4.1 CAPS-5
The German version of the CAPS-5 [33, 34] will be administered to assess the presence of full PTSD. The CAPS will be administered by licensed and trained psychiatrists or psychotherapists from our department.

4.4.2 Loud-tone procedure
The loud-tone procedure is a standardized procedure to assess stress sensitization of the central and autonomic nervous system. Auditory stimuli will consist of 500 msec, 95 db sound pressure level, white noise bursts presented 15 times with inter-trial intervals pseudorandomly varying between 16 and 36 sec. Subjects will be instructed to keep their eyes open. Stimuli will be presented through over ear headphones. For the loud-tone procedure to work, subjects will be required to detect 25 db tones in both ears. Therefore, monaural audiometric testing will be conducted before the loud-tone procedure using 125, 250, 500, 1000, 2000, 4000, and 8000 Hz tones. Psychophysiological data acquisition will be the same as in our previous studies [35].

4.4.3 Cardiovascular parameters, stress hormones
To assess cardiovascular parameters, 2x 5ml of venous blood will be collected in appropriate tubes. Measures of a prothrombotic state (D-dimer, PAI-1, fibrinogen) and of endothelial dysfunction (soluble tissue factor, VWF antigen, soluble ICAM-1)) will be determined in citrate plasma using the Clauss method (for fibrinogen) or commercial ELISA kits (D-dimer, PAI-1, VWF antigen, soluble tissue factor, soluble ICAM-1). Inflammatory markers will be measured in EDTA plasma with Luminex technology with magnetic bead-based immunoassays (IL-6, TNF-α) and with a high sensitivity reagent set for CRP (Beckman Coulter). Metabolic factors (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, glycosylated hemoglobin A1c) will be measured in serum using Cobas standard test kits (Roche Diagnostics). Our lab has long-standing and extensive expertise in collecting, measuring and interpreting these biochemical measures. The inflammatory markers will be incorporated in the task and resting state imaging models as predictors of treatment response.
Venous blood and saliva will be collected in appropriate tubes to assess stress hormone levels. Epinephrine and norepinephrine concentrations will be quantified in EDTA plasma using high-pressure liquid chromatography and electrochemical detection. To assess cortisol levels, saliva will be collected and stored at -20°C until analyzed using high performance liquid chromatography. Moreover, the systolic and diastolic blood pressure will be measured.

4.4.4 Psychometric data

Screening instruments
- PTSD Checklist for DSM-V (PCL-5): The third part of the PCL-5 will be used to screen for patients for a probable PTSD diagnosis. It comprises 20 items rated on a 5-point Likert-scale [27, 28].
- Mini International Neuropsychiatric Interview (M.I.N.I.): We will apply the German version of the M.I.N.I to assess the 17 most common mental health disorders. The M.I.N.I. is a 30 minutes structured psychiatric diagnostic interview. We will apply the German adaptation of the M.I.N.I based on DSM-IV (or DSM-V if it is available until the beginning of the study) [36].

Additional parameters (covariates and for exploratory purposes)

T2 = Baseline (week 4), T3 = Post Treatment (week,12), T4 = 6-months Follow-up (week 36)

	T2	T3	T4
Psychiatric symptoms and disorders Patient Health Questionnaire (PHQ-9) [37], Generalized Anxiety Disorder module (GAD-7) from the Patient Health Questionnaire [38, 39] Maastricht Vital Exhaustion Questionnaire (MQ) [40], , Atypical depression (IDR-SR), Adjustment Disorder (ADNM-20)	x	x	x
Personality Type D scale (DS14) [41, 42], Wagnild & Young Resilience Scale (RS) [43, 44]), Toronto Alexithymia Scale (TAS-20) [45]	x		
Cardiac-related variables Perceived threat during cardiac event [14], Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Social Support Inventory (ESSI), which has been designed to rate emotional, structural and instrumental support [46]; Life Events Checklist – DSM 5 (LEC-5) [47] (	x		
Brief self-rated revised illness perception questionnaire (BIPQ-R) [48], Heart Drawings [49], EuroQol group 5-dimension questionnaire (EQ-5D-5L) [50], Anxiety Sensitivity Index	x	x	x
*Purpose in Life Questionnaire, Short Form Health Survey (SF-12), Positive and Negative Affect Schedule (PANAS), Life-Orientation-Test – Revised (LOT-R)	x		

*We will validate the questionnaire "Purpose in Life Questionnaire". For construct validity, we will assess the Short Form Health Survey (SF-12), Positive and Negative Affect Schedule (PANAS), Life-Orientation-Test-Revised (LOT-R).

4.5 Withdrawal and discontinuation

A participant will be withdrawn from the project in the following cases: 1) Aggravation of the psychiatric or physical condition in the course of participation (as determined by the participant or by the investigator); 2) decision of the participant to withdraw informed consent; 3) non-compliance with the study protocol. If necessary, supportive measures will be taken (e.g., emergency service of the USZ). Data collected to this time point will be included in the analysis. Participants have been informed in the informed consent form that, after withdrawal, their data will neither be destroyed nor anonymized.

13 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan

Data will be analyzed using SPSS Statistics 25 or higher (SPSS Inc. Chicago, IL) or R [51] with significance level set at $p<0.05$ (two-tailed). Before analysis, all continuous variables will be tested for normality by the Kolmogorov-Smirnov test and, if necessary, transformed to obtain a normal distribution. Linear mixed models with three time points (assessments 1-3) as within-subject factors and the two groups (intervention vs. waitlist control) as between-subject factors will be applied to test for differences in primary and secondary outcomes between assessments and groups, probably taking sociodemographic, medical and psychometric covariates into account. The interaction effect between time and group is relevant to evaluate for different development depending on group membership. These models will be calculated for patients completing the intervention program per protocol (PP) as well as for those with intention to be treated at baseline (ITT). Probably the models will be controlled for differences in outcome measures at baseline. P-values will be adjusted for multiple tests according to Holmes-Bonferroni. An interim analysis will be conducted with 10 participants each group for using as pilot data to apply for a Swiss National Foundation grant.

5.2. Handling of missing data and drop-outs

We assume 15% of patients will drop-out after informed consent. Thus, we will recruit 30 patients per group instead of 25 minimally needed according to power analysis. Probably ITT-analyses will include missing replacement by last-observation-carried-forward (locf).

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [52], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [53] which supports particularly Clinical Trials Ordinance (ClinO) as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

6.2 (Serious) Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavorable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that 1) results in death or is life-threatening, 2) requires in-patient hospitalization or prolongation of existing hospitalization, 3) results in persistent or significant disability or incapacity, or 4) causes a congenital anomaly or birth defect. The Sponsor-Investigator makes a causality assessment of any SAEs to the trial intervention (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	**Description**
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

The Sponsor-Investigator makes a severity assessment of the SAE as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63,)
All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study. If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Sponsor-Investigator reports it to the Ethics Committee via BASEC within 15 days.

6.3 (Periodic) safety reporting

An annual safety report is submitted once a year to the local Ethics Committee by the Sponsor-Investigator (ClinO, Art. 43 Abs).

6.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

6.5 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g. ethical concerns,, insufficient participant recruitment, when the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive), alterations in accepted clinical practice that make the continuation of the study unwise, or early evidence of harm or benefit of the experimental intervention. Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38). Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38). For the notification of completion, discontinuation or interruption of the clinical trial, the respective templates on www.swissethics.ch will be used. Upon project termination, data will be stored according to the guidelines for archiving research data of the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine (USZ) for the duration of at least 10 years at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine.

6.6 Insurance

In the event of project-related damage or injuries, the liability of the Zürich Versicherungs-Gesellschaft AG (Police-Nummer: 14.970.888, “Versicherung für klinische Versuche und nichtklinische Versuche“) provides compensation, except for claims that arise from misconduct or gross egligence. The insurance certificate is being submitted online to the ethical committee along with this proposal.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

Social / scientific value: Cardiac events are highly prevalent and a leading cause of death in Western societies. The experience of cardiac events may have substantial psychological consequences such as intense fear of dying and distress resulting in PTSD. In addition to poor quality of life and impaired mental health, cardiac-induced PTSD is associated with a twofold increased risk of adverse clinical outcomes including major adverse cardiac events, cardiovascular-related hospital readmissions and all-cause mortality. Currently, patients with cardiac-induced PTSD are not routinely offered trauma-focused therapies, with a lack of scientific evidence likely being one major reason for this omission. To generate evidence on how to best treat cardiac-induced PTSD, the here proposed project wants to investigate the effectiveness of EMDR therapy, which is, according to the WHO, the therapy of choice in traditional PTSD. For cardiac-induced PTSD, EMDR may be most promising: The EMDR protocol includes the assessment of body sensations associated with the target event, which is followed by reprocessing. The bilateral eye movements during reprocessing seem to have de-arousing effects [22] and may thereby interrupt the positive feedback loop between cardiovascular sensations and anxiety-induced arousal [19] as explained by the enduring somatic threat model. If our randomized-controlled trial proves EMDR to be an effective treatment for the reduction of PTSD symptoms in patients with cardiac events, EMDR could be implemented as a first-line treatment. This knowledge might inform larger trials to test whether poor prognosis following major adverse cardiovascular events can be improved through EMDR in patients with cardiac events and other types of cardiac-induced PTSD.

Justification of the inclusion of vulnerable participants: Patients suffering from PTSD can be considered vulnerable and should be treated carefully. As EMDR is already well established and the therapy of choice for the treatment of PTSD, no harm is to be expected. Moreover, it has already been implemented in patients with PTSD resulting from other cardiac events, where EMDR was accepted by patients, emotional arousal was tolerable, and no cardiac complications occurred during EMDR confrontation [21].

Justification of the study design: In order to investigate the efficacy of EMDR, it is inevitable to include subjects with PTSD and assign them to a control group (wait-list group). Hence, participants in the control group may be at a disadvantage. However, this disadvantage is only temporary, as they are offered EMDR therapy on traumatic events upon completion of the study in week 36.

7.2 Risk-benefit assessment

The EMDR therapy follows an established standardized protocol, is widely used, and is a well-tolerated procedure. No serious adverse events with EMDR therapy were observed. Earlier studies with cardiac patients have shown that EMDR was accepted by patients, emotional arousal was tolerable, and no cardiac complications occurred during EMDR confrontation. Moreover, patients participating in this study may immediately benefit from EMDR treatment. The reactivation of traumatic memories can cause a minimal and transient burden for patients with PTSD. The collection of biological samples (saliva, blood) and health-related personal data (psychophysiological data: HR, BP, HRV, psychometric data from questionnaires) is not associated with any risks and burdens. Moreover, patients participating in this study may benefit from the EMDR therapy in different ways. EMDR may reduce posttraumatic stress symptoms like hyperarousal and re-experiences and enhance an adaptive dealing with ongoing threats. In addition, EMDR may improve quality of life, reduce distress, and minimize avoidance behaviors. This facilitates regular intake of medications and enhances cardiac treatment adherence (regular physical activities). Moreover, if treatment is successful, it may have a positive impact on the cardiac prognosis, which in turn can reduce medical costs. Hence, we see a favourable risk-to-benefit ratio for the here proposed study.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

All study procedures will be carried out under the close supervision of the principal investigator. Staff members complete the Good Clinical Practice (GCP) basic courses. Furthermore, only licensed and trained psychotherapists/psychiatrist will perform the CAPS-5 interview.
All EMDR psychotherapists are certified in EMDR therapy and will be supervised by Dr. Michael Hase, an experienced EMDR therapist.
On a regular basis, quality control will be carried out (e.g., investigation and assurance of the quality of data collection, entry, and processing). Study procedures will be documented (i.e., research activities such as trainings and supervision, quality controls, important project-related decisions, or decisions of participants to withdraw from the study) to ensure the transparency and replicability of the study for third parties. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

8.2 Specification of Source Documents

The following documents are considered source data, including but not limited to: 1) SE and other worksheets, 2) electronic master file data; 3) clinical information system (“KISIM”) data
Source data will be available at the site to document the existence of the study subjects and substantiate the integrity of study data collected. Source data will include the original documents relating to the study.

The following information (at least but not limited to) will be included in the source documents: 1) demographic data (age, sex, education, occupation, marital status); inclusion and exclusion criteria details; 3) participation in study and signed and dated Informed Consent Forms, 4) visit dates, 5) SEs (related) and concomitant medication, 6) reason for premature discontinuation

8.3 Data recording

Medical records will be collected using hospital charts (i.e., the Klinikinformationssystem; KISIM) and will from there be transferred into REDCap, the electronic Case Report Form (eCRF). Data obtained during the screenings at assessment 1-3 (CAPS-5, M.I.N.I., screening questions) will be documented on work sheets and consecutively be transferred into the eCRF. Data from blood and saliva (e.g., stress hormones, cardiovascular biomarkers) will be analyzed and relevant parameters for the final statistical data analyses will be recorded in the eCRF. Data from psychometric questionnaires will directly be entered into the eCRF by the participants. To that end, participants complete all questionnaires in REDCap (they will only have access to the questionnaire forms). REDCap was developed by an informatics core at Vanderbilt University in 2004, with ongoing support from US National Center for Research Resources (NCRR) and US National Institute of Health (NIH), grants NIH/NCATS UL1 TR000445. REDCap was specifically developed around HIPAA security guidelines and is GCP-compliant and fulfills the Swiss regulatory requirements regarding the collection of patient data in clinical trials or non-interventional studies and patient registries and the Swiss/EU data protections laws.

In contrast to other source data, psychophysiological data will be recorded by coded identification (e.g. subject identification number), which allows storing on special storage locations, such as network attached storage or external hard drives. The large amount of these types of data cannot be stored on regular servers of the University Hospital Zurich where the other source data are stored.

8.4 Confidentiality and coding

Health-related personal data and biological material will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. Data and biological material will be stored according to HRO, art. 5, at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine of the USZ.
To ensure confidentiality, personal data and biological material will be coded. Participants are only identified by a unique participant number. The assignment of the number to the participant is safely stored according to HRO, art. 5, at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine and protected against unauthorized access.
Personal data and biological material will only be disclosed in case of an emergency, if disclosure is necessary for the protection of the physical and psychological integrity of the participant, or if there is a legal basis. Appropriate coded identification (e.g. pseudorandomization) is used in order to enter subject data into the database. All data entered into eCRFs is transferred to a mySQL database using encryption post filtering and sanitization to various relational database tables. The server hosting the EDC system and the database is kept in an off-site locked server-room. Only system administrators have direct access to the server and back-up tapes.

8.5 Retention of study data and biological material

Health-related personal data are stored for a minimum of 10 years after publication of the research project either electronically or in physical folders at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine of the USZ. Only members of the project have access to these datafiles (with the exception of data from KISIM, to which attending medical staff of the USZ has access). Health-related personal data involves the following source data: 1) medical records (stored in KISIM), 2) paper-pencil data from screenings and assessments (CAPS-5, M.I.N.I., etc., stored in a physical or electronic folder); 3) physiological data (heart rate, skin conductance, etc., stored electronically); 4) psychometric questionnaires filled out by study participants (directly via eCRF).

The psychometric questionnaires will be securely stored by CTU Zürich for at least 15 years (after the regular end or a premature termination of the respective study). The sponsor further maintains essential documents and source data and archives interim and final reports in electronic format for at least 10 years.

For eligible participants who have been evaluated at the pre-screening procedure but are not included in the study (due to them not meeting the eligibility criteria), all data will be stored in the same way as for study participants. Biological materials (e.g., frozen plasma and saliva samples) will be coded and stored at a -80° freezer at the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine of the USZ. Materials are stored for a minimum of 10 years after publication of the research project. Destruction of materials will be done in accordance with biohazard requirements and documented in written form.

9 MONITORING AND REGISTRATION

Monitoring will be carried out under responsibility of the primary investigator according to the monitoring plan (attachment). The source data/documents and the eCRF are accessible to monitors and questions are answered during monitoring. The study will be registered at clinicaltrials.gov and SNCTP (Swiss National Clinical Trial Portal) upon approval of the study protocol by the KEK.

10 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The study is financed by intramural research funds of the Department of Consultation-Liaison Psychiatry and Psychosomatic Medicine of the USZ and private research foundations. Data will be published in major peer-reviewed cardiovascular, psychiatry/psychosomatic and general medical journals. On reasonable request and after presenting a proper research question and analytic plan, data access will be granted to interested researchers outside the study team (in close collaborations (e.g., authorship policy) and with the agreement of the local ethics committee only).

11 ADDITIONAL SIGNATURES

The external supervisor confirms hereby to participate in the study team and acts as a supervisor for the EMDR treatment in online videoconference meetings with the study therapist(s).

External supervisor:

Name: Dr. Michael Hase, OFA d.R., Psychiater - Psychotherapie - Akupunktur, Associate Editor European Journal of Trauma and Dissociation, EMDR Senior Trainer, Lüneburger Zentrum für Stressmedizin, Dorette-von-Stern-Strasse 14, 21337 Lüneburg

Date: 17.05.2022 Signature:

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