LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
CAMPUS INNENSTADT
INSTITUT FÜR ALLGEMEINMEDIZIN

Clinical Trial Protocol

PICTURE – PTSD after ICU Survival

Caring for Patients with Traumatic Stress Sequelae following Intensive Medical Care

A multi-center, observer-blinded, randomized, controlled trial with a psychological intervention

Principal Investigator („Leiter der klinischen Prüfung“):

Prof. Dr. Jochen Gensichen,

Institut für Allgemeinmedizin, Klinikum der Ludwig-Maximilians-Universität München

Pettenkoferstr. 10, 80336 München

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1 Clinical Trial Synopsis

Clinical trial title	**PICTURE – PTSD aftEr ICU SURvival** Caring for Patients with Traumatic Stress Sequelae following Intensive Medical Care: A multi-center, observer-blinded, randomized, controlled trial with a psychological intervention
Trial short title	PICTURE
Trial Registry – nat. **international**	**DRKS-ID** (German Clinical Trials Register): DRKS00012589 **ClinicalTrials.gov:** [to be allocated]
Medical Conditions	Post-traumatic stress disorder (PTSD) (ICD-10 F43.1; DSM-5 1.2.7) Post Intensive Care Syndrome (PICS) (Needham et al., 2012)
Interventions	**Experimental intervention:** A primary care version of a "Narrative Exposure Therapy" (**NET**-oriented, 3 sessions) delivered by the general practitioner (GP): *Session 1 (S1):* Diagnosis, psycho-education, and "lifeline", in which the patients constructs a chronology of their most significant life events *Sessions 2 (S2):* Narrative exposition, in which the patient recounts details of distressing situations that occurred in the Intensive Care Unit (ICU) *Session 3 (S3):* Narrative exposition of a stressful event, extracted from the patient's lifeline ("PDS event") *Telephone calls (TC) 1 – 7:* 7 telephone calls initiated by the GP practice affiliated medical assistant (MA) to support the narrative sessions (S2, S3) by checking upon patients' well-being and by reminding patients to reflect and take notes between sessions. **Control intervention:** Improved treatment-as-usual (**iTAU**). GPs in the control group will be instructed in evidence-based diagnosis and treatment of PTSD according to the S3-guideline. GPs will contact their patients for general checks and medical advice within 3 consultations (visit at GP's office).
Trial Population	Adult male and female post-ICU patients aged 18 to 85 years, with >5 days of mechanical ventilation and sequential organ failure during their ICU treatment, showing symptoms of PTSD

Trial Design	Prospective, national, multi-center, two-arm parallel-group (NET vs. iTAU), assessor-blinded, pragmatic, randomized controlled superiority trial with a psychological complex intervention delivered in the primary care setting
Trial Objectives	Primary objective: To demonstrate that the experimental intervention (NET) delivered by the GP is effective in reducing long-term post-traumatic stress symptoms after intensive care measured by the PDS-5 total severity score, as compared to improved treatment as usual (iTAU) Secondary objectives: To demonstrate that NET is effective compared to iTAU in improving a) symptoms of depression and anxiety b) health-related quality of life, disability, and patient activation measure To demonstrate a favorable cost-effectiveness of NET compared to iTAU ("PICTURE-Economics") To describe the experiences of GP's in learning and implementing a psychotherapeutic treatment method in practice and how patients perceive the offer and the performance of a psychotherapeutic treatment delivered by their family physician ("PICTURE-Psychotherapy") To check for the occurrence of adverse effects of the intervention
Trial Endpoints	**Primary Efficacy Endpoint:** • Posttraumatic Stress (Posttraumatic Diagnostic Scale for DSM-5): absolute change in PDS-5 total severity score from baseline to T1 (6 months after baseline) **Secondary Endpoints:** • Posttraumatic Stress: absolute change in PDS-5 total severity score from baseline to T2 (12 month after baseline) • Depression (PHQ-9 total score): absolute change from baseline to T1 and T2 • Anxiety (OASIS total score): absolute change from baseline to T1 and T2 • EQ-5D-5L: VAS at T1 and T2 • Disability (WHODAS 2.0 total score): absolute change from baseline to T1 and T2 • Patient Activation Measure (PAM-13 total score): absolute change from baseline to T1 and T2 • "PICTURE-Economics":

	Cost-effectiveness at T1 and T2 – based on direct/ indirect costs (modified CSSRI (Client Sociodemographic and Service Receipt Inventory) applied) and QALYs (EQ-5D-5L index values) • "PICTURE-Psychotherapy" Qualitative aspects of attitudes and care of PTSD-patients in primary care
Subject Number	To be assessed for eligibility: **N = 3000 patients (GPs) in total** To be allocated to the trial: **N = 340 patients (GPs) in total will be randomized** (i.e. 170 per treatment arm) To be analyzed: **N = 340 patients (GPs) in total** (missingness is included in the principal analysis according to intention-to-treat)
Patient level: **Inclusion Criteria**	Patients will only be included in the study if they meet all of the following criteria: Screening at ICU (T-1): • Montreal - Cognitive Assessment MoCA ≥ 24 • *probable* PTSD: PC-PTSD-5 Score ≥ 3 (5-item Primary Care PTSD Screen for DSM-5) • Mechanical ventilation duration ≥ 5 d • Sequential Organ Failure Assessment (SOFA) Score ≥ 10 (as measured by the maximum score during ICU stay) • Male and female patients aged 18 to 85 years • Life expectancy ≥ 9 months Key inclusion criteria at T0: • PTSD symptoms: PDS-5 Score ≥ 20 (20-item Posttraumatic Diagnostic Scale for DSM-5) • Montreal - Cognitive Assessment MoCA Score ≥ 24 • Patients must be able to follow study instructions and likely to attend and complete all required visits and telephone surveys • Written informed consent of the patient
Patient level: **Exclusion Criteria**	Subjects are not eligible for participation in the study if any of the following criteria applies: General Exclusion Criteria: • Patient not able to give written informed consent • Patient without legal capacity, who is unable to understand the

	nature, scope, significance and consequences of this clinical trial • Patient has an insufficient understanding of the German language • Subjects with a physical or psychiatric condition which at the investigator's or the GP's discretion may put the subject at risk, may confound the trial results, or may interfere with the subject's participation in this clinical trial • Known or persistent abuse of medication, drugs or alcohol as assessed by the GP Indication specific exclusion criteria at T0: • major depression (PHQ-9 Score ≥ 23) • Acute suicidality • Life expectancy < 6 months • Concomitant therapy: already receiving another psychotherapeutic trauma therapy such as EDMR or CBT at baseline • Medication: any neuroleptic, anticholinergic or anti-epileptic drugs 2 weeks prior to baseline Key exclusion criteria at T0: • Cognitive dysfunction: MoCA Score < 24 • PTSD symptoms: PDS-5 Score > 50
GP level: **Inclusion Criteria**	Key inclusion criteria: • GP has to provide family doctor services for two (or more) years within the German statutory health care system • GP has to hold a certificate for "Basic Psychosomatic Care" (Bundesärztekammer 2001) • Alternatively, if no certificate for "Basic Psychosomatic Care" can be provided, the GP has to be a family doctor within the German statutory health care system for at least 10 years with adequate psychological, psychosomatic or psychiatric qualifications • Written informed consent of the GP
GP level: **Exclusion Criteria**	Key exclusion criteria: • A patient population with >80% of patients with a specific medical condition • GP refused to give written informed consent
Trial Procedures	Screening period: • Pre-screening (in person) at or within 3 weeks after ICU discharge (T -1)

	• Re-screening 2 weeks before T0 by phone to check for the patient's eligibility GP level: • After re-screening of the patient, his/her GP will be contacted by phone, informed about the trial, checked for eligibility and asked for written informed consent T0 (Baseline) at the general practice: • final eligibility check and PTSD diagnosis, baseline data collection Randomization: ≤ 2 weeks after T0 GP training: • Within 4 weeks after randomization the GP will receive training material and training according to the assigned treatment group **NET group**: Schedule of intervention: • *S1*: 6 (+/- 4) weeks after baseline T0 • *S2*: 2 weeks after S1 • *Telephone Call (TC)*: between S2 and S3; a psychologist will contact the GP to offer support and guidance related to the NET intervention • *S3*: 4 weeks after S2 • *TC 1 – 7:* the patient will be contacted by the MA every 2-3 weeks between S1 and T1 by phone Duration of the intervention: from S1 until the last of 7 telephone calls initiated by the MA **iTAU group**: Schedule of intervention • 3 consultations (visits) at the GP practice for medical advice and guidance in line with the S3-Guideline for PTSD Duration of the control condition: from the first until the third consultation between T0 and T1 to be scheduled by the GP in accordance with the patient's needs Safety documentation: • safety in both the experimental and control group will be assessed and documented between T0 and T2 by the treating GP Telephone surveys at T1 (at month 6) and T2 (at month 12): • patient reported efficacy outcomes assessed by structured telephone interviews
Trial Specific	Patient questionnaires (including mode of administration)

Measurements	• PDS-5 (Posttraumatic Stress): self-complete version on paper (by default at T0, T1, T2); or (telephone-) interview version (for non-responders at T1, T2) • PHQ-9 (Depression) • OASIS (Anxiety) • EQ-5D-5L (visual analogue scale (VAS); descriptive system): validated self-complete version on paper at T0, validated telephone interview version at T1, T2 • Disability (WHODAS 2.0) • PAM-13 (Patient Activation Measure) • modified version of CSSRI: interview version (assessed by the GP at T0; telephone interview version at T1 and T2)
Regional Trial Centers	National, multi-center study, including 6 trial sites throughout Germany (as planned at time of finalization of the protocol): • Munich: Ludwig-Maximilians-Universität (LMU) • Munich: Technische Universität München (TUM) • Berlin: Charité – Universitätsmedizin Berlin • Dresden: Universitätsklinikum Carl Gustav Carus Dresden • Hamburg: Universitätsklinikum Hamburg Eppendorf (UKE) • Tübingen: Universitätsklinikum Tübingen
Statistical Rationale	Primary efficacy analysis: The primary efficacy endpoint is the absolute change in PDS total severity score from baseline at month 6 (time point T1) (no matter if derived from the PDS-5 questionnaire administered by mail or phone at T1). The combined null hypothesis for the primary efficacy endpoint at T1 is that distributions of absolute change score values are the same for NET and iTAU in patients with and without missing scores. Under the alternative hypothesis, we expect a shift in distributions with a clinically relevant standardized effect size in the order of 0.36 (Cohen's d). To test the null hypothesis of the confirmatory principal analysis, we will use an extended version of the nonparametric Wilcoxon-Mann-Whitney test ('worst rank score approach' according to Lachin 1999) designed to address missingness of PDS total score values (e.g. due to expected deaths during the follow-up period). The principal analysis will be performed according to the intention-to-treat (ITT) principle, unadjusted for baseline covariates or site. The significance level is set to alpha = 5% (two-sided).

	Secondary endpoints and secondary analyses: All secondary analyses will be exploratory, i.e. without adjustment for multiplicity, using adequate descriptive statistics. The corresponding 95% confidence intervals for treatment group effects will be reported. Safety analysis: Safety analyses will be performed in the safety population. All observed safety events will be summarized using standard descriptive statistics stratified by the NET vs. iTAU group. Health economic evaluation ("PICTURE-Economics"): On the basis of the EQ-5D-5L index values and data reported by means of the modified CSSRI questionnaire, cost-effectiveness will be described by the incremental cost-effectiveness ratio (ICER), i.e. the ratio between the cost and effect differences between intervention and control group. To assess the uncertainty associated with the ICER, a series of net-benefit regressions will be performed, and a cost-effectiveness acceptability curve will be constructed. Process evaluation ("PICTURE-Psychotherapy") - completely qualitative measures only
Time Schedule	Per subject: • 12 months in total, including 6 month follow-up after data collection of primary endpoint assessed at month 6 (T1) Trial duration: • Recruitment Period: 01.10.2017 – 30.09.2018 (estimated) • Planned Start Date (FPFV): 01.10.2017 • Planned End Date (LPLV): 31.12.2019

Date and version identifier

Revision Chronology:

August 2017	Original Version V2.0
xx.08.2017	Change in primary and secondary efficacy analyses (absolute change scores from baseline at T1, T2, instead of absolute; Safety documentation: specification of responsibilities and time period Changes in randomization procedure; changes in recruitment

	Change in inclusion/exclusion criteria, screening (life expectancy, SOFA) Changes in mode of administration with respect to the PDS-5 questionnaire. Several statements were added throughout the protocol to better clarify and define trial procedures, the applied instruments and the corresponding measurement variables.

2 Trial Administration Structure

Sponsor	**Universitätsklinikum der** **Ludwig-Maximilians-Universität München** **represented by Prof. Dr. Karl-Walter Jauch** Marchioninistraße 15 81377 München Mail: karl-walter.jauch@med.uni-muenchen.de Tel: +49 (0)89 4400 72101
Principal Investigator	**Prof. Dr. med. Dipl.-Päd. Jochen Gensichen, MPH** Direktor Institut für Allgemeinmedizin Ludwig-Maximilians-Universität München Pettenkoferstraße 10 80336 München Mail: Jochen.Gensichen@med.uni-muenchen.de Tel: +49 (0)89 4400 54479
Co-Principal Investigator	**Prof. Dr. rer. soc. Thomas Elbert** Klinische Psychologie und Klinische Neuropsychologie Universität Konstanz Universitätsstraße 10 78464 Konstanz Mail: Thomas.Elbert@uni-konstanz.de Tel: +49 (0)7531 88 4609
Principal Trial Coordinator, Project Management	**Dr. John Singhammer** Institut für Allgemeinmedizin Ludwig-Maximilians-Universität München Pettenkoferstraße 10 80336 München Mail: John.Singhammer@med.uni-muenchen.de Tel: +49 (0)89 4400 54972
Medical Trial Coordinator	**Dr. med. Susanne Schultz** Institut für Allgemeinmedizin Ludwig-Maximilians-Universität München Pettenkoferstraße 10

	80336 München Mail: Susanne.Schultz@med.uni-muenchen.de Tel: +49 (0)89 4400 54974
Psychological Advisor	**PD Dr. Maggie Schauer** Klinische Psychologie und Klinische Neuropsychologie Universität Konstanz Universitätsstraße 10 78464 Konstanz Mail: Maggie.Schauer@uni-konstanz.de Tel: +49 (0)7531 88 3151
Scientific Advisor	**Dr. med. Konrad Schmidt** Institut für Allgemeinmedizin Charité – Universitätsmedizin Berlin Charitéplatz 1 10117 Berlin Mail: Konrad.Schmidt@charite.de Tel: +49 (0)3641 939 5805
Data Management	**Dipl. Soz. Daniela Lindemann** Institut für Allgemeinmedizin Ludwig-Maximilians-Universität München Pettenkoferstraße 10 80336 München Mail: Daniela.Lindemann@med.uni-muenchen.de Tel: +49 (0)89 4400 54979
Randomization	**Randoulette Team** Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE) Ludwig-Maximilians-Universität München Marchioninistraße 15 81377 München Mail: randoulette@ibe.med.uni-muenchen.de Tel: +49 (0)89 4400 77484/ -77487

Statistician / Biometrician	**Dipl. Stat. Christine Adrion, MPH** **Prof. Dr. rer. nat. Ulrich Mansmann, Director** Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie (IBE) Ludwig-Maximilians-Universität München Marchioninistraße 15 81377 München Mail: adrion@ibe.med.uni-muenchen.de mansmann@ibe.med.uni-muenchen.de Tel: +49 (0)89 4400 77486/ -74491
Monitoring	to be confirmed
Data Safety and Monitoring Board (DSMB)	**Prof. Wolfgang H. R. Miltner** Lehrstuhl für Biologische und Klinische Psychologie Friedrich-Schiller-Universität Jena Am Steiger 3, Haus 1 07743 Jena Mail: wolfgang.miltner@uni-jena.de Tel: +49 (0)3641 945 140
	Univ.-Prof. Dr. med. Dr. rer. soc. Frank Schneider Klinik für Psychiatrie, Psychotherapie und Psychosomatik Universitätsklinikum Aachen, AöR Pauwelsstraße 30 52074 Aachen Mail: fschneider@ukaachen.de Tel: +49 (0)241 80 89633
	Dr. Jochem König Institut für Medizinische Biometrie, Epidemiologie und Informatik Universitätsmedizin der Johannes Gutenberg-Universität Mainz Langenbeckstraße 1 55131 Mainz Mail: jochem.koenig@unimedizin-mainz.de Tel: +49 (0)6131 17 5714

	Dr. med. Andreas Linde Zentrum Psychiatrie und Psychotherapie Psychiatrische Dienste Aargau AG Zürcherstraße 241 CH-5210 Windisch Mail: andreas.linde@pdag.ch Tel: +41 (0)56 462 21 11
"PICTURE-Genetics for PTSD" Genetic characteristics of patients with and without symptoms of post-traumatic stress disorder following an intensive care experience **[DFG grant:** **NET-Genetics GZ: GE 2073/9-1 | SCHU 1603/12-1]** – separate document to be submitted	**Prof. Dr. med. Dipl.-Päd. Jochen Gensichen, MPH** **Prof. Dr. med. Thomas G. Schulze** Institut für Psychiatrische Phänomik und Genomik Ludwig-Maximilians-Universität München Nußbaumstr. 7 80336 München Mail: Jochen.Gensichen@med.uni-muenchen.de Mail: Thomas.Schulze@med.uni-muenchen.de Tel: +49 (0)89 4400 55546
"PICTURE-Economics" health economic evaluation	**Prof. Dr. med. Dipl.-Päd. Jochen Gensichen, MPH** **Prof. Dr. med. Hans-Helmut König** Institut für Gesundheitsökonomie und Versorgungsforschung Universitätsklinikum Hamburg-Eppendorf Martinistraße 52 20246 Hamburg Mail: Jochen.Gensichen@med.uni-muenchen.de Mail: h.koenig@uke.de Tel: +49 (0)40 7410 54464
"PICTURE-Psychotherapy in general practice" qualitative aspects of attitudes and care of PTSD-patients in primary care	**Prof. Dr. med. Dipl.-Päd. Jochen Gensichen, MPH** **Dr. Sabine Gehrke-Beck** Institute für Allgemeinmedizin Charité - Universitätsmedizin Berlin Institut für Allgemeinmedizin Campus Charité Mitte Charitéplatz 1 10117 Berlin Mail: Jochen.Gensichen@med.uni-muenchen.de

	Mail: sabine.gehrke-beck@charite.de Tel: +49 (0)30 450 514 119
International Co-operations review of the study protocol	**Michael Von Korff, ScD** Senior Investigator Kaiser Permanente Washington Health Research Institute 1730 Minor Ave, Suite 1600 Seattle, WA 98101-1466, U.S.A. Mail: vonkorff.m@ghc.org Tel: + 1 206 287 2874
Investigational Trial Center (ITC)	**Prof. Dr. med. Dipl.-Päd. Jochen Gensichen, MPH** Institut für Allgemeinmedizin Ludwig-Maximilians-Universität München Pettenkoferstraße 10 80336 München Mail: Jochen.Gensichen@med.uni-muenchen.de Tel: +49 (0)89 4400 54479
Regional Trial Centers (RTC)	**Prof. Dr. med. Antonius Schneider** Institut für Allgemeinmedizin Technische Universität München Orleansstraße 47 81667 München Mail: Schneider. Antonius@tum.de Tel: +49 (0)89 614 658 13
	Prof. Dr. med. Christoph Heintze Institut für Allgemeinmedizin Charité – Universitätsmedizin Berlin Charitéplatz 1 10117 Berlin Mail: christoph.heintze@charite.de Tel: +49 (0)39 450 514226
	Prof. Dr. med. Martin Scherer Institut für Allgemeinmedizin Universitätsklinikum Hamburg Eppendorf Martinistraße 52

	20246 Hamburg Mail: m.scherer@uke.de Tel: +49 (0)40 7410 58559
	Prof. Dr. med. Antje Bergmann Medizinische Klinik III – Bereich Allgemeinmedizin Universitätsklinikum Carl Gustav Carus Fetscherstraße 74 01307 Dresden Mail: Antje.Bergmann@uniklinikum-dresden.de Tel: +49 (0)351 458 3687
	Prof. Dr. med. Stefanie Joos Institut für Allgemeinmedizin & Interprofessionelle Versorgung Universitätsklinikum Tübingen Osianderstraße 5 72076 Tübingen Mail: stefanie.joos@uni-tuebingen.de Tel: +49 (0)7071 85226
Intensive Care Departments	**Prof. Dr. Bernhard Zwissler** Klinik für Anästhesiologie Ludwig-Maximilians-Universität Marchioninistraße 15 81377 München Mail: Bernhard.Zwissler@med.uni-muenchen.de Tel: +49 (0)89 4400 74550
	Prof. Dr. med. Gerhard Schneider Klinik für Anästhesiologie Klinikum rechts der Isar Technische Universität München Ismaninger Straße 22 81675 München Mail: AINS@mri.tum.de Tel: +49 (0)89 4140 4291
	Prof Dr. med. Herwig Gerlach, MBA Anästhesie, operative Intensivmedizin und

	Schmerztherapie Vivantes Klinikum Neukölln Rudower Str. 48 12351 Berlin Mail: herwig.gerlach@vivantes.de Tel: +49 (0)30 130 14 2361
	Prof. Dr. med. Christian Zöllner Zentrum für Anästhesiologie und Intensivmedizin Universitätklinikum Hamburg Eppendorf Martinistraße 52 20246 Hamburg Mail: c.zoellner@uke.de Tel: +49 (0) 7410 52415
	Prof. Dr. med. Thea Koch Klinik und Poliklinik für Anästhesiologie und Intensivmedizin Universitätsklinikum Carl Gustav Carus Fetscherstraße 74 01307 Dresden Mail: thea.koch@uniklinikum-dresden.de Tel: +49 (0) 351 458 3453
	Prof. Dr. med. Peter Rosenberger Universitätsklinik für Anästhesiologie und Intensivmedizin Universitätsklinikum Tübingen Hoppe-Seyler-Straße 6 72076 Tübingen Mail: peter.rosenberger@med.uni-tuebingen.de Tel: +49 (0)7071 29 86622

Psychiatric Back-up Centers (for emergency)	**Prof. Dr. med. Peter Falkai** Klinik für Psychiatrie und Psychotherapie Ludwig-Maximilians-Universität Nußbaumstraße 7 80336 München

	Mail: Peter.Falkai@med.uni-muenchen.de Tel: +49 (0)89 4400 55511
	Prof. Dr. med. Hans Förstl Klinik und Poliklinik für Psychiatrie und Psychotherapie Klinikum rechts der Isar Technische Universität München Ismaninger Straße 22 81675 München Mail: hans.foerstl@tum.de Tel: +49 (0)89 4140 4201

	Prof. Dr. med. Dr. phil. Andreas Heinz Klinik für Psychiatrie und Psychotherapie Charité – Universitätsmedizin Berlin Charitéplatz 1 10117 Berlin Mail: andreas.heinz@charite.de Tel: +49 (0)30 45051 7002
	Prof. Dr. med. Jürgen Gallinat Klinik und Poliklinik für Psychiatrie und Psychotherapie Universitätklinikum Hamburg Eppendorf Martinistraße 52 20246 Hamburg Mail: j.gallinat@uke.de Tel: +49 (0)40 7410 52205
	Prof. Dr. med. Dr. rer. nat. Michael Bauer Klinik und Poliklinik für Psychiatrie und Psychotherapie Universitätsklinikum Carl Gustav Carus Fetscherstraße 74 01307 Dresden Mail: michael.bauer@uniklinikum-dresden.de Tel: +49 (0)351 458 2760
	Prof. Dr. rer. soc. Thomas Elbert Klinische Psychologie und Klinische Neuropsychologie Universität Konstanz Universitätsstraße 10 78464 Konstanz Mail: Thomas.Elbert@uni-konstanz.de Tel: +49 (0)7531 88 4609

3 Schedule of Activities and Assessments

	STUDY PERIOD						
	Enrolment		**Allocation**		**Post-allocation**		
TIMELINE	**T -1**	**2 weeks prior to T0**	**T 0**	**Randomi-zation** (≤ 2 weeks after T0)	***Intervention period (3 visits)***	**T 1 (6 month after T0)**	**T2 (12 month after T0)**
Patient Informed Consent	X						
Eligibility Screen	X	X					
Patient level: In-/Exclusion Criteria			X				
PC-PTSD-5	X	X					
MoCA	X		X				
GP level: In-/Exclusion Criteria; GP characteristics		X					
GP Informed Consent		X					
ICU Data (incl. SOFA score)	X						
Patient medical history, demographics/ characteristics	X						
*Experimental intervention (**NET**)*				←	- - - →		
*Control intervention (**iTAU**)*				←	- - - →		
Documentation of SAE*			←	- - -	- - -	- - - →	
PDS-5			X			X	X
PHQ-9			X			X	X
OASIS			X			X	X
EQ-5D-5L			X			X	X
PAM			X			X	X
WHODAS 2.0			X			X	X
Modified CSSRI (incl. concomitant (drug) therapy, sociodemographic data)			X			X	X
Documentation of concomitant medication / therapy			X		X		
Check of compliance, protocol adherence (patient and GP level)			X		X	X	X

***** Safety documentation: to be performed by the treating GP starting at T0 until T2 (assuming that information about specific safety issues experienced by the patient will be reported to his/her GP).

A deviation from the schedule of +/-3 weeks is acceptable for T1 and T2.

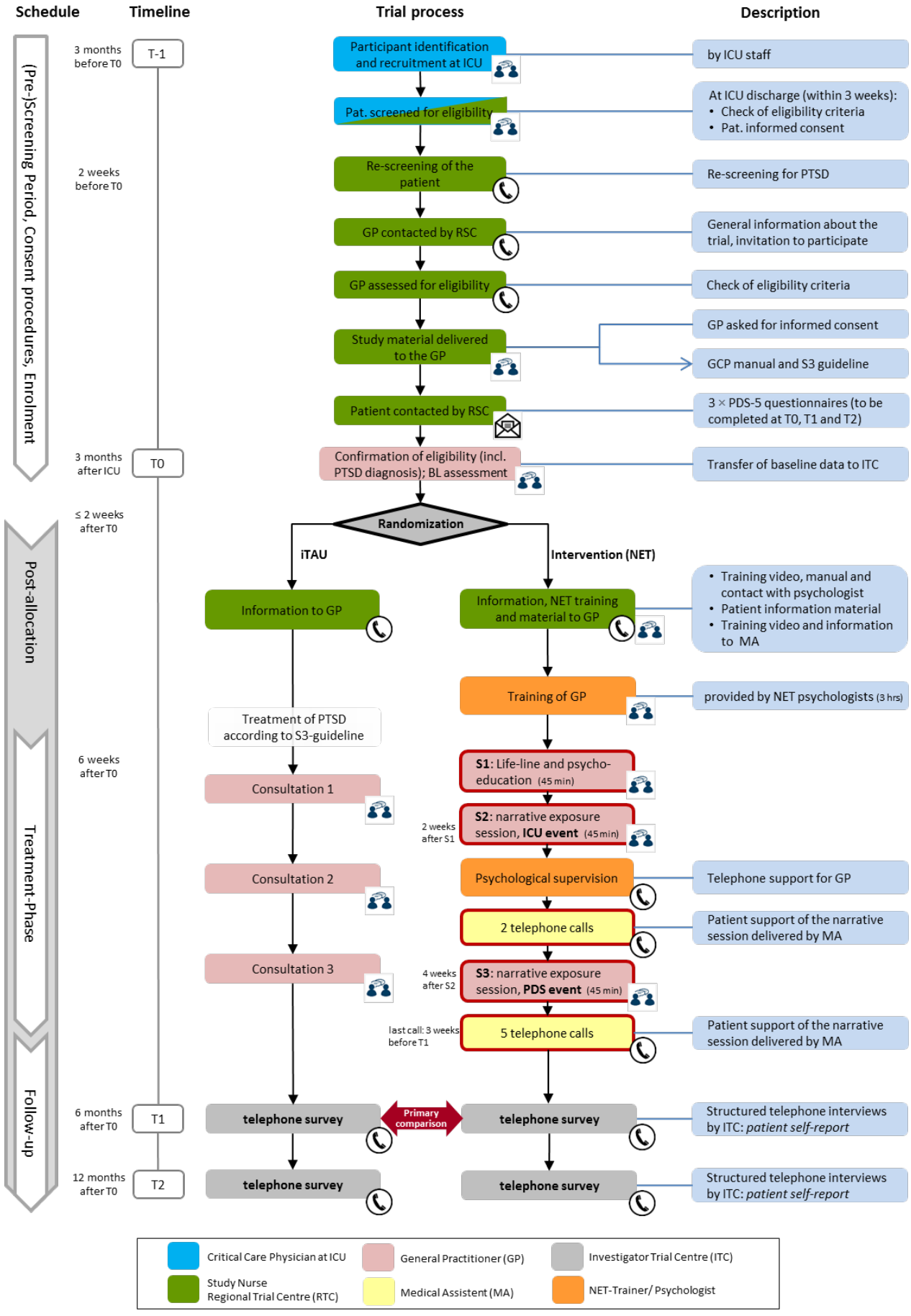

Figure 1*: Graphical depiction of study activities and components of intervention*

4 Abbreviations

CATI Computer assisted telephone Interview

CBT Cognitive Behavioral Therapy

CRF Case Report Form

CSSRI Client Sociographic and Service Receipt Inventory

DMP Data Management Plan

DSM Diagnostic and Statistical Manual

DSMB Data Safety and Monitoring Board

EC Ethics Committee

EQ-5D-5L EuroQuol-5D-5L

eCRF electronic Case Report Form

EDC Electronic Data Capture

EMDR Eye Movement Desensitization and Reprocessing

FPFV First Patient First Visit

GCP Good Clinical Practice

GP General Practitioner

GPID General Practitioner Identification Number

IBE Institute for Medical Information Processing, Biometry and Epidemiology

IC Informed Consent

ICD International Classification of Diseases

ICER Incremental Cost-effectiveness Ratio

ICH International Conference on Harmonization

ICU Intensive Care Unit

IES Impact of Event Scale

IES-R Impact of Event Scale Revised

IIT Investigator Initiated Trial

IN Interoceptive

IT Information Technology

ITC Investigational Trial Center (located at the site of the principal investigator)

ITT Intention to Treat

LKP Leiter der klinischen Prüfung

LPLV	Last Patient Last Visit
LRZ	Leibniz Rechenzentrum
MA	Medical Assistant in general practice
MD	Medical Director
MoCA	Montreal Cognitive Assessment
NET	Narrative Explorative Therapy
OASIS	Overall Anxiety Severity and Impairment Scale
PAM	Patient Activation Measure
PC-PTSD	Primary Care PTSD Screen
PDS	Post-traumatic Stress Diagnostic Scale
PE	Psycho-education
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PID	Patient Identification Number
PP	Per Protocol
PRS	Polygenic Risk Score
PTSD	Posttraumatic Stress Disorder
QALY	quality adjusted life years
QC	Quality Control
RCT	Randomized controlled trial
RTC	Regional Trial Center
S	Session
S3	S3-Leitlinie/Nationale Versorgungs-Leitlinie
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
PCA	Polymerase Chain Reaction
SNP	Single Nucleotide Polymorphism
SOFA	Sequential Organ Failure Assessment
SSH	Secure Shell Protocol
iTAU	improved Treatment as Usual
TC	Telephone Call
TFCBT	Trauma-focused Cognitive Behavioral Therapy

TSF Trial Site File

VAS Visual Analogue Scale

WHODAS 2.0 World Health Organization Disability Assessment Schedule

5 Introduction

5.1 Background

In Germany, two million treatment cases are encountered at the Intensive Care Units (ICUs) every year, and more than 350,000 of these undergo mechanical ventilation. Approximately half of the patients suffer long-term functional, psychological or medical sequelae as a result (Desai, Law, Bienvenu, & Needham, 2011). At an international consensus conference in 2012, "Post-intensive care syndrome" was defined (Needham et al., 2012). Posttraumatic stress disorder (PTSD) is a common sequela (25-44%, (Parker et al., 2015)) and has a substantial impact on quality of life and cost (Greenberg et al., 1999). Symptoms may remain for years after ICU discharge. Systematic screening and early interventions may improve primary care (McGovern, McGovern, & Parker, 2011). In Germany, a guideline for treating patients with PTSD in primary care exists (Flatten et al., 2013) but access to psychiatry/psychotherapy services is limited, and waiting periods of 6 months are the norm (Helbig, Hähnel, Weigel, & Hoyer, 2004). During this period the GP is the main health professional attending to the patient. Effective and feasible interventions in primary care are needed (Kuwert, Hornung, Freyberger, Glaesmer, & Klauer, 2015).

The trauma-related symptoms arise from a failure to construct adequate memories of the traumatic experiences. Memories are formed by emotionally arousing experiences that activate either approach or avoidance responses, and develop their own specific intrinsic dynamics. In PTSD, sensory, cognitive, and affective representations have lost association with the contextual and episodic memory system. The goal of trauma-related therapy is to reconnect the memory fragments. In “Narrative Exposure Therapy” (NET) (Schauer, Neuner, & Elbert, 2011), the patient builds a narrative, which focuses on the contextualization of traumatic experiences. Counsellor and patient together design a “lifeline”, consisting of relevant biographical events. This specifically relies on the GP’s skill at taking comprehensive medical and psycho-social histories. Subsequently, the patient recounts the stressful situations to recover contextual details of the traumatic event – rather than intrusive memories.

This has significant effects on the mind (Schauer et al., 2011), brain (Adenauer et al., 2011), and body (Morath et al., 2014) and is recommended in international ISTTS-guidelines (E.B. Foa, Keane, & Friedman, 2000). NET is effective, when delivered by medical non-professionals (Zang, Hunt, & Cox, 2014), even when limited to only three sessions (Hijazi et al., 2014). The applicants have completed a primary care-based intervention study to improve long-term sequelae in 290 post-ICU-patients (with sepsis or septic shock). The intervention consisted of case management by trained nurses, clinical decision support by a consulting physician for the patients’ GPs and education in evidence-based care for sepsis sequelae for both patients and GPs over a period of 12 months. The exploratory analyses showed possible positive effects on Quality of life and Activities in Daily Living (ADL) but no improvement of primary outcomes because the intervention may have been too unspecific (Schmidt et al., 2016).

Based on these results we expect improvement in long-term sequelae for post-ICU patients in primary care, when interventions are more disease-specific, i.e. when patients show posttraumatic symptoms.

A number of interventions support recovery from Post Intensive Care Syndrome (Needham et al., 2012). We performed a systematic literature review of these (Mehlhorn et al., 2014). Of an

identified 4,761 publications (1991-2012), 18 studies of 2,510 patients were included. 8 controlled trials investigated geriatric rehabilitation, ICU follow-up clinic, outpatient rehabilitation, disease management, and ICU-diaries. 5 of these trials assessed Post Traumatic Stress Disorder (PTSD), and 4 of them showed positive effects: ICU-diaries reduced new-onset PTSD (5% versus 13%, p = 0.02) after 3 months and also showed a lower mean Impact of Event Scale (IES-R) score (21.0 versus 32.1, p=0.03) after 12 months. Aftercare as conducted in an ICU follow-up clinic reduced IES in women (20 versus 31; p< 0.01), and a self-help manual led to a reduction in the number of patients scoring highly in the IES after 8 weeks (p=0.026), but not after 6 months. Interventions, which have a substantial impact in post- ICU patients, are rare. Positive effects were seen for ICU-diary interventions for PTSD. The results have been confirmed by a recent Cochrane Review (Jensen et al., 2015).

In another intervention trial for "panic disorders" conducted in small general practices, we determined whether a training on psychological exposure therapy is feasible in general practices and superior to usual care (Hiller, Breitbart, & Schelle, 2015). The cluster-RCT in 73 German general practices (2013-2015) enrolled 412 adult patients (mean age: 46.4 years, SD = 14.2 years; sex: 75% female) with panic disorders and with/without agoraphobia (ICD-10: F41.0 or F40.01). The GPs delivered exposure exercises during 4 structured face-to-face consultations. After a 6-month intervention, Beck's Anxiety Inventory (EZ 0.3) showed an improvement compared to usual care. After 3 hours of training for the GPs, treatment fidelity was excellent: psycho-education / PE (90.4%), PE and interoceptive / IN (76.1%), PE and IN and situate exposition (64.5 %).

Previous pilot studies

We designed and piloted a psychological intervention to improve posttraumatic symptoms in primary care. In the first pilot study, based on an 8-session version, 67% of trained physicians (n=7) implemented NET in their practice, and 77% of the physicians regarded it as effective. In conclusion, GPs seem to be able to deliver NET. Taking limited GP resources into account we designed a very brief primary care version of NET (3x45 min) for patients that had been discharged from an ICU. In a second pilot, 15 GPs were involved and evaluated. Most of them reported acceptance and the feasibility of the training program and manual and felt sufficiently well trained (theory and practice) to deliver NET primary care to their patients. Only two GPs reported limitations in their ability to deliver because of time constraints in their daily work (Schmidt et al., 2015).

5.2 Add-on projects

Three sub-studies will be conducted together with the PICTURE – PTSD after ICU Survival-trial ("PICTURE-Genetic", "PICTURE-Economics", and "PICTURE-Psychotherapy in general practice")

5.2.1 "PICTURE Genetic"

This sub-study considers ICU patients with PTSD compared to ICU patients without PTSD (no participants of the PICTURE trial) investigating genetic distinctiveness. All details pertaining to this

study will be described and submitted in a separate document. No further details will be provided in the protocol of the PICTURE trial.

5.2.2 Health economic evaluation ("PICTURE-Economics")

Background

PTSD poses a high economic burden on the German society. According to the "Deutsche Traumafolgekostenstudie" [German cost study on the consequences of trauma] the annual costs caused by the consequences of trauma amount to 11 billion € (Habetha et al., 2012). Based on data from the German statutory health insurance case-related treatment cost are high as well. The costs to treat one case of PTSD in a psychiatric hospital add up to 8.600€ (women) or 7.200€ (men). In the outpatient sector annual costs of psychotherapy for PTSD are 1100€ (women) and 900€ (men) (Wissenschaftliche Dienste des Bundestag 2016). Due to this high costs and the aforementioned observations, that PTSD is a frequent sequelae after ICU treatment (Parker et al., 2015), and that waiting periods for psychotherapy in Germany are quite long (6 months) (Helbig et al., 2004), the implementation of a structured and low threshold intervention is desirable - from an economic point of view, too.

Rationale

The objective of the heath economic evaluation is the assessment of the cost-effectiveness of the NET-oriented intervention in comparison to iTAU from a societal perspective. We will consider health care costs as well as productivity losses to describe the monetary consequences of the intervention and calculate quality-adjusted life years (QALY) as measure of effects.

These results will inform decision-makers in the health care sector about the economic aspects of the NET intervention and support them in the decision whether the intervention should be implemented in the German health care system. According to the results from prior studies, we expect to show that the NET-intervention is cost-effective compared to usual care.

Objective of "PICTURE-Economics"

To determine whether the NET intervention is cost-effective from a societal perspective compared to iTAU in patients diagnosed with PTSD after ICU survival.

We hypothesize that the NET-treated patients will cause lower health care costs and lower productivity losses compared to patients assigned to the iTAU group while gaining a larger number of quality-adjusted life years, according to a better quality of life.

Analyses

The cost-effectiveness of the NET intervention compared to iTAU will be determined from a societal perspective based on the ITT population. First, the incremental cost-effectiveness ratio (ICER) will be calculated as the difference in mean cost divided by the difference in mean QALYs:

$$ICER = (Cost_{NET} - Costs_{iTAU})/(QALY_{NET} - QALY_{iTAU}).$$

Second, net-benefit regressions will be conducted to determine the uncertainty of the point estimate (ICER) and to adjust for potential baseline differences and confounders (Hoch 2002). These results will be used to construct cost-effectiveness acceptability curves, which show the interventions' probability of being cost-effective at different willingness-to-pay margins (Range: 0€/QALY – 150.000€/QALY; raised in 10.000€/QALY steps) in comparison to iTAU. The underlying assumptions regarding the calculation of costs and benefits will be investigated in several sensitivity analyses.

Further methodological detail will be included in a separate section of the Statistical Analysis Plan (SAP) of the principal trial. The impact of incomplete documentation with respect to the applied CSSRI and EQ questionnaires will be discussed as well.

5.2.3 Process evaluation ("PICTURE-psychotherapy in general practice")

Background

Implementation of a primary care-adapted psychotherapeutic intervention for PTSD-patients in GP practice in Germany is not established and experiences of conducting psychotherapy in practice are only researched in few studies To gain insight into the process of implementing a narrative intervention in a general practice setting we investigate the experiences of GP's carrying out this brief narrative intervention in PTSD-patients in a primary care setting. At the same time, we are looking at patients' perception of this treatment in a GP practice and of the impact on the patient-GP-relationship (Davidsen, 2009). To gain further insight we also include the experiences and views of the psychologists that trains and supervises the GPs in the intervention group.

Rational

This psycho-education of GP's is a novel approach to treatment of patients with PTSD. However, knowledge is sparse about the experiences of GP's in learning and implementing a psychotherapeutic treatment method in practice and how patients perceive the availability and the performance of a psychotherapeutic treatment delivered by their family physician. The rationale for the PICTURE-Psychotherapy study is to capture and describe GP's first-hand experiences of the trial process as well as the patients' experiences of availability and quality of the treatment received, in order to enable identification of potential facilitating or hindering factors to further implementation of the treatment in primary care.

Objective of "PICTURE-Psychotherapy"

The objective of "PICTURE-Psychotherapy" is to answer the question: "How do patients with PTSD symptoms and their respective GP's experience the primary care-based NET-oriented therapy, and is this therapy manageable for GP's in a primary care setting?"

Therefore, we investigate the subjective perception of the narrative intervention for patients and GPs respectively, as well as the perception of GP's in terms of delivering and usability of the NET-oriented therapy and the perception of patients in terms of relevance and impact.

Procedures

In the NET group, semi-structured interviews will be conducted with patients, GP's and supervising psychologist, after T1. An estimated 10 to 15 interviews of patients and GP's, respectively and 3-5 expert interviews of supervising psychologists is needed to reach saturation of data.

There will be a purposeful sampling trying to involve a broad range of aspects. On enrolling interviewees we aim to include patients and GP's from urban and rural background, male and female gender, different age groups, patients of different social background and GP's in single and partner practices and with varying length of working experience.

Patients and GP's will be recruited from the NET-group at the Charité site of the trial and one other trial site (– *to be decided later*). If we cannot include enough interviewees to cover all relevant aspects, patients and GP's from other sites may be approached as well.

Patients and GP's will be contacted by phone or letter asking for their willingness to participate. Conditional of their acceptance, they will receive the study information and consent form. Interviews will be scheduled by phone or mail after informed consent has been given. Interviews will take place at the preferred site of the interviewee, either at the interviewee's home or practice or in a quiet room at the Institute.

Interviews are expected to last 30-60 minutes but time range may vary according to the amount and length of information interviewees want to give.

Expert interviews with psychologists will be carried out by phone and are expected to last 20-30 minutes. All interviews will be audio-recorded.

During transcription of the interviews, all names, places etc. that can identify the person interviewed will be omitted and the anonymous text file will be stored in the server of the Charitè Universitätsmedizin Berlin and the server of the co-operating Institute in a file only accessible by researchers working on the project. Interview tapes, contact addresses of GPs, patients and psychologist and consent forms will be kept secured in a fire insulated safe.

Analyses

Transcribed interview data will be analyzed using thematic analysis to explore process and implementation experiences (Braun & Clark, 2006). The analytic process is structured and includes 6 defined phases (Phase 1: Becoming familiar with the data, Phase 2: Generating initial codes, Phase 3: Searching for themes, Phase 4: Reviewing themes, Phase 5: Defining and naming themes, Phase 6: Producing the report). A separate document with further details concerning conduct and analyses will be provided before any project-specific procedures commence.

5.3 Trial Rationale

We conduct this trial to evaluate whether a primary care-based brief NET–oriented intervention for post-ICU patients with posttraumatic stress symptoms effectively improves clinical outcomes as assessed using the Posttraumatic Diagnostic Scale PDS-5 [2016] (Posttraumatic Diagnostic Scale for DSM-5) in comparison to improved treatment-as-usual (iTAU), which is representable for regular follow-up on patients after hospitalization including ICU-care. The regular follow-up on these patients is usually symptom-oriented and does not necessarily include a pro-active approach towards PTSD-symptoms by the treating GP. Instead, PTSD is often not verbalized and patients are treated symptomatically or referred for specialist care. However, waiting times of several months remain rather common in the German mental health care system and patients suffering from PTSD must often wait 6 month before receiving psychological treatment (Helbig et al., 2004). Hence, there is a need to investigate the potentials of implementing a structured and low threshold primary care intervention delivered by the patients GP.
A Cochrane Review presented a number of evidence-based treatments for (chronic) PTSD (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013). A recent qualitative study pointed out the need to investigate patients' memories after ICU discharge (Chahraoui, Laurent, Bioy, & Quenot, 2015).
Schnyder and the pioneers, who developed these empirically supported psychotherapies for trauma-related disorders, provide brief summaries, highlighting the following commonalities (Schnyder et al., 2015): psychoeducation, emotion regulation and coping skills, imaginal exposure, cognitive processing, restructuring, and/or meaning making, emotions, and memory processes. NET implements these elements by taking advantage of the universal capability of humans for story-telling and was originally developed for treatment in resource-poor countries where psychotherapists and psychiatrists are not available. It is the only method that has been proven effective, even when applied by paramedics, nurses or local counsellors, and it is therefore also suitable for use by physicians with no extensive training in psychotherapy.

6 Trial Objectives and Endpoints

The overall goal of the PICTURE trial is to evaluate whether a primary care based NET-oriented intervention improves patient-reported outcomes such as PDS total severity score, quality of life, common co-morbidities depression and anxiety in patients with PTSD after ICU discharge.
This study aims to describe and compare the real-world effectiveness safety and applicability of a primary care based complex psychological intervention with improved “usual care”.

6.1 Primary Objective

The primary objective of the trial is to determine the long-term effect of the NET-oriented therapy compared to iTAU, on patient-reported PTSD symptoms measured by the PDS total severity score after 6 month.

Primary study hypothesis:

The NET–oriented intervention is more effective in improving the PDS total severity score than iTAU.

6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the absolute change in PDS-5 total severity score from baseline to T1, i.e. the difference between the 6-month post-randomization score and baseline score assessed at T0.

6.3 Secondary Objectives

The secondary objectives of this trial are:

a) To assess the efficacy of the NET-oriented intervention compared to iTAU with respect to

- *depression symptoms*
- *anxiety symptoms*

Hypothesis: Depression is a comorbid disorder commonly associated with PTSD (Campbell et al., 2007) and observed post ICU (Davydow, Gifford, Desai, Bienvenu, & Needham, 2009). Anxiety disorders are common prevalent comorbidities following posttraumatic symptoms (Zlotnick et al., 2006). NET effects were demonstrated in reduction of severity/diagnosis, depression, suicidality, anxiety and drug abuse (Schauer et al., 2011).

b) To assess the efficacy of the NET-oriented intervention compared to iTAU with respect to

- *health-related quality of life*
- *Disability*
- *Patient Activation Measure*

c) To check for the occurrence of adverse effects of the intervention

6.4 Secondary Efficacy Endpoints

- PDS-5 total severity score: absolute change from baseline at T2
- PHQ-9 total score: absolute change from baseline to T1 and T2
- OASIS-D total score: absolute change from baseline to T1 and T2
- EQ-5D-5L: VAS at T1 and T2
- WHODAS 2.0 total score: absolute change from baseline to T1 and T2
- PAM total score: absolute change from baseline to T1 and T2

6.5 Additional secondary efficacy endpoints for “PICTURE-Economics”

- Costs (CSSRI)
- QALYs (calculated using the EQ-5D-5L index values)
- incremental cost-effectiveness ratio

at T1 and T2

6.6 Safety Variables

The occurrence of safety events (SAE) between T0 and T2, e.g. death, major depression or suicidality, hospitalization, and referral for psychiatric care, will be assessed systematically by the GP during the consultations. Any indications of SAE will be documented and reported to the PI and the data safety and management board (DSMB) (See section 13).

7 Trial Design

7.1 General design issues:

This investigator-initiated study is designed as a prospective, randomized, multi-center, two-arm parallel-group, assessor-blinded, controlled, comparative effectiveness trial with a fixed sample design and a pragmatic attitude.

7.2 Number of centers

The trial will be conducted in 6 centers across Germany, which must meet the structural and personnel requirements for performing the planned regular trial-related investigations. If necessary, additional qualified centers may be included to enhance recruitment.

7.3 Number of subjects

A total a number of N = 340 patients together with their treating GPs will be enrolled.

7.4 Time Schedule

Per patient:

- duration of intervention, NET group: 18 weeks (6 weeks narrative session plus 12 weeks telephone monitoring)
- duration of intervention, iTAU group: 3 consultations with the GP between randomization and T1
- duration of follow-up: 6 months
- total individual study duration: 12 months

Expected Trial duration:

- Recruitment Period (FPFV to LPLV): 12 months (at least)
- Planned Start Date (FPFV): 01.10.2017
- Planned End Date (LPLV): 31.12.2019 (including FUs)
- First patient in to last patient out (months): 30 months
- Duration of the entire trial (months): 36 month

The end of the clinical trial is defined by the last individual trial-specific examination during the last visit of the last patient to be part of the trial.

8 Trial Population and Eligibility Criteria

This trial can fulfill its objectives only if appropriate patient and GPs are enrolled. On the patient level, eligibility criteria are defined to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

8.1 Inclusion Criteria for GP practices

- The GP practice has to be registered since at least two years in the German statutory health care system as a family doctor.
- The participating GP must have a qualification in "basic psychosomatic care" (Bundesärztekammer, 2001) to ensure basic qualification for mental health problems and patients' safety.
- Alternatively, if no certificate for "Basic Psychosomatic Care" can be provided, the GP has to be a family doctor within the German statutory health care system for at least 10 years and has to provide evidence for adequate psychological, psychosomatic or psychiatric education. This is to ensure equivalent psychological knowledge in primary care for all participating GPs.
- Written informed consent

8.2 Exclusion Criteria for GP practices

- GP practices with >80% of their patients having a specific medical condition will be excluded from the trial to ensure the practice being a representative of German primary care.
- GP refused to give written informed consent

8.3 Gender Distribution - Patients

No gender ratio has been stipulated in this trial as the results of preclinical and / or clinical studies or medical literature did not indicate any difference in the effect of the investigated therapy in terms of efficacy and safety.

8.4 Inclusion Criteria for Patients

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

- PTSD symptoms: PDS-5 Score ≥ 20 (20-item Posttraumatic Diagnostic Scale for DSM-5)
- Montreal - Cognitive Assessment: MoCA Score ≥ 24
- Patients must be able to follow study instructions and likely to attend and complete all required visits and telephone surveys
- Written informed consent of the patient

8.5 Exclusion Criteria for Patients

Patients will not be included in the study if any of the following criteria applies:

General Exclusion Criteria:

- Patient not able to give written informed consent
- Patient without legal capacity who is unable to understand the nature, scope, significance and consequences of this clinical trial
- Patient has insufficient understanding of the German language
- Patients with a physical or psychiatric condition which at the investigator's or the GP's discretion may put the subject at risk, may confound the trial results, or may interfere with the patient's participation in this clinical trial
- Known or persistent abuse of medication, drugs or alcohol as assessed by GP

Indication specific exclusion criteria:

- Major depression PHQ-9 Score ≥23 (referral to specialist care)
- Acute suicidality (diagnosed by GP; referral to specialist care)
- Life expectancy < 9 months
- Concomitant therapy: already receiving another psychotherapeutic trauma therapy such as EMDR or CBT at baseline
- Medication: any neuroleptic, anticholinergic or anti-epileptic drugs

Key exclusion criteria at T0:

- Cognitive dysfunction: MoCA < 24
- PTSD symptoms: PDS-5 Score > 50 (referral to specialist care)

8.6 Patient Information and Recruitment

During their stay at ICU potentially eligible patients will be identified by the critical care physician at the ICU. If a patient appears to be eligible for the trial, the study nurse will inform the patient about the study, ask for written informed consent to participate and written consent to contact the respective GP and complete screening within 3 weeks of ICU discharge. If the patient is unable to respond adequately, his/her relatives will be asked for permission to approach the patient later, as participation in the study is considered to benefit the patient. Also, in case the patient is unconscious or otherwise unable to respond adequately, a medical physician independent of the trial will sign the informed consent form on behalf of the patient to enable collection of data at the ICU. When the patient has reached again full legal capacity he will be informed about the study and asked for written informed consent. If he refuses to participate, all data will be deleted. The RTC will inform the respective GP about the trial, check his/her eligibility and ask for his/her written informed consent.

It is a requirement that written consent (patient as well as GP level) is obtained prior to any trial-specific procedures.

8.7 Screening and Re-Screening instruments and study enrolment procedures

Screening (in-person) and re-screening (by phone) will be performed by the critical care physician at the ICU and a study nurse affiliated at the RSC. Patients fulfilling inclusion criteria such as male or female patients aged 18 to 85 years, mechanical ventilation of a duration ≥ 5 days and a Sequential Organ Failure Assessment (SOFA) Score ≥ 10 (as assessed by the maximum SOFA score during the ICU stay) will be assessed by the electronic patient data monitoring system (PDMS) and documented by case number. In case the patient has reached again full legal capacity, the critical care physician will inform the patient about the objective of the study and trial procedures, and will ask for written informed consent. Then the critical care physician will inform a study nurse affiliated at the RSC on the informed patient. Within 3 weeks while the patient is still hospitalized (time point T-1) the study nurse will check additional inclusion criteria using validated scores for posttraumatic stress disorder (PC-PTSD-5) and cognition (MoCA) derived by semi-structured face-to-face interviews.

Primary Care PTSD Screen for DSM-5 (PC-PTSD-5):

The PC-PTSD-5 is a 5-item screening instrument used in the primary care setting. This interview-administered questionnaire was designed to identify patients with PTSD, who require further assessment. The PC-PTSD-5 assesses whether the patient had any exposure to traumatic events at all. If exposure is denied, the score is 0 and the test complete. In case the patient answers ‘yes’, there will be five more questions about how the traumatic event has affected him/her *over the past month*, e.g. as nightmares, avoidance, guilt etc. For each question the patient scores one point,

showing signs for possible PTSD with a total score ≥3 points. For patients screened positively at T-1 and who provided written informed consent this screening instrument will be again be applied 2 weeks prior to T0 as telephone-administered structured interview performed by the study nurse of the RTC.

Montreal Cognitive Assessment (MoCA):

The MoCA is a brief one-page 30-point test administered in approximately 10 minutes to assess different aspects of cognitive abilities, incl. orientation to time and place, short-term memory, executive function, language abilities, attention, concentration and working memory, and visuospatial ability. MoCA scores range between 0 and 30 (low total score indicates high cognitive impairment). A score of 26 or over is considered to be normal. At T-1, the study nurse will carry out the MoCA test and the test result will be interpreted and verified by an RTC affiliated physician. At T0, this test will again be applied by the treating GP during the baseline visit serving as one of the key inclusion criteria.

Sequential Organ Failure Assessment (SOFA) Score

The SOFA score is used to evaluate the level of organ dysfunction and commonly used to determine the mortality risk in ICU patients. The score takes the evaluation of 6 organ systems into account (respiratory, cardiovascular, hepatic, renal, coagulation and neurological). Patients score a maximum of 4 points for each organ system, leading to a total maximum score of 24 points, associated with a high ICU mortality. Severity of illness and risk of mortality is best predicted by the highest score taken during treatment in the ICU and will be used as an inclusion criterion in this study if the score at any time exceed 10 (Vincent et al., 1996)

9 Randomization and Blinding

9.1 Randomization procedure and allocation concealment

All patients together with their GP who give consent for participation and who fulfil the eligibility criteria (both on the patient- as well as on the GP-level) will be randomized after all recruitment and screening activities are completed. This includes confirmation of PTSD diagnosis by the treating GP of the trial participant, together with baseline assessment at T0.

Randomization of the patients is requested no later than 2 weeks after baseline visit at T0.

The randomization number consists of a consecutive three-digit tracking number. The identification number results from a combination of the regional trial centre number and a tracking or screening number.

Concealed randomization to both treatments (NET; iTAU) will be performed with a 1:1 allocation ratio. The allocation sequence will be generated by an independent person affiliated to the 'Randoulette team' of the Institute for Medical Informatics, Biometry and Epidemiology (IBE) of the University of Munich who is not involved in assessing the outcomes of the study. The investigators (at the study site) and the GP will be informed about the treatment arm to which his patient is allocated (randomization unit: patient). Neither the investigator, the patient, the GP (including the practice staff), the study personnel including the biometrician, nor the interviewers affiliated to the ITC at the Institute of General Practice, University of Munich, can get access to the randomization list. The randomization is based on a permuted balanced block design with random block length. The procedure considers stratification by study site.

The IBE will provide the internet-based randomization tool '*Randoulette*' (https://wwwapp.ibe.med.uni-muenchen.de/randoulette/) which assigns a specific treatment (NET vs. iTAU) when a new patient and the corresponding GP fulfils the inclusion criteria. In this way, an immediate registration and randomization of enrolled participants is guaranteed.

Since neither the patient, nor the GP can be blind to the allocated treatment, emergency unblinding of single patients is not applicable in this trial.

The RTC will inform the GP practice about the respective allocation status (NET vs. iTAU) after randomization via an official letter and ask the GP to inform the participating patient.

9.2 Blinding

This trial is designed assessor-blinded: Neither the participant nor those who are administering the experimental intervention (GP with support of the MA) or the GP providing usual care in the control group are blind to group assignment.

The trained interviewer staff affiliated to the ITC at the Institute of General Practice, University of Munich, will assess the patient-reported primary and secondary efficacy outcomes blind to group assignment (*blindness of outcome assessors*). Post-randomization data will be collected through structured telephone interviews at T1 and T2 by ITC staff without access to additional patient data (including paper-based CRFs) or the study database.

The trial statistician will remain blinded to randomisation codes throughout the course of the trial, i.e. until the study database has been finalised and locked for the final analyses after LPLV.

10 Intervention Groups

GPs in both groups will receive training through written materials and via video in diagnostics and treatment of PTSD according to the German S3-Guideline on PTSD (patient-stabilization, referral to specialist care) (Flatten et al., 2013). Furthermore, GPs and MAs will receive video instructions on Good Clinical Practice (GCP).

10.1 Experimental intervention (narrative exposure (NET)-oriented therapy)

GPs in the intervention group will be trained in delivering NET-primary care by NET-experienced psychologists in a group setting (3h) and by a training video, providing information on the theoretical background and practical applications. If group training is not applicable, training will be delivered one-to-one. According to the modified "NET Primary care Manual" patients in the intervention group should receive 3 NET sessions (S) (*The NET-primary care study group. Behandlung posttraumatischer Belastungen bei Patienten nach ITS-Aufenthalt durch Narrative Exposition in der Hausarztpraxis*, 2015).

Session 1 (45 min): structured diagnosis of posttraumatic symptoms - psychoeducation and relevant life events ("lifeline"):
Psychoeducation: The patient will be informed about the symptoms. The memory model and the treatment procedure are described.
Lifeline: Subsequently, the 'lifeline' provides in chronological order the life story of the patient in terms of symbolic events and sorts these events (loads and resources). To the patient this symbolizes the main events of her/his life along a rope that serves as a timeline. The doctor gets an overview of stressful events in the patient's biography as well as positive experiences that can serve as resources. At the end of the session the ICU event will be implemented in the 'lifeline' as well. The GP will give an outlook on the following sessions and explain the next steps to the patient.

Session 2 (45 min) – **ICU event**. *A narrative exposition in which the patient recounts in detail stressful situations at the ICU and locates stressful events in time and space*:
This meeting is intended to bring about "the new review" of the stressful experience of ICU-time. For the treatment to be effective, it is important to focus and to recall experiences before and during the period at the ICU. The contextual information should be clearly verbalized while the event is discussed in detail. During the session the GP will take notes of the patient's description in a structured manner.
At the end of the session the GP will explain the content of the next session with the patient and encourage him to reflect between sessions.

Telephone support for GP provided by the NET-experienced psychologist (approx. 45 min): The psychologist will give guidance and advise where needed and will help the GP to prepare the following session (S3) when necessary.

Session 3 (45 min) – **PDS event.** *Narrative exposure of a key traumatic life event, which is suspected to have caused or added to the current PTSD*:
An additional stressful life event will be the topic of this session. Important general aspects of each event are time and setting: to determine as accurately as possible, when the incident occurred, at what stage of life, where and when it happened. Patients shall recall the cognitions, emotions and physiological responses then and there, and contrast them with the experience of recalling the traumatic event and verbalize them.

Telephone support of the patient by the MA: the GP practice affiliated medical assistant will call the patient 7 times (duration approx. 15 minutes) regularly every 2-3 weeks between S1 and T1 to check up on the patient's PTSD symptoms and wellbeing and remind the patient to reflect between sessions.

10.2 Control intervention iTAU

Standard of care for post-ICU patients is characterized by low use of psychotropic medication and specialist care, or e.g., prescription of anti-depressive medication. Patients in the control group will receive usual care from their GP without any patient-individualised recommendations from the study protocol.
However, participating GPs will be instructed in evidence-based diagnosis and treatment for PTSD based on recommended standards (the S3-guideline; for example referral to psychiatric treatment, medication (e.g. anti-depressive), and general information about symptoms associated with PTSD). Based on the S3-guideline, the GP and the patient in the iTAU-group will conduct three medical consultations ("improved" treatment-as-usual, iTAU) between T0 and T1.

11 Prior and Concomitant care

11.1 Prohibited Concomitant Therapy/ Medication for trial specific illnesses at baseline

Adjuvant psychotropic medications will be permitted, as recommended by the S3-guideline (Flatten et al., 2013). Patients taking neuroleptic, anticholinergic and/or antiepileptic drugs at baseline will be excluded as these medications adversely affect cognitive performance, especially in measures of learning and memory (Vinogradov et al., 2009).

To minimize performance bias, patients with additional psychotherapeutic trauma therapy, i.e. eye movement desensitization and reprocessing (EMDR) (Shapiro & Maxfield, 2002) or individual trauma-focused cognitive behavioral therapy (TFCBT) (Ponniah & Hollon, 2009) at baseline will be excluded from the trial, and not randomized.

11.2 Concomitant therapy / medication for other indications

The doses of other concomitant medications for e.g., chronic diseases should be kept as constant as possible throughout the trial and will be documented on the CRF at baseline T0.

12 Trial Procedures

12.1 Methods of Assessment

The following section will give an overview and adequate explanations to the examinations and procedures (assessment instruments) to be performed in this trial. Screening instruments are described in section 8.7. Several clinical scores derived from patient questionnaires (mode of administration: paper-based self-administered or by telephone interview) will be defined as primary and secondary outcomes.

12.1.1 PDS-5 total severity score (PTDS symptoms)

The PDS-5 total severity score is derived from the 'Posttraumatic Stress Diagnostic Scale', a patient-reported questionnaire assessing the PTSD-related symptoms according to DSM-5 [German translation, validation study of the German version ongoing – personal e-mail communication Wittmann, 31.05.2017]. Each of the 20 items refers to symptoms experienced in the past month only and is answered on a 5-point Likert scale ranging from 0 (not at all) to 4 (more than 5 times per week/ severe). This results in a total score with a range from 0 to 80 points. The PDS-5 total severity score has been found to have excellent psychometric properties and correlates with similar instruments for the diagnosis of posttraumatic stress, with high scores serving more severe PTSD symptoms (Edna B. Foa et al., 2016).
In this trial, the PDS-5 total severity score serves as key inclusion and exclusion criterion for the severity of PTSD symptoms at the beginning of the study prior to randomization.

12.1.2 PHQ-9 (Depression)

Depressive symptoms experienced over the last 2 weeks will be assessed by means of the primary care validated Patient Health Questionnaire-9 (PHQ-9) (Kroenke & Spitzer, 2002). Each of the 9 items is scored from 0 'not at all' to 3 'nearly every day'.

The PHQ-9 total sum score as a measure of depression severity ranges from 0 to 27, whereas a high score indicates severe impairment.

12.1.3 OASIS (Anxiety)

The brief OASIS questionnaire is the only measure of anxiety severity and impairment applicable to multiple anxiety disorders that has been validated for use in primary care (Campbell-Sills et al., 2009) (Norman et al., 2011). The five items are inspired by the ICD-10 F40-43 criteria (for phobic and other anxiety disorders, obsessive-compulsive disorder, reaction to severe stress and adjustment disorders) and refer to all aspects of anxiety symptoms, including panic attacks, situational anxieties, worries, flashbacks, hypervigilance of startle, experienced over the past week.

There are five different response options for each item, which are coded 0–4 and summed to obtain the OASIS total score ranging from 0 (no anxiety) to 20 points.

The five items ask about anxiety and fear, including frequency, intensity of symptoms, avoidance behaviour and impairments in daily life through these symptoms.
The OASIS-D is the German version of the validated original Anglo-American questionnaire, which was translated according to international standards for cross-cultural adaptation of self-report measures (Beaton DE, 2000) (Hiller TS, 2014) (Zlotnick et al., 2006)

12.1.4 Disability (WHODAS 2.0)

The WHODAS 2.0 instrument is commonly used to assess disability (Üstün TB, Kostanjsek N, Chatterji S, & J, 2010). The WHODAS-2 contains 36 items on functioning and disability with a recall period of 30 days covering 7 domains: *Understanding and Communicating* (6 items), *Getting around* (5 items), *Self-care* (4 items), *Getting along with others* (5 items), *Life activities: household* (4 items), *Life activities: work/school* (4 items), and *Participation in society* (8 items). Response options go from 1 (no difficulty) to 5 (extreme difficulty or cannot do). WHODAS-2 scores are computed for each domain by adding the item responses and transforming them into a range from 0 to 100, with higher scores indicating higher levels of disability. A global sum-score across all domains are also computed. WHODAS 2.0 has good psychometric qualities, including good reliability and item-response characteristics, and its robust factor structure remains the same across cultures and in different patient populations (Üstün TB et al., 2010).

12.1.5 PAM-Score (Thirteen-Item Patient Activation Measure)

As the promotion of active participation is one of the duties of the GP (Hibbard, Mahoney, Stockard, & Tusler, 2005), (Hollnagel & Malterud, 1995), the PAM measures the active participation of patients and the self-management of their state of health (Hibbard, Stockard, Mahoney, & Tusler, 2004) in form of a self-assessment. A short German version (PAM13) has been developed for use in clinical practice and research, that has good reliability and validity (Brenk-Franz et al., 2015) (Zill et al., 2013). The 13-item self-administered questionnaire assesses the knowledge of the patient regarding his/her health problems, the ability and the confidence to cope with these problems independently. Each item has four response categories with scores from 1 to 4: (1) strongly disagree, (2) disagree, (3) agree, and (4) strongly agree. The fourth item has an additional category with (5) not applicable. Evaluation is made by adding the raw values with a range of 13-52. For standardization of the gross total value, the sum-scale will be calibrated to a 0 to 100 metric.

12.1.6 EQ-5D-5L (Quality of Life)

The EQ-5D-5L is a generic instrument to measure HRQoL, and validated for several modes of administration (in-person, phone, mail). It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with five possible levels for each dimension,

describing the severity of problems in the specific dimension experienced today (*EQ descriptive system*): no problems, slight problems, moderate problems, severe problems, extreme problems.

The EQ-5D-5L is applicable to a wide range of health conditions and treatments and provides a single index value derived from the severity of problems in the five dimensions. It takes only a few minutes to complete.

Additionally, the EQ-5D-5L includes a visual analogue scale (*EQ VAS*), a thermometer-like rating scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Participants are asked to mark their current overall state of health on the scale.

12.2 Questionnaires for the health economic evaluation

The efficacy outcome of "PICTURE-Economics" is the *incremental cost-effectiveness ratio*. To assess the incremental cost-effectiveness ratio, two measures, one for costs, one for effects, are necessary.

- ***Costs*** will be assessed by means of a modified (shortened) German version of the Client Sociographic and Service Receipt Inventory (**CSSRI**) (Chisholm et al., 2000). This questionnaire considers the resource utilization for inpatient services, outpatient physician services, outpatient therapeutic services, medications as well as formal and informal care. Additionally, the questionnaire captures productivity losses caused by absenteeism. Resource utilization will be monetarily valued by means of administrative and market prices according to the German manual for standardized unit costs by Bock et al (Bock et al., 2015). Absenteeism will be valued according to the human capital approach by means of gross hourly wage plus non-wage labor costs.
- ***QUALYs****:* As measure of effects, we will use QALY, a composite measure consisting of the duration of life multiplied by a measure of preference-based HRQoL. In this study, the EQ-5D-5L index values will be employed (Herdman et al., 2011).

12.3 Experimental group

GP Training:

After randomization, GPs in the intervention group will additionally receive a NET manual, a NET video and will be trained (3h) in delivering the NET-oriented intervention (in groups of 3-6 GPs) delivered by locally based and trained master psychologists or MDs within 4 weeks after baseline visit. The training video shall provide information on the theoretical background and practical application of the NET-therapy. If group training is not possible, training will be delivered on a one-to-one basis.

MA Training:

MAs will receive the NET-oriented intervention manual and a teaching video within 4 weeks of baseline.

Session 1 (45 min):

Within the framework of the PICTURE-study, the patient visits her/his GP within 6-10 weeks after T0. During session 1 (S1) psycho-education and recall of relevant life events ("drawing of a lifeline") will take place. During psychoeducation the patient will be informed about the symptoms usually associated with PTSD. The treatment procedures are described to the patient.

Together with the GP, the patient will construct his “lifeline”. This symbolizes the patient’s main events of his life along a rope that serves as a timeline. The GP gets an overview of stressful events in the patient’s biography, as well as positive experiences that may serve as resources.

At the end of session 1, the patient is introduced to a MA, who will assist her/him throughout the study period. A photo of the lifeline is to be taken for monitoring purposes.

Additionally, the following session will be planned and the two PDS events to be discussed in S2 and S3 will be identified. PDS events are traumatic experiences in the patients’ life, which may have left unpleasant memories. If these memories have lost association with the contextual and episodic memory system, these patients might develop PTSD.

The ICU experience being the event to be discussed during session 2 and another major life event to be discussed in session 3.

Session 2 (45 min):

Session 2 is conducted 2 weeks after S1: a narrative exposition, in which the patient recounts in detail stressful situations at the ICU and locates stressful events in time and space. This session is intended to bring about "the new review" of the stressful experience of the ICU-time. For the treatment to be effective, it is important to focus and to recall experiences before and during the period at the ICU. The contextual information should be clearly verbalized while the event is discussed in detail. During the session the GP should take detailed notes about the patients’ experience to be able to follow up on these during the next session, if necessary, and for monitoring purposes.

At the end of session 2, the GP will encourage the patient to reflect about the session during the interim period and will address the content of the following session.

Interim period:

In the time period between session 2 and session 3, the patient should write down the ICU story, preferably including all positive and negative events. The written assignment is later to be handed over to the MA.

Telephone call to GP by psychologists (approx. 45min):

Between S2 and S3, the GP will be contacted via telephone by the respective certificated study psychologists, to ensure the intervention is carried out sufficiently, to answer questions about the NET-intervention and for general support about the choice of the key PDS event to discuss with the patient.

MA phone calls 1 and 2:

About a week after session 2, the MA conducts the first of 7 phone calls. At the first and by all subsequent calls, the patient is asked about her/his well-being and whether notes are taken about the event discussed during S1. The MA will encourage the patient to reflect upon the last session and to take notes about the event discussed in a diary to enhance the effectiveness of the intervention.

The patient receives the second call about 2 weeks later from the MA.

Session 3 (45 min):

Session 3 is to be scheduled 4 weeks after session 2 and consists of a narrative exposure of an additional key traumatic life event apart from the ICU-stay. Important general aspects of each event are time and setting. The patient should determine at what stage in life and under which circumstances the incident(s) occurred. Similarly, the patient should recall the cognitions, emotions and physiological responses associated with the event, and contrast these with the experience of recalling the traumatic event. The recalled responses should be verbalized. Again the GP should take structured notes during the session for monitoring purposes.

MA phone calls 3 – 7

After S3 and before T1 the patient receives the remaining 5 calls from the MA, each within 3 weeks. The phone-based procedure conducted during the first two telephone calls by the MA is repeated.

12.4 Control group

Between T0 and T1, the patient will be invited to consult her/his GP three times. These consultations should be performed as a face-to-face appointment. Further consultations may be conducted if needed. The content of the medical consultation is based on recommended standards (the S3-guideline; for example referral to psychiatric treatment, medication (e.g. anti-depressive), and general information about symptoms associated with PTSD).

12.5 Protocol adherence

a. Patient level:

Patient's compliance will be assessed regularly throughout the trial during the assessments at T0, T1 and T2 by the GP *for both groups*, additionally in the intervention group during the sessions (S1 – S3) and by the MA during the telephone calls between S2 and T1 (TC1 – TC7), and in the iTAU group during each one of three GP consultations.

b. GP level:

The protocol adherence of the participating GP will be documented throughout the trial by requesting copies of the notes taken during NET sessions, photos of all patients' lifeline and documentation about the time and duration of sessions/ consultations. In the iTAU group, the number of consultations will be documented.

12.6 Time schedule of Measurements

All visits and telephone calls will be performed according to (Schedule of Activities and Assessments) (Section 3) and the flowchart in Figure 1.
All subjects must have the following procedures completed prior to enrollment:

12.6.1 Screening period

T -1 = Day -90 (prescreening visit)

As part of the selection and recruitment process, patients invited during their ICU stay will be screened for eligibility at the ICU or within 3 weeks after ICU discharge (screening instruments, amongst others, SOFA, MoCA, PC-PTSD-5).

- Patient information and written informed consent
- Patient consent to contact his/her GP
- Documentation of medical history
- Demographic and patient characteristics
- ICU data: SOFA score of ≥ 10 (the maximum SOFA score measured during ICU stay serves as the point of reference), mechanical ventilation [days] during ICU, ICU duration [days], ICU medication at T-1 [yes/no] in terms of glucocorticoids, benzodiazepines, propofol, ketamine, neuroleptics, anticholinergic, anti-epileptics, opioids, anti-depressants.

2 weeks before T0 (Re-sreening)

All patients screened at T -1 will be contacted *via telephone* by the study nurse of the RTC for a brief second screening by using the PC-PTSD-5 instrument only.
If the patient is still eligible for the trial, the respective RTC will contact his/her GP by phone to inform about the trial and assess the GP for eligibility. If the GP is willing to participate, study material (S3 Guideline, GCP manual) will be sent to the GP by mail. The GP's written informed consent has to be completed within 2 weeks and sent back to the RTC.

12.6.2 T0 (Baseline visit, Enrolment)

At baseline visit T0, 3 month after T -1 (+/- 2 weeks), the GP will finally check the patient's inclusion and exclusion criteria (i.e. **final confirmation of eligibility,** screening instrument: MoCA). Furthermore, baseline data collection during this face-to-face visit will be performed. This also includes the completion of self-administered questionnaires (PDS-5, PHQ-9, OASIS, PAM, WHODAS 2.0 , EQ-5D-5L, CSSRI).

A follow-up appointment to be scheduled after randomization will be determined.

12.6.3 Randomization

Allocation to one of the treatment arms will be concluded no later than 2 weeks after T0.

12.6.4 Treatment period

NET-group

The treatment period will include 3 visits ("sessions") over a period of 6 weeks 6 to 10 weeks after T0.

- S1: Part 1 of intervention, to be scheduled 6 weeks (+/-4 weeks) after T 0
- S2: Part 2 of intervention, to be scheduled 2 weeks after S 1
- S3: Part 3 of intervention, to be scheduled 4 weeks after S 2

The following procedures will be performed regularly with about 2 week's interval:

- 7 short TCs (without documentation of any study data) to be scheduled every 2-3 weeks after S2 to support NET sessions: 2 calls between S2 and S3, and 5 calls between S3 and T1.

The last TC will be performed 3 weeks before telephone interview T1

iTAU-group

There will be three GP consultations between T0 after randomization and T1 to be scheduled as required by the patient and are based on recommended standards (the S3-guideline; for example referral to psychiatric treatment, medication (e.g. anti-depressive), and general information about symptoms associated with PTSD). The consultations should be performed as a face-to-face appointment.

12.6.5 Follow-up period

The structured telephone interview "**T1"** for the primary comparison will be scheduled 6 months (+/-3 weeks) after T0.

The final evaluation will be performed during a structured telephone interview "**T2"** to be scheduled 12 months (+/-3 weeks) after T0. This will be defined as the regular end of trial on the patient-level. For patients who terminate the trial prematurely (treatment discontinuation), but without withdrawing her/his consent, this will be defined as the "dropout telephone interview".

13 Safety Data Collection, Recording and Reporting

For this trial, the rules of safety data collection, recording, and reporting as known from pharmaceutical trials do not apply. Hence, we make no distinction between adverse and severe adverse events. All events are hereafter referred to as severe adverse events (SAE).

Serious adverse events (SAE) will be regularly monitored and investigated as of beginning of the intervention at S1 in the NET-group and the first of three GP-consultations in the iTAU-group until the end of trial at T2. The GP is the first point-of-contact during the intervention period and telephone interviewers at T1 and T2. If a patient cannot be reached via telephone at T1 and T2, the RCT will contact the respective GP for further information with regard to the patient's possible SAE-status. Any SAE will be reported to the Principal Investigator (PI) and the Data and Safety Monitoring Board (DSMB). The respective SAE-Form (see appendix) will be faxed by the GP or RTC immediately (within 24 hours the latest) to the PI. In addition to the reporting of the event to the PI and the DSMB, any SAE recorded during telephone interviews at T1 and T2 will immediately be entered into the study database via OpenClinica.

SAE include psychiatric emergency treatment, psychiatric inpatient treatment/hospitalization, significant deterioration of depression or PTSD-symptoms, acute suicidality and suicide.

In case of SAE, psychiatric back-up specialist of the following institutions are available to provide immediate support through the Depts. of Psychiatry affiliated to the ITC in Munich and to the RTCs in Berlin, Dresden, Hamburg and Tübingen (letter of declaration). These emergency back-up centers will be instructed accordingly.

13.1 Serious Adverse Event (SAE)

Any untoward medical occurrence that:

- have caused the patient's death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is qualified as another medically significant event or condition

- will be classified as serious.

13.2 Criteria to be evaluated by the investigator (1st assessment)

Special attention is to be paid to the occurrence of SAE throughout every stage of the clinical trial. The GP and subsequently the PI should evaluate all events according to the criteria and steps mentioned below.

13.2.1 Assessment of intensity

Any observed SAE has to be graded regarding its intensity.	
MILD	Does not interfere with patient's usual function, easily tolerated.
MODERATE	Interferes to some extent with patient's usual function.
SEVERE	Interferes significantly with patient's usual function, incapacitating with inability to work or carry out usual activity.

13.2.1 Assessment of causality

Decision as to whether the intervention (narrative therapy and improved treatment-as-usual) is causally related to the SAE is determined by evaluation of all accessible data (classification: suspected; not suspected).

When the final causality assessment is unknown and it is uncertain whether or not the investigational therapy caused the event, then the event should be handled as an SAE related (suspected) to the investigational therapy for reporting purposes.

13.3 Risk benefit Assessment

The only potential SAE is the possibility of triggering a severe depression, psychosis, an episode or a secondary hypochondriacally disorder by frequent interrogation of disease symptoms. The same applies to signs of acute suicidal behavior. After consultation with the principal investigator and the DSMB, inpatient treatment centers are available for both indications.

13.4 Criteria to be evaluated by the Data and Safety Monitoring Board (2nd assessment)

In addition to the first evaluation of any serious adverse event that is performed by the PI, a second evaluation with respect to seriousness, causality and expectedness and a risk-benefit assessment is performed at the investigator’s discretion by the DSMB to process safety evaluation according to a four-eyes principle.

13.5 Documentation and Reporting of Serious Adverse Events

Any SAE has to be reported immediately to the PI.

Documentation and evaluation of each SAE occurring:

- after the subject has been randomized and has received intervention
- up to the end of trial at T2

13.5.1 Initial reporting of SAE

SAE shall be reported using a report form with the following information (see appendix):

Report SAE to the Principal Investigator
Prof. Dr. med. Jochen Gensichen, MPH
IMMEDIATELY
after becoming aware of this event
Fax: +49 (0)89 4400-53779

13.5.2 Reporting to the ethics committee

The DSMB will be informed on a regular basis. If a relationship between the intervention and the SAE cannot be ruled out, the PI will report the event to the ethics committee including following information:

- A full description of the event(s)
- Trial Site
- Severity
- Criteria for regarding the event as serious
- Description of specific symptoms
- Description of specific diagnosis.

All SAEs will be followed up and a follow-up report as well as a closing report will be sent to the ethics committee by the investigator.

14 Safety and Quality management

To reduce the risk of inefficient clinical management (i.e. exposition), GPs will be trained in accordance to GCP- and S3-Guidelines in their ability to care for patients with PTSD and to detect and deal with SAE appropriately. GPs will be trained to prompt immediate referral to specialist care (clinical pathway or trial back-up clinic) in case of SAE (i.e. of symptom deterioration). Clinical checklists will aid in detection of and reporting of deterioration in symptoms. Departments of Psychiatry in Munich, Berlin, Hamburg, Dresden and Tübingen have guaranteed to provide priority access to mental health services and psychiatric emergency treatment.

Similarly, telephone interviewers collecting data at T1 and T2 will be trained in detecting indications of SAE. All instructions and processes related to any interaction with the patient (face-

to-face or per telephone), to detection and handling of SAE and to handling of data will be described additionally accordingly as standard operating procedures (SOPs) for all staff involved.

14.1 Data Safety and Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) has been installed. The DSMB will monitor recruitment, feasibility, the integrity of the trial, safety of study participants, and will review recruitment rates and accumulating safety summaries on a regular basis; additional data may be requested during the conduct of the trial. A DSMB *Charter* will outline the roles and responsibilities of its members. The DSMB may recommend discontinuation of the trial or modification of the protocol for safety reasons at any time during the trial

Particular attention will be paid to the incidence of particular SAE reported during the trial period, including death, suicidal behaviour, "severe intrusions", clinically significant intervention-related symptom deterioration, and referral to psychiatric care (e.g. psychiatric back-up centres located at the Departments of Psychiatry) or hospitalization.

14.2 Safety Assessment

Patient's safety will be monitored regularly by the GP between T0 and T2. Safety issues will be reported for all participants during their appointment at the GP's office (3 sessions S1 to S3 in the intervention group; 3 visits between T0 and T1 in the iTAU group). The monitoring form consists of 15 items assisting the GP in assessing the patients' current state of health with regard to detection of SAE. Scoring of the various items assessed by a coloring code (red, yellow, green) allows the GP to identify single issues that may be suspected for SAE as well as providing the GP with an overall impression of the patients state of health enabling the GP to respond appropriately, should the patient show signs of mental deterioration. Safety data will subsequently be stored in the patient's medical record and in the CRF (paper-and-pencil format).

14.2.1 Early termination of the trial by the patient

A patient may withdraw their consent to participate in the study at any time without giving reasons. In such a case the patient is asked to name a possible withdrawal reason, but there is no obligation to do so. Time and reasons for withdrawal (if known) will be documented in the CRF. By discontinuing the study, the patient does not suffer any disadvantages for further treatment.

14.2.2 Exclusion of a patient from the trial

Patients can be excluded from the study if a breach of the inclusion or exclusion criteria is post-hoc detected. In the case the family physician terminates the participation in the trial his/her patient will be excluded from the study as well.

Data from patients who drop out of the study after randomization, either through withdrawal or exclusion, are included in an intention-to-treat (ITT) analysis.

14.3 Quality management

Quality management will be carried out on several levels by the ITC and the regional study centers (RTCs).

To ensure accurate, complete, consistent, and reliable data, the ITC will provide advanced support for documentation and study management in order to ensure high quality during all processes in both treatment arms.

The ITC will independently compare and check data base entries of 10% of patients against completed CRFs.

Photos of the life-line and copies of notes collected at S2 for all patients will be sent by the GP pseudonymously to the ITC who will verify if the intervention has been carried out according to the protocol.

15 Statistical Methods

15.1 Planned Statistical Analyses

15.1.1 Analysis of primary efficacy endpoint

Primary efficacy endpoint is the absolute change in the PDS total severity score from baseline at month 6 (Δ_6PDS := $PDS_{T1} - PDS_{T0}$). By default, the mode of administration is a self-administered paper-based version. For patients who did not complete and send back the paper-based patient questionnaire (non-responding survivors), the PDS-5 total score will be assessed during the telephone survey T1, scheduled 6 months after randomization.

The null hypothesis

$$H_0: G_{NET}(x) = G_{iTAU}(x) \quad \underline{\text{and}} \quad K_{NET}(t) = K_{iTAU}(t) \quad (0 < t \leq T)$$

is that the treatment groups NET and iTAU will not differ with respect to the distributions of the observed outcome measure Δ_6PDS, whereas $G_i(x)$ is the cumulative probability distribution of the observed change in PDS severity scores at T1 in group *i (i* = NET or iTAU*)*, and the distribution of times of death (most likely cause of missingness), whereas $K_i(t)$ is the cumulative distribution of informative event times in group *i*.

The null hypothesis will be tested using a nonparametric model (Lachin, 1999) which is a modified version of the Wilcoxon-Mann-Whitney U-test and which basically allocates the (tied) worst ranks to all missing values (*worst rank score analysis*). The null hypothesis can be rejected if the two-sided *p*-value related to the test statistic for the treatment effect is equal to or smaller than the significance level α=0.05 (two-sided). Note that the test strategy provided in Lachin (Lachin, 1999) is tailored to a particular alternative hypothesis – i.e.,

- NET will either be superior to iTAU in terms of absolute change in PDS severity scores from baseline at T1, but with no impact on survival,
- NET will be superior to iTAU in terms of survival, but with no impact on the absolute

change in PDS severity scores from baseline at T1,

- or NET will be superior to iTAU for both the absolute change in PDS severity scores from baseline at T1 and survival.

Explanation of the allocation of the worst ranks to all missing values: If the PDS total severity scores are not informative for future death events, the worst rank replacement will simply lead to a power loss and no inflation in the type I error rate. Should the PDS total severity scores be informative for future death events, the worst rank replacement will result in an unbiased test (as shown by (Lachin, 1999)) of a particular alternative.

The principal analysis will be performed according to the intention-to-treat (ITT) principle, and unadjusted for screening or baseline covariates or site. The significance level is set to alpha = 5% (two-sided).

Missings prior to the time of the follow-up measurement will occur because of an informative, disease-related event (e.g. death, morbidity) and for other reasons (e.g. non-responders at follow-up measurements T1, T2, loss to follow-up, consent withdrawn). To address the impact of several missingness mechanisms (MAR; MNAR) sensitivity analyses will be performed, e.g. mixed effect models assuming MAR ("all observed data approach") using the whole observed PDS profile of the surviving patient; multiple imputations techniques; or even complete case analyses using ANCOVA (absolute change score as response variable, treatment group as covariate, adjusting for the baseline score value) for responding survivors until T1.

Moreover, we plan sensitivity analyses in the per protocol population, using linear mixed effects models to explore the role of covariates (e.g. age and gender) and to address the Behrens- Fisher problem.

Further methodological details will be provided in the SAP to be written in a blinded fashion.

15.1.2 Analyses of secondary efficacy endpoints

All secondary analyses will be exploratory, i.e. performed without adjustment for multiplicity, using standard methods of inferential statistics appropriate for the given secondary outcome measure. Two-sided tests for detecting treatment differences will be carried out.

If not revised in the SAP, descriptive comparisons of, e.g. change scores measured at T1 and T2, or patient characteristics, will be mainly conducted with the Mann-Whitney-Wilcoxon test or, in the case of a binary outcome, with the Fisher's exact test, as appropriate. With respect to missing score values, the same considerations used for the primary outcome will apply equally to the pre-specified secondary efficacy outcomes. Analyses of secondary efficacy endpoints for the "PICTURE–Economic" are described in Section 5.2.2 and from the "PICTURE-psychotherapy in general practice" in Section 5.2.3.

15.1.3 Safety analysis

Safety analyses will be conducted for SAE reported during the trial period. The frequency of events and the possible relationship to the treatment group will be analysed descriptively. Besides, the data quality including potential underreporting will be discussed.

15.2 Interim analysis

A fixed sample design is planned without confirmatory statistical testing for early decision making. There is no pre-planned efficacy interim analysis.

15.3 Sample size calculation

We performed sample size calculations and additional simulations to detect a clinically relevant and empirically justified effect with respect to the PDS-5 total severity score (range 0-80 points).

Planning figures

Calculation of the reliable change index for previous NET trials indicates that a drop of about 25% (e.g. 23% in (Jacob, Neuner, Maedl, Schaal, & Elbert, 2014)) in the baseline score is a threshold that reflects a reliable change. To achieve mean baseline scores of about 40 points in this score, a mean change of at least $0.25 \times 40 = 10$ points would be necessary. Since post-ICU patients suffer from severe multiple medical conditions (SMOOTH data, (Schmidt et al., 2016)), a more conservative assumption of 60% was assumed for a minimum clinically important difference (MCID), resulting in a study arm mean difference of 6 points in PDS total score at T1.

A sample size of 131 patients (GPs) in each group (i.e., 262 patients in total) will have 80% power to detect a probability of 0.400 that an observation in Group NET is less than an observation in Group iTAU using a Wilcoxon (Mann-Whitney) rank-sum test with a 0.05 two-sided significance level (Software used: nQuery Advisor® 7.0).
The probability of $P(X_{NET} < X_{iTAU}) = 0.4$ was calculated with a presumed normal distribution – a difference in means ($\mu_{iTAU} - \mu_{NET}$) of 6 points and a common standard deviation of about 17 points – and an effect size of 0.36.

To address the properties of the complex (non-parametric worst rank score) analysis approach, we decided to randomize an additional 78 patients (+ ~30% (=39/131)). Thus, the sample size **to be allocated** to the trial is $N= 2 \times 170 =$ **340 patients (GPs) in total**.

In accordance with ICU/ regional study center commitments, 3000 patients can be screened, of which N=1000 (33%) are expected to show posttraumatic symptoms (Parker 2015). N=650 (65%) are expected to be willing to participate (patients and GPs) (SMOOTH: 20% non-participants; however, NET is more intense, therefore the rate of non-participation is expected to be higher in this trial), N=550 (~85%) to be screened by the treating GP 3 months post ICU (SMOOTH mortality after 6 months: 18%), N=400 (~70%) to meet inclusion criteria, and N=340 (85%) to consent to study participation at T0.

We assume a 30% drop out rate from T0 to T1 (primary analysis), and a 15% drop out rate from T1 to T2 (secondary analyses).

Simulations to validate the results of the sample size planning:

Using Lachin's strategy (Lachin, 1999) will result in analyses of all patients randomized. This is one intention of the ITT principle. However, this comes at the price of attrition due to missing values. To overcome this power-loss we have added another 30% to the original sample size. This choice was evaluated via a small simulation study by varying the number of patients per study arm to support our planning figures: for each setting we performed 10,000 replications and varied the study arm size from 100 to 170 per study arm (1:1 allocation). The results of the simulations to check for a sufficient sample size are displayed in the following figure:

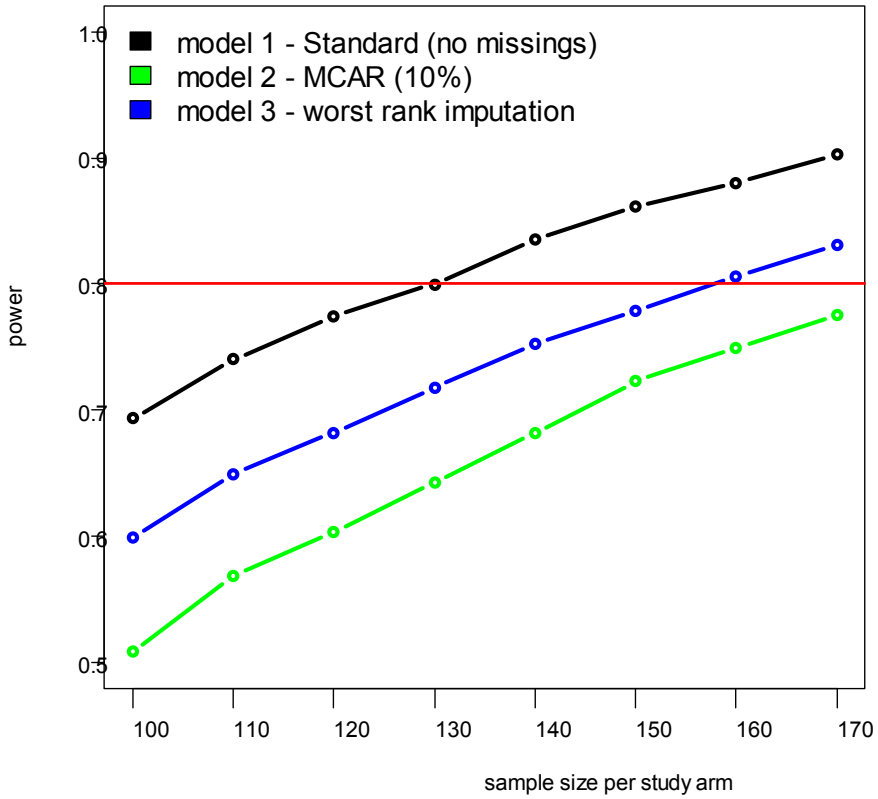

Figure 2 Results of the simulations to validate the sample size planning.

15.4 Definition of populations included in the analyses

This clinical trial will be analyzed according to the ITT principle. This means that the subjects will be analyzed in the treatment arms to which they were randomized, irrespective of whether they refused or discontinued the treatment, or whether other protocol violations are revealed.

The per-protocol (PP) population is a subset of the ITT population.

An analysis per-protocol (PP) will exclude or censor endpoint information considering major protocol deviations potentially effecting subjects' specific endpoint value, e.g., in the case of major violation of eligibility criteria (patient or GP level), lack of sufficient treatment per protocol (e.g., predefined number of sessions or consultations between T0 and T1) or unsatisfactory evaluations for endpoint assessment at predefined time points (telephone survey). The PP analyses excluding

data from protocol non-adherers will be performed for the purpose of a sensitivity analysis and investigating robustness of results. For per-protocol analyses, missings will not be imputed.

15.5 Protocol Violations

Protocol violations are major deviations from the procedures outlined in this document, and may include

- missed evaluations (in particular, telephone interview T1)
- missed consultations (iTAU arm) or sessions (NET arm)
- non-adherence to the assigned intervention
- any non-adherence to the protocol that would have an impact to the subject's rights, safety or welfare.

Minor protocol deviations may include, but are not limited to, e.g.:

- unscheduled visits at the GP's office
- NET arm: one or more missed phone calls between MFA and the patient

Through close contact between the RTC and GP practices, deviations from the protocol and reasons for missing data will be documented throughout the course of the trial.

All protocol violations will be listed and the impact on the evaluation of the corresponding patient (or GP) will be discussed in a blinded manner prior to the statistical analyses.

15.6 Handling of Drop-outs, Withdrawal, and Missing Data

- Subjects and/or GPs dropping out of the trial prior to randomization after T0 will be listed including the reason for "drop-out" (e.g., screening failure, PTSD diagnosis not confirmed, IC withdrawn).
- Subjects dropping out of the trial after randomization will be analyzed using all available data according to the ITT principle. Drop-outs will not be replaced.

Sensitivity analyses will be performed to explore several testable and untestable assumptions including various scenarios of informative missingness, in order to assess the robustness of the overall trial result.

16 Data Collection, Handling and Record Keeping

Data management will be performed at the Institute of General Practice at the site of the PI.

Details concerning data management procedures and query management will be described in a data management (DMP) and data validation plan (DVP).

16.1 Data Forms and Data Entry

In the PICTURE Trial, all data will be documented on paper-based and electronic case report forms (eCRFs). This may be done at the ITC or at the RTC where the data are originated. Original study forms will be entered in a web-based software tool (OpenClinica) and kept on paper file at the RTC. Participant files are to be stored in numerical order in a secure and accessible place and manner. For the creation of a study database the data manager creates a specification as a basis for the implementation of eCRFs/paper-based CRFs.

16.2 Data Transmission an Editing

The data input screens are based on the CRFs. Data integrity is enforced by a variety of mechanisms, referential data rules, valid values, range checks, and consistency checks against data already stored in the database (i.e., longitudinal checks). Checks will be applied at the time of data entry into a specific field and/or before the data is written (committed) to the database. Modifications to data written to the database will automatically be documented through either the data change system or an inquiry system. Data entered into the database will be retrievable for viewing through the data entry applications. The type of activity that an individual user may undertake is regulated by the privileges associated with his/her user identification code and password.

At telephone interview T1 and T2, patient-reported outcomes will be collected by means of a computer assisted telephone interview (CATI) conducted by staff at the ITC. An electronic questionnaire (based on the pre-specified patient questionnaires) will be designed to ensure a standardized documentation.

Telephone interviewers will be trained accordingly before conducting the interviews (this includes standard operating procedures or communication templates, which also contains retention strategies for hard-to-find participants) (Lepkowski et al., 2007). Information about the patient screening identification number (PSID) (and the associated general practitioner identification number (GPID)), name and telephone number/numbers are available to the interviewers. The data files will be stored in accordance with regulatory norms for storage of personal data as described above. Telephone interviewers are obliged to sign a written duty of confidentiality.

16.3 Data Security and Back-Up of Data

Clinical Trial data are entered into a web-based electronic data capture system (OpenClinica) and stored in a password-protected file at the Leibniz-Rechenzentrum (LRZ). The LRZ is the main computer center for Munich's universities and for the Bavarian Academy of Sciences and Humanities. Data input requires an internet connection and a browser. Authorization of users is granted via login and password. For the security of the entered data the web accesses are encrypted

via SSL certificates. All data collected throughout the study period will be accumulated in a secured server at the LRZ. A secure file folder will be constructed before initiation of the trial. Access is limited to the PI, the data manager and the statistician.

A complete back up of the primary ITC database at the LRZ will be performed twice a day. At the LRZ archive data is stored for 10 years (back-up data for 6 months). In addition to the system back-ups, additional measures will be taken to back-up and export the database on a regular basis at the database management.

After data entry at any point in time, all questionnaires are kept locked in a fire insulated safe. Access is limited to the PI.

16.4 Archiving

The sponsor must retain all essential documents inclusively the case report forms (Subject Master File) for the duration of at least 10 years after end or stop of trial. The sponsor must archive all trial related documents according to regulatory requirements.

The investigator should maintain all subject documents as specified in Essential Documents for conduct of a clinical trial (see ICH-GCP, section 8) and as required by the applicable regulatory requirement(s) after completion of the clinical trial so that they will be available for audits and inspections by the authorities. The investigator will be responsible for the storage.

The following retention periods will apply after completion or stop of the clinical trial:

- all essential documents and trial related data must be retained securely for at least 10 years (GCP-V § 13 (10), the subject identification list for at least 15 years, medical records and other source documents for the longest possible period allowed by the hospital, the institution or the private practice.
- The investigator/institution should take arrangements to prevent accidental or premature destruction and illegitimate access to these documents.
- To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e. g. CRFs, patient questionnaires and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e. g. letters, meeting minutes, telephone calls reports).
- The RTCs will maintain a file of essential subject documentation (Trial site File). It is the responsibility of the site to retain copies of all completed CRFs for the subject and their trial file on site.

17 Monitoring

An independent clinical monitor will ensure that the trial is conducted in accordance with the protocol and the GCP Guideline. Monitoring tasks include evaluation of compliance to the protocol

(e.g. check of in-/exclusion criteria during the screening period and diagnosis (T0), written informed consent from patients and their treating GPs, documentation of SAE), supplies (distribution of educational materials), procedures (risk management in case of SAE), check for accuracy, completeness, consistency and reliability of the CRFs by comparing documented data with source data, and that data are collected, stored and managed appropriately. Source data will be collected and stored by the RTC in the RTC-file. Frequency and scope of the monitoring visits will be defined in the *Monitoring Plan* which also includes the extent of source data verification that is required. All tasks will be documented in a report, signed by the monitor.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and resolved, and therefore ensures the accuracy and consistency of the trial with GCP and all applicable laws. The investigator allows the monitor to have access to all trial related original data and documents relevant for the monitoring of the trial.

In all participants, source data verification has to be performed for the following data: name, contact details, date of birth, gender, inclusion and exclusion criteria, and written informed consent.

18 Reporting

18.1 Statistical Report

After database lock, a statistical report will be prepared by the responsible biometrician and signed jointly with the PI. All data in this report are strictly confidential.

19 Definition of End of Trial

19.1 Regular End of the Trial

The regular end of trial is defined as last participant's (telephone) visit (LPLV).

19.2 Premature Termination of the Trial for Individual Subjects

If the clinical trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the subjects and ensure appropriate therapy and follow-up.

There are different grades of deviations from the study flow ranging from minor, major protocol violations, (such as delayed or unscheduled (telephone) visits, discontinuation of intervention, taking medication listed under prohibited therapy / concomitant medication (see protocol violations section 15.5) to complete withdrawal. Complete withdrawal should be a rare exception.

Whenever a subject is withdrawn totally from the trial, a complete final examination as scheduled for the premature termination/dropout visit should be conducted, and the circumstances of the withdrawal or discontinuation have to be recorded in detail in the medical file and the CRF.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject (e.g. by telephone to assess and document treatment compliance, safety, or concomitant medication/ therapy) in order to avoid loss-to follow-up or dropout. These efforts have to be documented in the medical file.

Regardless of any decision to modify or discontinue their assigned intervention, study participants should be retained in the trial whenever possible to enable follow-up data collection and prevent missing data. In any circumstance, every effort should be made to document (key) subject outcomes, if possible. The subject has to be requested to return all unused investigational product(s), if applicable, and followed-up regarding any unresolved adverse events.

19.2.1 Termination by the patient

A patient may withdraw from the trial at any time at their own request without stating the reason(s) for withdrawal. They will experience no disadvantage as a result of this decision, and no alternative therapy will be withheld by the investigator.

19.2.2 Termination by the Investigator

Subjects may also be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons, e. g.:

- Occurrence of intolerable events which would constitute an unacceptable high risk for the subject
- Medically indicated e.g. because it is found that inclusion / exclusion criteria were violated
- Continuation is unacceptable because risks outweigh the benefits
- Lack of compliance of the subject
- Significant protocol violations
- Logistical reasons (e.g. subject changes his/her doctor or hospital or moves to another location)

Whenever a subject is withdrawn from the trial, the circumstances of the withdrawal or discontinuation have to be recorded in detail in the CRF and a final examination as scheduled for the termination visit or telephone interview should be conducted.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

In any circumstance, every effort should be made to document subject's primary efficacy outcome (PDS total score), if possible. The investigator should inquire about the reason for withdrawal. The subject has to be followed-up regarding any unresolved SAE.

19.3 Premature Termination of the Entire Trial

The PI is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of the entire trial. The PI will be supported in this responsibility by the DSMB.

The entire clinical trial must be terminated prematurely if an insufficient recruitment rate makes a successful conclusion of the trial appear impossible. The reasons for premature termination of the trial must be documented in written form.

19.4 Termination of the Trial in Individual Regional Sites

Both the PI and the sponsor/sponsor delegated person in agreement have the right to terminate the trial at one of the centers at any time for instances:

- Unforeseeable circumstances have arisen at the RTC, which precludes the continuation of the clinical trial.
- The PI considers that the resources for continuation are no longer available.
- The PI considers that the continuation of the trial is no longer ethically or medically justifiable.
- Subject recruitment or willingness of GPs to participate is inadequate.
- Serious problems arise with regard to the quality of the collected data which cannot be resolved.
- Withdrawal of the opinion of the EC

Premature termination at one of the RTCs does not automatically mean a termination of already enrolled trial subjects. A separate decision on further treatment must be made for each subject, depending on the overall situation. It has to be clarified that:

- An adequate further treatment and follow-up of already enrolled subjects must be ensured.
- The documentation of already enrolled subjects will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the centre is closed.
- The ethics committee(s) must be duly notified of the centre's closure, including reasons, within the specified period(s).

20 Ethics and Good Clinical Practice

The trial will be conducted in accordance with the ICH Guideline on Good Clinical Practice, the relevant national regulations, and the Declaration of Helsinki (WMA - The World Medical Association, 2013).

20.1 Responsibilities of the Sponsor

The sponsor is responsible for obtaining the approval of the respective main research ethics committee ("federführende Ethikkommision") before initiation of the trial.

The sponsor announces a Leader of the clinical trial (LKP) who has more than two years of experience in the field of clinical trial and holds a medical license.

20.2 Responsibilities of the Investigator

By signing this protocol the regional investigator at the respective RTC declares his/her commitment:

- to not enrol any person dependent on him/her or the sponsor in accordance with the principles of ICH-GCP
- to follow the regulations for data security according to § 7 Abs. 3, Nr. 15 GCP-V. (Verbraucherschutz, 2004)
- to inform the subjects of the transmission of their pseudonymized data according to documentation and transmission obligations (§ 12 and § 13 GCP-V) and to make sure that subjects unwilling to give consent to the processing of their data are not included into the trial
- to be qualified by education, training and experience to assume responsibility for the proper conduct of the subject
- to be aware of, and comply with GCP and applicable guidelines or widely accepted recommendations dealing with nonpharmacological trials with a psychological intervention in the primary care setting, as described in the protocol
- to maintain a list of appropriately qualified persons to whom the investigator has delegated significant subject related duties (if applicable).

20.3 Compliance with the Protocol

The investigator conducts the clinical trial in compliance with this protocol. For this purpose, the document will be signed by the PI and the biometrician. As a general rule, the investigators should not deviate from the protocol or make amendments to the protocol without the agreement of the PI and the ethics committee (unless subject safety is at risk).

Any deviations from the approved protocol should be documented and explained by the investigator or an individual who is designated by the investigator.

The investigator may deviate from the protocol or make an amendment to the protocol without prior approval of the ethics committee to eliminate immediate risks to the subject subjects. The deviation or amendment should be reported subsequently to the PI, and, if necessary, to the ethics committee.

20.4 Notification of General Amendments to the Protocol

The PI can make general amendments to the protocol after the clinical trial has started. These may be of an administrative nature (logistical/administrative amendments) or substantial.

Substantial Amendments are changes that likely affect and /or change:

- the safety of the persons concerned,
- the interpretation of the scientific trial documents or the scientific informational value of the trial results,
- the nature of management or conduct of the clinical trial (e.g. change of principal investigator (German LKP), sponsor or sponsor's deputy),

Substantial amendments require a new favorable opinion by the Ethics Committee (EC).

The clinical trial may only be continued when a favorable opinion has been obtained from the EC and has not raised any objections accompanied by reasons.

If applicable, an updated written Informed Consent Form has to be signed by all subjects enrolled in the trial who are affected by the amendment.

Amendments have to be approved by the EC (e.g. changes in an advertisement for subjects to participate in the trial or changes in facilities for the trial). If administrative protocol changes (e.g. change of monitoring, telephone numbers) are necessary, the EC will be notified only.

20.5 Notification of the end of the trial

The end of the clinical trial is the date of the last visit of the last patient undergoing the trial (LPLV). The EC will be notified after the trial has ended. Within one year of the end of the complete trial, a summary of the trial report will be provided to the EC.

20.6 Patient / GP Information and Informed Consent

The study nurse of the respective RTC is responsible for obtaining written informed consent both from the patient and from his/her GP, before any protocol-specific screening procedures will be performed or any investigational intervention will be carried out. The written informed consent documents have to be prepared and provided in German.

Patients (and GPs) must understand that it is their own free will to participate and that they can withdraw consent at any time without giving reasons and without penalty or loss of benefits to which the subject is entitled. Also, patients must understand that they will experience no disadvantage as a result of this decision and that no alternative therapy will be withheld by the investigator.

The written consent form will be personally dated and signed by the patient and the by investigator conducting the informed consent discussion. The informed consent forms of both the participating patients and the GPs will be filed in the Trial Site File at each RTC.

A copy of the signed and dated informed consent form will be given to the patient or legally acceptable representative and a copy will be held in the subject’s medical records. The existence of

written informed consent has to be confirmed before any trial-specific test/treatment has been performed.

Changed trial procedures can only be carried out if they have been approved by the leading Ethics Committee, and if the patient has been appropriately informed and has given his/her written consent.

20.7 Subject Insurance

All subjects included in this trial are satisfactorily insured through their own existing health care insurance against any injury caused during the duration of the study. All appointments in the GP practice will take place during regular practice hours. Hence, there is no need for additional insurance through the investigator/sponsor.

20.8 Data Protection and Subject Confidentiality

The pertinent provisions of the German legislation on data protection must be fully complied with.

The collection, transmission, archiving and evaluation of personal data in this clinical trial are performed according to locally applicable laws (Data Protection Act). Prior to trial participation each subject must be informed by the investigator about the trial and must give his/her written informed consent. The same holds for the patient's general practitioner.

20.9 Financing of the Trial

The present study is an investigator initiated trial (IIT). The trial is funded by the Deutsche Forschungsgemeinschaft (DFG), grant code GE 2073/8-1.

21 Trial Reports

After completion of the analyses by the responsible biostatistician, a statistical report will be prepared.

Except when required by law, no one will disclose a result of the clinical trial to third parties unless all parties involved have first agreed on the results of the analyses and their interpretation.

22 Publication policy

The trial will be prospectively registered in a public database (DRKS: http://www.germanctr.de; Clinical Trials: https://clinicaltrials.gov). Efficacy and safety results will be submitted for at least one main scientific publication in a peer-reviewed journal. Publication or lecture of data or trial results needs a previous annotation and approval of the PI. All subject-related data will be published in a pseudonymous form.

The right of publication rests primarily with the PI and the other investigators and researchers involved.

All data collected in connection with the clinical trial will be treated in confidence by the PI and all others involved in the trial, until publication of the main results.

Interim data and final results may only be published (orally or in writing) with the agreement of the PI and the other investigators. This is indispensable for a full exchange of information between the above-named parties, which will ensure that the opinions of all parties involved have been heard before publication.

The agreement, which does not include any veto right or right of censorship for any of the parties involved, may not be refused without good reason.

Specific regulations concerning the publication policy in the applicable contracts will precede this trial protocol in any case.

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Appendix

Serious Adverse Event Form

PICTURE trial – PTSD after ICU survival

DRKS00012589 **SAE-MELDEBOGEN** Seite 1 / 2

PROTOKOLLTITEL: **INDIKATION:** **SPONSOR:**					
BITTE ALLE INFORMATIONEN VOLLSTÄNDIG, MIT EINEM SCHWARZEN KUGELSCHREIBER, LESERLICH, IN DRUCKBUCHSTABEN EINTRAGEN					
PATIENTENKENNDATEN					
Patienten-Nr.	Geschlecht ☐ m ☐ w	Alter (Jahre)	Größe (cm)	Gewicht (kg)	SAE-Nr.

REPORT INFORMATION		
☐ ERSTBERICHT Datum:	NAME DES PRÜFARZTES:	
☐ FOLGEBERICHT Datum:	PRÜFZENTRUM-Nr.: INSTITUTION: E-MAIL:	LAND: TELEFON: FAX:

KRITERIEN FÜR SCHWERWIEGENDE UNERWÜNSCHTE EREIGNISSE ODER MELDEGRUND	
☐ führt zum Tod	☐ führt zu einer dauerhaften oder erheblichen Behinderung
☐ ist lebensbedrohlich	☐ stellt ein kongenitale Anomalie oder einen Geburtsdefekt dar
☐ erfordert Krankenhausaufenthalt / oder Verlängerung	☐ ein anderes, klinisch relevantes Ereignis

SCHWERWIEGENDE UNERWÜNSCHTE EREIGNISSE (SAE)	
SAE: Diagnose (falls vorhanden) ansonsten Symptom(e) _____ _____ _____ _____ _____ _____	Datum Auftreten des SAE (DD/MM/JJJJ) _____ Datum des SAE-Endes (DD/MM/JJJJ) _____ Todesdatum (falls zutreffend) (DD/MM/JJJJ) _____

ENTBLINDET:	nicht anwendbar ☐		nein ☐	ja ☐		
Kausalität:	sicher	wahrscheinlich	möglich	unwahrscheinlich	ausgeschlossen	nicht abschätzbar
	☐	☐	☐	☐	☐	☐

SAE <u>UMGEHEND</u> melden an

Principal Investigator
Prof. Dr. med. Jochen Gensichen, MPH

Fax: +49 (0)40 4400-53520

PICTURE trial – PTSD after ICU survival

DRKS00012589 **SAE-MELDEBOGEN** Seite 2 / 2

BITTE ALLE INFORMATIONEN VOLLSTÄNDIG, MIT EINEM SCHWARZEN KUGELSCHREIBER, LESERLICH, IN DRUCKBUCHSTABEN EINTRAGEN

PATIENTENINFORMATION

Patienten-Nr.	Alter (Jahre)	SAE-Nr.	☐ ERSTBERICHT Datum: ☐ FOLGEBERICHT Datum:

Anamnese (Vor- bzw. Begleiterkrankungen)	Startdatum	Enddatum
1.		
2.		
3.		

RELEVANTE BEGLEITMEDIKATION

	Indikation	Tagesdosis, Einheit, Applikationsform	Datum der ersten Verabreichung	Datum der letzten Verabreichung
1.				
2.				
3.				

RELEVANTE LABORBEFUNDE ODER UNTERSUCHUNGEN

	Normbereich	Datum	Befund
1.			
2.			
3.			
4.			

BEHANDLUNG DES (S)AEs

☐ keine
☐ medikamentöse Behandlung
☐ sonstige

Bitte angeben:

_____
_____
_____
_____

ÄNDERUNG DER INTERVENTION

☐ nein
☐ ja, Datum: _____

SAE AUSGANG

☐ genesen / beendet
☐ erholt / im Prozess der Genesung
☐ nicht genesen / nicht beendet
☐ genesen / mit bleibenden Schäden beendet
☐ tödlich

Todesursache:

_____

Autopsie? ☐ ja ☐ nein

☐ unbekannt

Kommentar:

UNTERSCHRIFT DES PRÜFARZTES

Name Unterschrift Datum (DD/MM/JJJJ)

INNERHALB VON 24 STUNDEN FAXEN
AN DAS INSTITUT FÜR ALLGEMEINMEDIZIN DER LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN :
FAX-Nr. 089/4400-53520

CV of the Principal Investigator

Kontaktinformation	Prof. Dr. Jochen Gensichen (professor and chair) Institut für Allgemeinmedizin, Klinikum der Ludwig-Maximilians-Universität München, Pettenkoferstr. 8a/10, 80336 München, tel: 089 4400-53779, fax: 089 4400-53520 email: jochen.gensichen@med.uni-muenchen.de web: www.allgemeinmedizin.med.uni-muenchen.de
Geburtsdatum, -ort	25.06.1964
Ausbildung	2010 Habilitation im Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main 2000-2003 Studium der Gesundheitswissenschaften, Medizinischen Hochschule Hannover 1990-1997 Studium der Humanmedizin, Universität Köln 1985-1989 Studium der Erziehungswissenschaften, Universität Köln
Beruflicher Werdegang	Seit Okt 2016 Direktor des Institut für Allgemeinmedizin, Klinikum der Ludwig-Maximilians-Universität München Seit Dez 2013 Vorstand der „Stiftung Allgemeinmedizin“ seit Dez 2011 Mitglied der Fakultät für Sozial- und Verhaltenswissenschaften der Friedrich-Schiller-Universität Jena seit 2008 Direktor / Lehrstuhl Institut für Allgemeinmedizin 2006-2007 Max-Kade-Fellow am Group Health Research Institute und am Department for Psychiatry & Behavioral Science University of Washington, Medical School, Seattle WA. 2004-2008 Wissenschaftlicher Assistent (C1) bei Prof. F.M. Gerlach, Institut für Allgemeinmedizin der Universität Frankfurt a.M., Leiter des Arbeitsbereiches „Chronische Krankheit und Versorgungsforschung“ 2001-2004 Wissenschaftlicher Assistent (C1) bei Prof. F.M. Gerlach, Institut für Allgemeinmedizin Kiel
Veröffentlichungen	Schmidt K, Worrack S, Von Korff M, Davydow D, Brunkhorst F, Ehlert U, Pausch C, Mehlhorn J, Schneider N, Scherag A, Freytag A, Reinhart K, Wensing M, Gensichen J, for the SMOOTH Study Group. Effect of a primary care management intervention on mental health-related quality of life among survivors of sepsis: a randomized clinical trial. JAMA. 2016;315(24):2703-11. Freund T, Peters-Klimm F, Boyd CM, Mahler C, Gensichen J, Erler A, Beyer M, Gondan M, Rochon J, Gerlach FM, Szecsenyi J. Medical assistant–based care management for high-risk patients in small primary care practices: A cluster randomized clinical trial. Ann Intern Med. 2016;164(5):323-30. Gensichen J, Petersen JJ, Von Korff M, Heider D, Baron S, König J, Freytag A, Krauth C, Gerlach FM, König H-H. Cost-effectiveness of depression case management in small practices. BJPsych. 2013;202:441-6. Gensichen J, von Korff M, Peitz M, Muth C, Beyer M, Güthlin C, Torge M, Petersen JJ, Rosemann T, König J, Gerlach FM. Case management for depression by health care assistants in small primary care practices - a cluster

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Begründung, weshalb eine Versicherung für nicht notwendig erachtet wird

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN | CAMPUS INNENSTADT INSTITUT FÜR ALLGEMEINMEDIZIN

Klinikum der Ludwig-Maximilians-Universität München · Institut für Allgemeinmedizin
Pettenkoferstr. 8 a · 80336 München

Ethikkommision bei der LMU München
Pettenkoferstr. 8a
80336 München

Institut für Allgemeinmedizin
Direktor: Prof. Dr. med. Jochen Gensichen

Teamkoordinatorin/Chefsekretärin: Frau Sandra Nauerz
Telefon +49 (0)89 4400 - 53779
Telefax +49 (0)89 4400 - 53520
Email: Sandra.Nauerz@med.uni-muenchen.de

www.allgemeinmedizin.med.uni-muenchen.de

Postanschrift: Pettenkoferstr. 8 a
Hausanschrift: Pettenkoferstr. 10
D-80336 München

Ihr Zeichen: Unser Zeichen: München, den

Für die Studie *PICTURE – PTSD after ICU Caring for Patients with Traumatic Stress Sequelae following Intensive Medical Care. A national, prospective, randomized, multi-center, two-arm, observer-blinded, controlled superiority psychological intervention trial (PICTURE-trial) (DFG Kennzahl: GZ/GE 2073/8-1)* ist keine spezielle Versicherung notwendig, da es sich um keine medikamentöse Studie handelt.

Mit freundlichen Grüßen,

Prof. Dr. Jochen Gensichen
(Antragsteller/Studienleiter)