CLINICAL INVESTIGATION PLAN

BrainSTEADy

Title of Clinical Investigation: A multi-center, patient-blind and investigator-blind, randomized, parallel-group, superiority study to investigate a neurobiological mechanism of affect instability, comparing four sessions of amygdala fMRI-BOLD neurofeedback with sham-feedback in Borderline Personality Disorder

Sponsor Name and Address: Central Institute of Mental Health, J5, 68159 Mannheim

BfArM-Kennnummer: DE-24-00015271

Registry Number of the Clinical Investigation: ClinicalTrials.gov Identifier: NCT06626789

Modification No. / CIP Date and Version: Version 04, 30.06.2026

Modification History:

Modification No.	Date of Approval	Modification Type
Version 02	10.03.2025	'Concluding questionnaire' added to assessments (adapted sections: Schedule of assessments, 6.10. Assessments, section 6.6 Clinical Investigation Visits).
Version 02	10.03.2025	fMRI-task was removed due to time constraints (adapted sections: Schedule of assessments, previous section 1.5. Learning and transfer of Neurofeedback, section 2.2.1 Main Investigation, section 6 Clinical Investigation Visits, Figure 5 Patient Time Flow, Figure 6 Decision tree of missed/interrupted MR visits).
Version 02	10.03.2025	DTI measurement added to V2b and V5, removed DTI from V4 (adapted sections: Schedule of assessments, section 6 Clinical Investigation Visits).
Version 03	21.11.2025	Protocol improvement: Herbal or homeopathic remedies, and nutritional supplements not required in assessment of medical history (section 6.10 Assessments)
Version 03	21.11.2025	Correction: Blind check-questionnaire should be assessed in V5b, not V5a (changed Schedule of Assessments, c.f. 6.6 Clinical Investigation Visits).
Version 03	21.11.2025	Clarification, excl. crit. #7, added phrase (here in italics for review): Treatment with any neurofeedback *other than investigational device* three months prior to or during the study participation (changed Synopsis, Section 4.4 Exclusion Criteria)
Version 03	21.11.2025	Adapted trial duration (Synopsis)

Version 03	21.11.2025	Added 2 more trial sites (changed Synopsis, Section 4.1 Number of Subjects and Sites)
Version 03	21.11.2025	Clarification: Interviews and assessments of the screening phase should be collected on the same day as the informed consent is given or within 7 days thereafter (changed Section 6.1).
Version 03	21.11.2025	Correction, excl. crit. #13.c (here in italics for review): Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months prior to ~~randomization~~ *screening* or during screening period.
Version 03	21.11.2025	Correction, Appendix 2, p. 75 (sentence removed; WOCBP do not need to do pregnancy test at screening visit; c.f. Schedule of Assessments).
Version 03	21.11.2025	Correction, Patient Time Flow (Figure 5): Minimum time period between Baseline EMA and V2 Baseline questionnaires is 4 instead of 5 days.
Version 03	21.11.2025	Clarification, section 6.3: AE/SAE are to be assessed following randomization, in beginning of each visit. Additional AE assessment to be done in the end of V2, V3, V4, V5a.
Version 03	21.11.2025	Protocol improvement: If Neurofeedback 3 cannot be administered, the Survey of NF transfer (questionnaire) can be skipped (changed Figure 6).
Version 03	21.11.2025	Correction to achieve consistency with DSM-5 diagnostic instrument and protocol change to allow mild substance use disorder: Excl. crit. #2 (here in italics for review): Current *moderate or severe* alcohol or substance ~~dependence~~ use disorder within 1 month prior the initial screening
Version 04	29.06.2026	Change of excl. crit #6 (here in italics for review): Change of treatment (psychopharmacologic, psychological) 2 weeks prior to ~~or during the~~ study participation *or before completion of the post-assessment.*

CONFIDENTIAL: This Clinical Investigation Plan contains confidential information and is intended solely for the guidance of the clinical investigation. This Clinical Investigation Plan may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written consent of the principal investigator.

CIP SIGNATURE PAGE

The present clinical investigation plan was subject to critical review and has been approved in the current version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal device,
- the moral, ethical, and scientific principles governing clinical research as set out in the latest relevant version of Declaration of Helsinki, the principles of the ISO 14155:2020(E) and the applicable legal and regulatory requirements.

Investigators will be supplied with details of any significant change of the benefit-risk-assessment of the clinical investigation.

It will be ensured that the first subject is enrolled only after all ethical and regulatory requirements are fulfilled. Written consent from all subjects is received after detailed oral and written information and according to the requirements of local law (MPDG). According to MPDG §29 (1) it will be confirmed that all clinical investigation subjects will be informed on the type of encoding their personal data (pseudonymization) and who receives or has access to such data. Subjects who do not agree to this data encoding and transfer will not be enrolled into the clinical investigation. In this context it will be assured (according to Annex 15, Chapter II, 4.5 MDR 2017/745) that all investigational sites comply with the local regulatory requirements for data protection.

According to §47 (1,4.) MPDG the Sponsor states that it is not planned to include subjects in a relationship of any dependence to the investigators or sponsor.

Via current versions of the clinical investigation plan and the investigator's brochure it will be ensured that all investigators are informed about the applicable general safety and performance requirements according to Annex I MDR. This includes the technical and biological safety testing and pre-clinical evaluation regarding the benefits and risks of the clinical investigation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art (MDR, Article 62 (4l)).

Date:	_____	Signature:	_____
		Name (Print Name):	_____
		Function:	Sponsor Representative
Date:	_____	Signature:	_____
		Name (Print Name):	
		Function:	Biometrician
Date:	_____	Signature:	_____
		Name (Print Name):	
		Function:	Author (Principal Investigator)

INVESTIGATOR SIGNATURE PAGE

I have read the above-mentioned clinical investigation plan and confirm that it contains all information to conduct the clinical investigation. I pledge to conduct the clinical investigation according to the clinical investigation plan, the principles of the ISO 14155:2020(E) and the applicable legal and regulatory requirements.

I will enroll the first subject only after all ethical and regulatory requirements are fulfilled. I will obtain written consent for participation in the clinical investigation from all subjects after detailed oral and written information and according to the requirements of local law (MPDG). According to MPDG §29 (1), I declare that all clinical investigation subjects will be informed on the type of encoding their personal data (pseudonymization) and who receives or has access to such data. Subjects who do not agree to this data encoding and transfer will not be enrolled into the clinical investigation. In this context I confirm (according to Annex 15, Chapter II, 4.5 MDR 2017/745) that my investigational site complies with all local regulatory requirements for data protection.

Furthermore, I declare (according to §47 (1,4.) MPDG) that to the best of my knowledge no subjects in a relationship of any dependence to the investigators or sponsor will be included.

I know the applicable requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the clinical investigation plan.

I declare that I am informed about the applicable general safety and performance requirements according to Annex I MDR. This includes the technical and biological safety testing and pre-clinical evaluation regarding the benefits and risks of the clinical investigation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art (MDR, Article 62 (4l)) by reading the description in the clinical investigation plan and in the current version of the investigator's brochure (IB). I ensure that all investigators / relevant staff at my site will be informed of these results and possible new risks that are forwarded by the sponsor later on (e.g. via new version of the investigator's brochure).

I confirm that every staff will be adequately trained to guarantee compliance to the clinical investigation plan incl. subsequent modifications, the clinical investigation procedures and investigation specific duties and tasks. I will maintain a list specifying the tasks delegated to each team member.

I will retain all investigation-related documents and source data as described. I will provide a Curriculum Vitae (CV) before start of the investigation. I agree that the CV and the Declaration of Interest may be submitted to the responsible EC.

As the clinical investigation and the results have to be published in a clinical investigation register and forwarded to the EC and competent authority I agree that my name and clinic address will be part of this clinical investigation (summary) report / public register and are disclosed pursuant to §64 (3) MPDG.

Date: _____ Signature: _____

Name (Print Name): _____

Function: _____

Investigational Site (Address) _____

_____

_____

INVOLVED PARTIES

Contact information of all parties involved, incl. all principal investigators, participating sites and institutions can be found in a central list. Relevant contact information will be provided to each site in the Investigator Site File.

ADMINISTRATIVE INFORMATION

Table of Content

CIP SIGNATURE PAGE 3
INVESTIGATOR SIGNATURE PAGE 4
INVOLVED PARTIES 5
ADMINISTRATIVE INFORMATION 6
TABLE OF CONTENT 6
CIP SYNOPSIS 9
SCHEDULE OF ASSESSMENTS 14
ABBREVIATIONS 16
1. INTRODUCTION 18
1.1 Neurofeedback-approach to Borderline Personality Disorder (BPD) 18
1.2 Preclinical investigation 18
1.3 Clinical investigation 19
1.4 Relevance of Neurofeedback RCTs (Randomized Controlled Trials) for Evidence of Specificity 19
1.5 Health economic effects of neurofeedback treatment in Borderline 20
1.6 Neuroplasticity: Alterations of white matter structure 20
1.7 Dissociation in the Context of Amygdala-Neurofeedback 21
1.8 Neurofeedback and non-response to standard therapy 21
1.9 Clinical Investigation Rationale 21
1.9.1 State-of-the-Art BPD treatment 21
1.9.2 Justification for this trial 22
1.9.3 Expected Clinical Benefits 23
1.9.4 Expected Adverse Device Effects 23
1.9.5 Residual Risks Associated with the Investigational Product 23
1.9.6 Risks Associated with the Participation in the Clinical Investigation 24
1.9.7 Possible Interactions with Concomitant Medical Treatments 24
1.9.8 Control or Risk Mitigation Strategies 24
1.9.9 Justification of the Positive Risk-Benefit-Ratio 24
2. OBJECTIVES AND ENDPOINTS OF THE CLINICAL INVESTIGATION 25
2.1 Primary Objective and Primary Endpoint 25
2.2 Secondary Objectives and Secondary Endpoints 25
2.2.1 Main Investigation 25
2.2.2 Accompanying Research 26
3. DESIGN OF THE CLINICAL INVESTIGATION 27
3.1 Overall Clinical Investigation Design 27
3.2 Planned Interim Analysis 28
3.3 Overall Duration of the Clinical Investigation 28
3.4 Duration of Clinical Investigation for each Subject 28
3.5 Definition of End of Investigation 30
3.6 Patient Involvement 30
3.7 Measures to Minimize Bias 31
3.7.1 Randomization and blinding 31
3.7.2 Breaking the Blind 31
4. SUBJECT SELECTION 32
4.1 Number of Subjects and Sites 32
4.2 General Criteria for Subjects' Selection 32
4.3 Inclusion Criteria 32
4.4 Exclusion Criteria 32
4.5 Lifestyle Considerations 33
4.6 Subject Assignment 33
4.6.1 Identification Numbers 33
4.6.2 Screening Failures 34

5. INVESTIGATIONAL DEVICE 34
5.1 Description of the Investigational Device 34
5.2 Supplies of Investigational Device 34
5.3 Device Accountability and Traceability 34
5.4 Use of the Investigational Device 34
5.5 Specific Medical or Surgical Procedure Involved 34
5.6 Comparative Devices 34
6. CLINICAL INVESTIGATION VISITS AND INVESTIGATIONS / ASSESSMENTS 35
6.1 Screening Visit / Baseline (T0), V1 35
6.2 Baseline Visit (T0) continued, V2a 35
6.3 Neurofeedback 1-3 (V2b, V3, V4) 36
6.4 Interim weeks between Neurofeedback 3 (V4) and Neurofeedback 4 (V5a) 37
6.5 Neurofeedback 4, Post-assessment visit (T1), V5a 37
6.6 Post-assessment visit (T1) continued, V5b 37
6.7 Follow-up assessment 1 visit (T2), FUP1 38
6.8 Follow-up assessment 2 visit (T3) 38
6.9 Planned Treatment after End of Investigation Participation 38
6.10 Assessments 38
7. DISCONTINUATION AND EARLY TERMINATION 41
7.1 Temporary Discontinuation from Treatment 41
7.2 Permanent Discontinuation from Treatment 41
7.3 Discontinuation from the Clinical Investigation 42
7.3.1 Withdrawal of Consent 42
7.3.2 Loss to Follow-Up 42
7.4 Temporary Halt 42
7.5 Early Termination of the Clinical Investigation 43
7.6 Premature Closure of a Site 43
8. ADVERSE EVENTS 43
8.1 Definitions 43
8.1.1 Adverse Event 43
8.1.2 Serious Adverse Event 44
8.1.3 Adverse Events of Special Interests 45
8.1.4 Device Deficiency 45
8.2 Expectedness / Anticipatedness 45
8.3 Characteristics of Adverse Events 45
8.3.1 Grading of AEs 45
8.3.2 Causal Relatedness 45
8.3.3 Outcome of AEs 47
8.3.4 Countermeasures 47
8.4 Period of Observation and Documentation 48
8.5 Investigator's Vigilance related Reporting Obligations 48
8.5.1 Reporting of Serious Adverse Events 48
8.6 Sponsor's Vigilance related Reporting Obligations 48
8.6.1 Sponsor's Assessment (Second Assessment) 48
8.6.2 Expedited Reporting to the National Competent Authority 49
8.6.3 Periodic Reporting to the German Competent Authority (BfArM) 49
9. STATISTICAL PROCEDURES 50
9.1 Definition of Population to be analyzed in the Clinical Investigation 50
9.2 Analysis Variables 50
9.3 General Considerations 50
9.4 Primary Analysis 50
9.5 Secondary Analyses 51
9.6 Interim Analyses 51
9.7 Sensitivity Analyses 52
9.8 Subgroup Analyses 52
9.9 Sample Size / Power Calculation 52
10. DATA MANAGEMENT 53

10.1 Data Collection and Handling 53
10.2 Data Cleaning and Quality Checks 53
11. ARCHIVING AND STORAGE 54
11.1 Essential Records and Source Data 54
11.2 Collection, Storage and Future Use of Biological Samples and Corresponding Data 54
12. REGULATORY, ETHICAL AND OVERSIGHT CONSIDERATIONS 55
12.1 Compliance Statement 55
12.2 Data Protection and Subject Privacy 55
12.3 Approval of the Clinical Investigation 55
12.4 Subject Information and Informed Consent 55
12.5 Committee Structure 56
12.5.1 Data Safety Monitoring Board (DSMB) 56
12.6 Steering Committee (SC) 56
12.7 Insurance 57
13. QUALITY CONTROL AND QUALITY ASSURANCE 58
13.1 Quality Assurance 58
13.2 Monitoring 58
13.3 Source Documents 58
13.3.1 Direct Access to Source Documents 58
13.4 Audits and Inspections 59
13.5 Deviations from the CIP (Protocol Deviations) 59
14. ADMINISTRATIVE AGREEMENTS 61
14.1 Financing of the Clinical Investigation 61
14.2 Financial Disclosure 61
14.3 Publication Policy / Dissemination of Data of the Clinical Investigation 61
14.4 Registration of the Clinical Investigation 62
14.5 Declaration regarding Data Sharing 62
15. REFERENCES 63
APPENDIX 1: LIST OF TECHNICAL AND FUNCTIONAL FEATURES OF THE INVESTIGATIONAL DEVICE 68
APPENDIX 2: CONTRACEPTIVE AND BARRIER GUIDANCE 72
APPENDIX 2: INFORMED CONSENT AND RECRUITMENT PROCESS 74
APPENDIX 3: PROVISIONS REGARDING EXCEPTIONAL CIRCUMSTANCES 75

CIP SYNOPSIS

Full Title	A multi-center, patient-blind and investigator-blind, randomized, parallel-group, superiority study to investigate a neurobiological mechanism of affect instability, comparing four sessions of amygdala fMRI-BOLD neurofeedback with sham feedback in Borderline Personality Disorder Deutsch: Eine multi-zentrische, patientenverblindete und prüferverblindete, randomisierte Parallelgruppen-Studie zur Erforschung eines neurobiologischen Mechanismus der Affektinstabilität, durch den Vergleich von vier Amygdala-fMRT Neurofeedback Sitzungen mit Sham-Feedback bei der Borderline Persönlichkeitsstörung
Clinical Investigation Code	Brain Signal Training to Enhance Affect Down-regulation - BrainSTEADy Deutsch: BrainSTEADy - Hirnsignal-Training zur Verbesserung der Gefühlsregulation
Rationale	Individuals with Borderline Personality Disorder (BPD) experience intensive, instable negative emotions. Hyperactivity of the amygdala is assumed to drive exaggerated emotional responses in BPD. Neurofeedback is an endogenous neuromodulation method to address the imbalance of neural circuits. Downregulation of amygdala hyperactivation with neurofeedback may ameliorate dysregulated emotions in BPD. The BrainSTEADy trial is designed to determine whether amygdala-fMRI-BOLD neurofeedback has a specific effect on affect instability in BPD beyond nonspecific benefit.
Primary Objective and Endpoint	To determine whether amygdala-fMRI-BOLD neurofeedback has a specific effect on dysregulated affect in BPD beyond nonspecific benefit. The main hypothesis to be tested is whether downregulation training of amygdala activation with neurofeedback reduces the intensity of negative affect assessed before treatment (T0) as compared to after treatment (T1) and whether this change is greater in the treatment group as compared to the control group. Primary endpoint: Affect intensity, group difference of change from T0 to T1 measured via experience sampling using ecological momentary assessment (EMA).
Main Secondary Objectives and Endpoints	To assess whether downregulation training of amygdala activation with neurofeedback reduces the intensity of negative affect assessed before treatment (T0) as compared to 3-months follow-up (T2). To assess symptom

	severity and neural regulation success through fMRI-neurofeedback. To investigate the reduction in health economic burden and an improvement in patient reported outcomes in terms of utilities, before treatment (T0) as compared to 6-months follow-up (T3). For all endpoints, we expect that the change is greater in the treatment group as compared to the control group. Secondary endpoints A) Affect intensity, group difference of change from T0 to T2. B) Borderline Symptom Severity, group difference of change from T0 to T1 and … C) … from T0 to T2, assessed with the Zanarini Rating Scale for BPD, interview version (ZAN-BPD). D) Amygdala response, group difference of change from T0 to T1. E) Amygdala self-regulation, group difference of change from T0 to T1 F) Improvement in quality-adjusted life years (QALY), group difference of change from T0 to T3.
Clinical Investigation Design	Multi-centre, investigator-blinded, patient-blinded, placebo-controlled, randomised, parallel-group design, prospective study with 2 treatment groups. The individual treatment duration per patient is approximately 20 weeks from screening to 3-months follow-up, with a baseline visit, 4 Neurofeedback visits, and a post-assessment visit. A limited number of scales will be assessed at a second follow-up assessment 6 months after the post-assessment. This is a two-staged trial with planned interim-analysis after inclusion of 50% of the full sample, and decision to continue recruitment dependent on the interim-analysis result.
Sample Size	Stage 1: 82 patients, stage 2: 82 patients
Clinical Investigational Population	Inclusion Criteria 1. 18-65 years 2. Diagnosis of Borderline Personality Disorder according to DSM-5 3. Insufficient response to ≥2 therapies. The criterion is fulfilled if the patient reports: a) 2 or more psychotherapy treatments with 12 or more sessions each OR: b) 2 or more psychotherapy treatments with a duration per treatment of at least 12 weeks OR: c) a medical history of 2 or more psychopharmaceutic treatments, each over the course of at least 4 weeks OR:

	d) a combination of 2 or more treatments such as: i. psychotherapy with 12 or more sessions, ii. psychotherapy with a duration of 12 weeks or longer, iii. psychopharmaceutic treatment over the course of at least 4 weeks. 4. Sufficient German language skills to give informed consent to the study, to understand questions posed by used instruments, and capable of completing the fMRI tasks 5. Ability of subject to understand character and individual consequences of clinical investigation 6. Written informed consent (must be available before enrollment in the clinical investigation) 7. For women of childbearing potential (WOCBP) adequate contraception (as defined in Appendix 2). <u>Exclusion Criteria</u> 1. Treatment with benzodiazepines within 7 days prior the initial screening 2. Current moderate or severe alcohol or substance use disorder within 1 month prior the initial screening 3. Meeting the diagnostic criteria for a psychotic disorder or schizophrenia (life-time), as determined by clinical interview at initial screening 4. Current or history of significant neurological condition (such as stroke, traumatic brain injury, space occupying lesions, multiple sclerosis, Parkinson's disease, vascular dementia, transient ischemic attack) 5. Significant visual impairment that might interfere with the performance of the behavioural tasks or fMRI tasks 6. Change of treatment (psychopharmacologic, psychological) 2 weeks prior to study participation or before completion of the post-assessment. 7. Treatment with any neurofeedback other than investigational device three months prior to or during the study participation. 8. Unable or unwilling to comply with study procedures, including study prohibitions and restrictions 9. History of claustrophobia or inability to tolerate scanner environment 10. Fulfilling any of the MRI contraindications on the standard site radiography screening questionnaire (e.g. history of surgery involving metal implants) 11. Clinically relevant structural brain abnormality as determined by prior MRI scan

	12. Planned medical treatment within the study period that might interfere with the study procedures 13. Participants deemed to be at significant risk of serious violence or suicide based on any one of the following: a. Significant risk of committing violent acts, homicide, or suicide based on history, routine psychiatric status examination, or according to the investigator's experience OR b. Any suicide attempt in the past 3 months (i.e., actual attempt, interrupted attempt, aborted attempt) prior to screening and during the screening period OR c. Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months prior screening or during the screening period. 14. BMI of 16.5 or lower 15. Participation in other clinical trials or observation period of competing trials, respectively 16. Previous participation in this trial (Re-Screening possible, c.f. Chapter 4.6.2) 17. Pregnancy and lactation 18. Held in an institution by legal or official order 19. Legally incapacitated.
Interventions and Treatments	Experimental intervention: Real-time fMRI neurofeedback from amygdala's blood oxygenation level dependent (BOLD) signal + negative emotional picture viewing. Instruction to regulate feedback via down-regulation of one's emotional response. Neurofeedback is a class I device manufactured by BrainInnovation (Maastricht, Netherlands). Control intervention: Yoked feedback + negative emotional picture viewing. Instruction to regulate feedback via down-regulation of one's emotional response. Duration of intervention per patient: Four training sessions within 4 weeks. Diagnostic instruments: International Personality Disorder Interview (IPDE), Structured Clinical Interview for DSM-5 (SCID-5)
Ethical Considerations	Risk-analysis has been conducted according to ISO 14971 and measures mitigating identified risks have been implemented successfully. Risks of neurofeedback using the software Turbo-BrainVoyager MED Borderline Personality Disorder (TBV MED BPD) have been weighted against those from alternative treatments and non-treatment, taking into account benefits from neurofeedback that were identified with literature analysis. Overall, the result of the risk-benefit analysis is positive. Mitigation measures were successfully implemented by the software developer and are reflected in the

	investigator's brochure and in this document wherever necessary. Constant monitoring of risks will be implemented during conductance of the trial. Thus, the clinical trial is in line with ethical standards devised by ISO 14155.
Number of Sites	6
Trial duration	Total trial duration: 48 months Duration of clinical phase: 36 months Beginning of the preparation phase: Q2 2024 FSI (first subject in) stage 1: Q2 2025 LSI (last subject in) stage 1: Q3 2026 LSO (last subject out) stage 1: Q1 2027 FSI stage 2: Q3 2026 LSI stage 2: Q3 2027 LSO stage 2: Q1 2028 DBL (database lock): Q1 2028 Statistical analyses completed: Q2 2028 Trial report completed: Q3 2028
Financing	Deutsche Forschungsgemeinschaft (PA 3107/4-1, SCHM 1526/26-1)

SCHEDULE OF ASSESSMENTS

Week in trial		**0-2**	**1-4**			**2-5**	**3-6**	**4-7**	**5-8**	**6-10**	**18-22**	**30-34**
Visit Description	**V1** Screening	**V2a** Baseline-assess-ment (T0) part 1	**V2b** Baseline-assess-ment (T0) part 2, Neurofeed-back 1	**V3** Neurofeed-back 2	**V4** Neurofeed-back 3	Interim week 1	Interim week 2	Interim week 3	**V5a** Neurofeed-back 4, Post-assess-ment (T1) part 1	**V5b** Post-assess-ment (T1) part 2	**FUP1** Follow-up (T2)	**FUP2** Follow-up (T3)
Procedures ↓												
Informed consent, eligibility (incl. SCID, IPDE, C-SSRS, medical history, concomitant medication), demography	x											
Randomisation		x										
Pregnancy test, if applicable			x	x	x				x			
Assess last menstruation, if applicable	x		x	x	x				x	x		
fMRI-neurofeedback			x	x	x				x			
DTI			x	x					x			
EMA (Smartphone-based assessment)		x								x	x	
AE/SAE			X	X	X				X	X	X	

Questionnaires & interviews ↓												
AQoL-6D		x										x
BSL-23	x	x								x	x	x
BDI	x									x	x	x
Blind check										x		
CGI	x									x		
Concluding questionnaire										x		
DERS-36	x									x	x	x
DES	x											
DSS-4			x	x	x				x			
DSS-acute		x								x	x	x
FimPsy	x											x
MSQ-NF			x	x	x				x			
PCL		x										
RSQ		x										
SCL-27	x									x	x	x
Survey of NF transfer						x	x	x	x			
WPAI:GH	x											x
ZAN-BPD	x									x	x	

All measures are study specific. For a detailed overview of planned timing of procedures and allowed flexibility of visit scheduling and data collection ref. to Chapter 3.4 Figure 5, Patient Time Flow

ABBREVIATIONS

ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse Event
AESI	AE of Special Interest
AQoL-6D	Assessment of Quality of Life
ASADE	Anticipated serious adverse device effect
ASQ	Ages & Stages Questionnaire
BDI	Beck Depression Inventory
BOLD	Blood-oxygenation-level-dependent
BPD	Borderline Personality Disorder
BSL-23	Borderline Symptom List, short version
CGI	Clinical Global Impression
CIMH	Central Institute of Mental Health
CIP	Clinical Investigation Plan
CIOMS	Council for International Organizations of Medical Sciences
CRO	Clinical Research Organization
CRF	Case Report Form
CRP	Clinically Relevant Parameter
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CV	Curriculum Vitae
DBL	Data Base Lock
DBT	Dialectal Behavioral Therapy
DD	Device Deficiency
DERS	Difficulties in Emotion Regulation Scale
DES	Dissociative Experiences Scale
DiMIS	Diversity Minimal Item Set
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSS	Dissociation-Tension-Scale
DTI	Diffusion Tensor Imaging
DVP	Data Validation Plan
eCRF	electronic Case Report Form
EMA	Ecological Momentary Assessment
EU	European Union
FA	Fractional anisotropy
FAS	Full Analysis Set
FimPsy	Fragebogen zur Inanspruchnahme medizinischer und nicht medizinischer Versorgungsleistungen bei psychischen Erkrankungen (Questionnaire for the Assessment of Medical and non Medical Resource Utilisation in Mental Disorder)
fMRI	Functional Magnetic Resonance Imaging
FSI	First Subject In
FUP	Follow-up
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH GCP	ICH harmonized tripartite guideline on GCP
IEC	Independent Ethics Committee
IFU	Instruction for Use
IIT	Investigator-Initiated Trial
INR	International Normalized Ratio
IPD	Individual Participant Data
IRB	Independent Review Board
ISF	Investigator Site File
ISO	International Organisation for Standardisation

ISRCTN	International Standard Randomized Controlled Trial Number
ITT	intent-to-treat
KKS	Coordination Centre for Clinical Trials (Koordinierungszentrum für Klinische Studien)
LDR	Legally Designated Representative
LKP	Coordinating Investigator according to MPDG (Leiter der Klinischen Prüfung)
LSLV	Last Subject Last Visit
MD	Medical Device
MDR	Medical Device Regulation
MPDG	Medizinprodukterecht-Durchführungsgesetz (German Medical Device Implementing Act)
MSQ-NF	Mental State Questionnaire
NF	Neurofeedback
PCL	Paranoia Checklist
PD	Protocol Deviation
PI	Principal Investigator
PRB	Patient Review Board
PV	Pharmacovigilance
Q	Quarter (time span)
RCT	Randomized Clinical Trial
RDE	Remote Data Entry
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SCID-5	Structured Clinical Interview for DSM-5
SMD	Standardized Mean Difference
SOP	Standard Operating Procedure
SPM	Standard Progressive Matrices
VAS	Visual analogue scale
TBV MED BPD	Turbo-BrainVoyager MED Borderline Personality Disorder
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect
ePRO	Electronic Patient-Reported Outcomes
WM	White matter
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health
WOCBP	Women of Childbearing Potential
ZAN-BPD	Zanarini-Rating-Scale for BPD

1. Introduction

1.1 Neurofeedback-approach to Borderline Personality Disorder (BPD)

Research on the point prevalence of BPD in adults converges to a rate of 1-3 % in nonclinical samples[1]. Lifetime suicide rates are very high[2]. Psychotherapy programs tailored to BPD are effective, although there is need to increase the effectivity and stability of treatment effect [3]. BPD is a disabling condition, associated with high individual suffering and high costs for health care and social security systems – comprising approximately 15% of all costs for psychiatric disorders in Germany[4]. Total societal cost-of-illness per BPD patient in the year preceding a standard psychotherapeutic treatment, Dialectical Behavior Therapy (DBT), amounted to 31.130 € [5].

Individuals with BPD compared to healthy controls experience highly negative emotions[6]. Their affect is characterized by high instability [6], a decreased response threshold, and a slow return to baseline[7]. This is reflected in a hyper-response of the amygdala to pictures with emotional content[8]. Current psychobiological models of BPD postulate an imbalance between hypersensitive emotional brain systems such as the amygdala and hypo-active “emotion regulation systems”, encompassing the medial and dorsolateral prefrontal cortex. This makes individuals with BPD vulnerable to intense emotions, for which they compensate with dysfunctional regulation behaviors (e.g. non-suicidal self-injury), leading to frequent medical treatment, social turbulences and negative emotions against the self. Accordingly, the proposed trial is strongly rooted in current psychobiological theory. While patients lie in the MRI machine and view pictures with aversive content, they see a live-display of their neural response, called NF. Changing neural response patterns via NF training may change dysfunctional behaviors that arise from abnormal neural functioning. We suppose that an alteration of a neural process, i.e. amygdala hyper-responding, will have effects on the related psychological process, i.e. emotion processing, and change affective experience. We therefore ask the question: **Does NF improve affect intensity via the modulation of neural responding to emotional cues?**

1.2 Preclinical investigation

148 of the 365 original research publications used Turbo-BrainVoyager (TBV), with 94 of these studies targeting healthy participants and 54 studies targeting clinical populations. Two of the clinical publications using fMRI neurofeedback focused on BPD. TBV is used in 41% of the 365 original studies. In 8 of the 148 studies (5%) using TBV, side effects have been reported (Table 7 of the Literature Search Report provided by BrainInnovation, version BPD-CE-REC-Literature-search-report-TBV-Med-BPD_20240709). This is slightly below the percentage of side effects found in all studies (6%: 23 of 365). In all cases, the side effects are mild and did often occur in the non-experimental group as well or only in the control group.

In most cases, light side effects were due to the use of MRI; the mentioned effects were for example sleepiness, fatigue, headache, nausea, drowsiness and, for some tinnitus patients, concern about noise. Another category of side effects were slight increase of symptoms 1) in low/non-responders, like motor decrease in Parkinson’s Disease patients 2) after a certain period (worse mood on 3rd day in schizophrenia patients) 3) when targeting the wrong region-of-interest (intraparietal region for depressed patients) 4) in the control group, for example self-injurious behaviour in PTSD patients. Finally, there were unrelated side effects, such as a case of non-lethal overdose of paracetamol in the control group (alcohol dependence patients) or “frustration with the questionnaire”, which is not relevant to either the use of TBV MED BPD, neurofeedback or MRI. No side effects seem to have been observed where the amygdala served as target region. The reported side effects and adverse events demonstrate that it is a safe, risk-free device. The reported results also show that it is a beneficial device.

1.3 Clinical investigation

While NF is an established medical procedure used for decades for treating mental disorders, real-time fMRI has only become available for NF training around the turn of the millennium[9]. More and more studies investigate the utility of fMRI-NF to train emotion regulation, both in healthy samples and in patient populations[10]. The amygdala has been targeted by a number of NF studies to treat disorders of emotion and mood in BPD[11,12], Posttraumatic Stress Disorder[13,14] and MDD[15].

A meta-analysis assessed amygdala regulation across nine studies that compared amygdala-NF to a control treatment[16]. The results show a high aggregated effect size (Cohen's d=0.75, **Figure 1**) confirming improved amygdala regulation in treatment groups compared to control groups. Due to the novelty of the real-time fMRI-NF method, clinical RCTs are still an exception in this field. BPD pilot studies indicate that NF has the potential to change emotion processing at several levels, including psychophysiology, behavior and subjective experience. In a four-session fMRI amygdala-NF training, administered to eight female patients with BPD, we had observed down-regulation of amygdala activation and increased functional connectivity between the amygdala and prefrontal cortex[11]. While this study demonstrated feasibility and was well tolerated by patients who participated in a DBT-based psychotherapy program in parallel, the second study extends previous findings[12]. In this study we investigated which aspects of emotion dysregulation would be malleable by NF. Twenty-five female BPD patients participated in three NF sessions and were tested again six weeks later. For inclusion, patients needed to be on constant medication or outpatient treatment throughout the study period. Emotion regulation was assessed on the physiological, behavioral and self-report level. After training, patients reported reduced negative affect intensity (Cohen's d=0.71, P<0.05). BPD symptoms were reduced, too (ZAN BPD, d=0.65, P<0.05). In the psychophysiology lab, patients revealed improved emotion regulation skills after training, indicated by decreased startle responses to negative pictures (P<0.05). This study revealed significant improvement in emotion regulation and reductions in affective intensity in daily life after fMRI-NF in BPD.To retain stability of training effects, additional 'booster' sessions may be beneficial. Conclusions are limited due to the lack of control groups in these studies. An ongoing open-label, preregistered trial (NCT04333888) aims to assess feasibility and training effects in a psychotherapy setting including a no-NF control group. This research will inform potential clinical effects, but is not designed to show specificity of amygdala NF (vs. feedback from another bio-signal). A blinded RCT is needed to confirm efficacy.

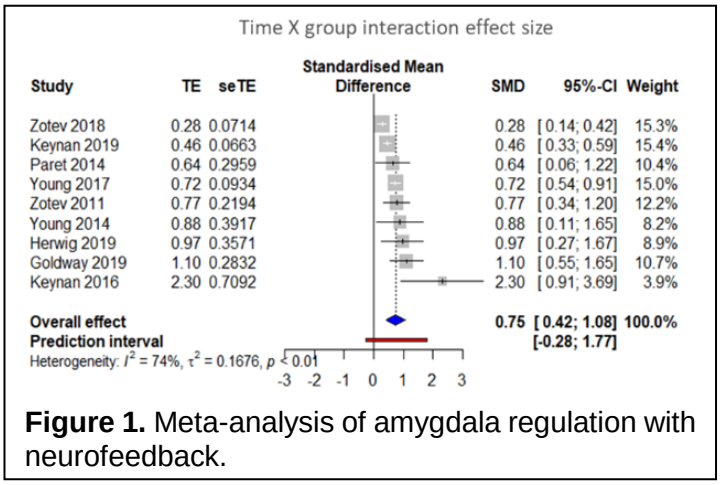


Figure 1. Meta-analysis of amygdala regulation with neurofeedback.

1.4 Relevance of Neurofeedback RCTs (Randomized Controlled Trials) for Evidence of Specificity

The assumed mechanism of NF is that changing a neural process will change related cognitions and behaviors. While this model is widely accepted, non-specific effects may mediate NF treatment outcomes as well[17]. The current state of evidence is best represented by a synthesis-model of both NF specific and non-specific factors accounting for psychosocial and placebo mechanisms[18]. To show that amygdala-NF is effective, it is necessary to control for non-specific factors in a RCT design. A widely used approach in NF trials is not to provide participants in the

control group with their own feedback signal. Instead, a signal of another participant ('yoked feedback') is presented[19]. Advantages of yoked feedback: a) the matching of the amount of reward received by both groups and b) unforeseen training effects are excluded that could be induced by other, conservative control conditions such as the training of alternative signals (e.g. different brain region). Although the risk of patient unblinding with non-contingent feedback has been raised and will be monitored in this project, many studies found that participants remained unaware that they had received yoked feedback[19].

1.5 Health economic effects of neurofeedback treatment in Borderline

BPD is one of the burdensome and costly illnesses in the German health care system. The total annual costs of BPD (including loss of productivity) amounted to €31,130 per person[22]. BPD causes higher treatment costs than other mental disorders, combined with higher utilization of healthcare services[23]. The individual burden of illness in BPD is very high and is characterized by a marked tendency towards hospitalization, increased somatic comorbidity, increased mortality and severe constraints on the social integration, on the employment and occupational situation. Therefore, it is important to evaluate the impact of different therapeutic treatments on costs and effects for people with BPD. Currently, knowledge of health economic effects of therapeutic procedures in BPD is very limited. We aim to assess the health economic impact of neurofeedback in BPD from a societal perspective. Therefore, we measure utilization of healthcare services, medication, remedies (direct cost), loss of productivity (indirect costs) and estimate costs of neurofeedback treatment (micro-costing) and measure utilities (i.e. quality adjusted life years, QALY) to calculate incremental cost-effectiveness ratios (ICER) and the net-monetary benefit (NMB).

1.6 Neuroplasticity: Alterations of white matter structure

Alterations in functional and structural connectivity have been found to play an important role in the development of borderline personality disorder (BPD)[24–26]. To date, only few and mostly small diffusion tensor imaging (DTI) studies have been conducted investigating white matter (WM) microstructure or connectivity in patients with BPD[27,28]. Although the results of previous studies are not universally consistent, there is some converging evidence of differences in WM pathways of the prefronto-limbic system including the orbitofrontal and anterior cingulate regions as well as the corpus callosum and fornix[29–38]. These results are interpreted as supporting the fronto-limbic dysfunction hypothesis of BPD[35,36] and were found to be related to BPD-related symptoms such as anger or affective instability[31].

A fronto-limbic disconnection would explain the observed deficits in emotion and amygdala regulation[38,39] and may be partly responsible for the hyperreactivity of the amygdala to negative affective stimuli in BPD, as reported in various studies including a meta-analysis[8,40].

We therefore hypothesize that differences in the WM structure of fronto-limbic pathways in individuals with BPD may have an impact on their emotion regulatory abilities and consequently on their individual success in affect regulation following amygdala neurofeedback training. This project will be conducted as a sub-project of the BrainSTEADy clinical trial.

In addition to differences in DTI measures that may be predictive of treatment success, DTI allows tracking of learning-related neuroplasticity[41]. Effects on functional amygdala-prefrontal connectivity following neurofeedback training have been reported earlier[42]. However, it remains unknown what neuroplastic effects neurofeedback training has on the targeted structure (amygdala) itself as well as on structures that exert a regulatory influence on the amygdala (e.g. prefrontal regions and hippocampus). A recent neurofeedback study[43] on regulating the activity of sensorimotor cortices showed rapid effects on WM structure measured with DTI. In a sham-controlled neurofeedback study, healthy individuals performed a motor imagery task (1 h) and showed increased fractional anisotropy (FA) in sensorimotor segments of corpus callosum.

Changes in the mean diffusivity (DTI) of grey matter structures are well-established in memory research, where plasticity sets in rapidly after learning[41,44,45] and is known to persist for at least several days.

1.7 Dissociation in the Context of Amygdala-Neurofeedback

If the main project confirms that fMRI-NF is an efficacious tool for treating BPD symptoms it will be important to define its role in BPD care. In particular, it will be interesting to see whether i) fMRI-NF works for patients who do not respond well to traditional treatments such as DBT and ii) to study the potential of a rational combination of psychotherapeutic approaches and fMRI-NF.
High levels of dissociation emerged as a predictor of poor response to psychotherapies addressing BPD[46,47] and in naturalistic studies including BPD patients (e.g., [48]). Furthermore, there seems to be a subgroup of patients who tend to show consistent dissociation during DBT sessions[49]. However, it is unknown whether dissociation moderates the outcome to fMRI-NF. As successful fMRI-NF relies on learning which is known to be hampered by dissociation[50] it is plausible that patients who tend to dissociate profit less from fMRI-NF than those who tend to show less or no symptoms of dissociation. On the other hand, fMRI-NF is targeting mechanisms associated with dissociation while circumventing elements of psychotherapies that might trigger dissociation. Hence, fMRI-NF might emerge as a much needed tool for diminishing dissociation proneness in a difficult to treat subgroup of patients. Actually, previous studies [11,12] found medium (not significant) to large (statistically significant) reductions of dissociation after amygdala fMRI-NF. However, this finding is awaiting confirmation from an RCT. While of clinical relevance, the interplay between dissociation and amygdala fMRI-NF has not sufficiently been investigated.

1.8 Neurofeedback and non-response to standard therapy

Woodbridge et al.[51] identified factors contributing to non-responding to psychotherapy in patients with a diagnosis of BPD. They found attachment style and high levels of paranoid symptoms to be indicators of therapeutic success. Patients with preoccupied attachment patterns in their adult relationships were more likely to be non-responders regarding BPD symptoms after 12 month of psychotherapy and were more likely to be non-responders regarding general psychological distress at follow up. Patients with a high baseline level of paranoia and a dismissive adult relationship style had a higher risk of being non-responders with regard to global functioning[51].
Landes et al.[52] examined predictors of dropout from Dialectical Behavior Therapy (DBT), which is currently the gold standard of treatment, in a community mental health setting. Results of a logistic regression showed that younger age, higher levels of baseline distress, and a higher level of baseline non-acceptance of emotional responses were significantly associated with dropout[52]. It is comprehensible, that those factors make it difficult to establish a reliable attachment in the psychotherapeutic setting or to follow a psychotherapy continuously. Hence, an alternative treatment might be of special value for patients fulfilling those criteria for a high risk of not responding to psychotherapy or not completing DBT.

1.9 Clinical Investigation Rationale

1.9.1 State-of-the-Art BPD treatment

Psychotherapy is the first-choice treatment of BPD[53]. Treatment with BPD-specific psychotherapy programs is more effective as compared to standard psychotherapy treatment for the improvement of symptom severity, psychosocial functioning, self-injurious behavior and suicidal behavior. Evidence-based treatments are structured programs that have been tailored to meet the specific needs of persons suffering from BPD. They are based on Cognitive Behavior Therapy (CBT) and psychodynamic psychotherapy. Pivotal aspects to consider in BPD therapy as compared to the treatment of other mental disorders is the focus on the therapeutic relationship

and the treatment of self-injurious behavioral tendencies including suicidal behavior. Dialectical Behavior Therapy (DBT) and Mentalisation Based Therapy (MBT) are the most researched diagnosis-specific treatment programs for BPD. The treatment period is between 6 months and 2 years. About one third of patients reached the state of remission after 12 months in BPD-specific treatment. Those with BPD presenting strong self-injurious behavior (including suicidal as well as non-suicidal self-injury) should be treated with DBT or MBT. Usual treatment plans include at least one session per week. As in DBT, group psychotherapy sessions are part of the treatment plan and are to be given additionally to single therapy sessions. In case no single-therapy is available, patients should be offered to start treatment with BPD-specific group sessions (e.g. Skills-Training).

There is not sufficient evidence for the effectiveness of medication on BPD symptoms. Patients with BPD should not be treated primarily with medications. However, medications may be used to treat comorbid mental disorders or psychiatric symptoms in line with current guidelines as part of a coherent treatment plan. For example, on-demand medication may be prescribed for suicidal crises, when psychotherapeutic treatment alone is not sufficient. The risk of substance dependence and overdosing should be considered critically when determining the type of medication. Psychotherapy should not be replaced by medication as standard treatment of BPD. Other symptoms or comorbid psychiatric disorders need to be considered during BPD treatment and should be integrated in the treatment plan.

Outpatient treatment is preferable, although short-term in-patient treatment may be necessary for crisis intervention. Alternatively, patients may seek a residential BPD-specific treatment program if outpatient treatment is not available or if the in-patient setting is deemed preferable. However, longer in-patient clinic treatments without a structured, BPD-specific treatment program should be avoided. Care givers and teams who treat patients with BPD should be trained in an empirically validated BPD-specific program and should be supervised regularly.

1.9.2 Justification for this trial

As reviewed above, previous NF-studies with BPD showed promising improvements in symptoms and emotion regulation skills. Adverse device-related effects have not been reported. Access to effective BPD treatment is limited, because the capacity of qualified therapists and of clinical settings meeting above mentioned specific requirements is limited. As a result, patients wait half a year and sometimes even longer until they can start therapy sessions. If effective, neurofeedback could be offered to patients during this waiting phase. Otherwise, neurofeedback could be integrated in the treatment plan to support the training of emotion regulation skills or to reduce the general stress level of patients. As emotion regulation training is a major building block of BPD-specific treatment programs such as DBT, neurofeedback could be offered to patients that will likely benefit from extra-sessions – for example, patients with pronounced dissociation tendencies or patients with difficulty engaging in therapeutic lessons. If supported by research, neurofeedback could be a treatment option for patients who did not benefit from other treatment.

The low dosage required for fMRI-NF (clinically significant changes after 2 sessions of NF training were observed in a previous RCT[15]) speaks in favor of future usage in health care. Treatment costs are competitive (about 350 € per fMRI session and 3-4 sessions per treatment, if they can help to significantly reduce costs for residential as well as outpatient psychotherapy treatment. Although availability of MRI scanners is still limited, an increasing number of psychiatric hospitals have access to MRI. Hence, fMRI-NF may become a treatment option for many psychiatric patients in Germany in the near future. While the precise role of fMRI-NF in standard BPD care will be determined in clinical practice, it may be especially suited for treatment resistant patients. Therefore, the proposed project will focus on patients who have not responded sufficiently to prior conventional treatments. Taken together, fMRI-NF is assumed to be low-risk, demonstrably precise and fast acting, and arguably provides a positive cost-benefit ratio. Amygdala-NF could

be used to change neural patterns associated with psychopathological states, to meet special needs of patients with emotion dysregulation.

1.9.3 Expected Clinical Benefits

The following clinical benefit is claimed for medical device software TBV MED BPD. For some of the BPD patients, psychopathology, emotion dysregulation, and affective instability may improve. This includes self-reported experience in everyday life[12]. Other research found that 37% (of a very small sample) of the BPD patients were able to downregulate the right amygdala[11]; it is also possible that the connectivity between the amygdala and lateral prefrontal cortex is modified; additionally, a `lack of emotional awareness' score may decrease.

Schmahl, Niedtfeld & Herpertz[54] indicate that BPD occurs frequently, with 15-20% of patients in psychiatric hospitals consisting of BPD patients, and up to 15% of visits made by BPD patients. Also, Babaskina et al[55] mention that psychotherapy for patients with personality disorders can be challenging “because of their unstable emotions, anger, impulsivity, and poor interpersonal skills“. Therefore, even though more evidence is needed, it may be good not to exclude fMRI neurofeedback as supplement on beforehand due to lack of evidence.

At the same time, although side effects of NF for BPD patients have not occurred, researchers need to explicitly focus on any potential side-effects, due to the high mortality rate (8-10%) from suicide of people with BPD[56].

Personalization might be a strategy to improve the effectiveness of the treatment, since Babaskina et al[55] expect that personalization will increase the success of neurofeedback training for personality disorders, with the suggestion that machine learning methods could be used for personalizing neurofeedback protocols.

We conclude that TBV MED BPD can be a beneficial supplement for treatment of Borderline Personality Disorder.

1.9.4 Expected Adverse Device Effects

None

1.9.5 Residual Risks Associated with the Investigational Product

Clinically relevant parameters (CRPs) are established to be able to demonstrate the general safety and performance of the device as well as the claimed benefit of the device and to prove the device-specific claims.

1.9.5.1 Safety Parameters

Based on the Literature Search Report (provided by BrainInnovation, version BPD-CE-REC-Literature-search-report-TBV-Med-BPD_20240709), we formulate the clinically relevant parameters (CRPs) concerning safety as based on patient health and device safety. The CRPs that demonstrate the safety of TBV MED BPD are as follows:

- Mortality (pre-clinical data): 0 reported
- Amount of light adverse events, mostly related to MRI and less to neurofeedback itself: 6% (see elsewhere in text)
- Amount of severe adverse events: 0 reported
- Device malfunctions per year: 0 or close to 0

1.9.5.2 Performance Parameter

The CRP that demonstrate the performance of TBV MED BPD is as follows:

- Minimally relevant difference (MIREDIF). For BPD symptom severity the current version of the Cochrane Review „identified a MIREDIF of −3.0 points on the ZAN-BPD"[3].

1.9.6 Risks Associated with the Participation in the Clinical Investigation

Based on the extensive analysis of potential adverse events (see 1.2 Preclinical investigation), there has been no reports of worsened symptoms or any other severe adverse events.

1.9.7 Possible Interactions with Concomitant Medical Treatments

Interactions of neurofeedback with medications have not been reported systematically in the literature. It can be assumed that medications that can potentially affect attention, learning and memory could have a disadvantageous effect on the neurofeedback training outcome.

1.9.8 Control or Risk Mitigation Strategies

To mitigate potential medication interactions, ongoing treatment with Tranquilizers and with substances that were proven to inhibit dopamine functioning in the brain are prohibited in this trial.

1.9.9 Justification of the Positive Risk-Benefit-Ratio

The safety CRPs indicate that the expected mortality risk, risk of adverse events and device malfunction are very low when using TBV MED BPD. The performance CRP suggests that BPD patients may either not respond to this supplementary treatment, but will in that case not experience harmful effects, or BPD patients do experience beneficial effects. These beneficial effects can consist of decreased activity of the amygdala, possibly increased connectivity in circuits where the amygdala is involved and possible reduction of BPD symptoms.

Since the total clinical population was small, consisting of about 34 patients, it is not clear how these results extrapolate to a wider patient population, but thus-far the results for BPD patients seem slightly promising for neurofeedback by TBV MED BPD.

Based on the findings from literature, pre-clinical data as well as risk analysis, it can be inferred that the probability of a patient experiencing benefit when using TBV MED BPD outweighs the probability of suffering harm due to a residual risk of the device. Therefore it can be concluded that TBV MED BPD represents a safe addition to the portfolio of available treatments for Borderline Personality Disorder symptoms as a potential additional or supporting non-first-line approach. Due to the potential costs of this additional MRI neurofeedback treatment, further research would be beneficial in determining individuals who would benefit most of this treatment. Also, due to the high risk of self-harm (suicide 8-10%[56]), carefully monitoring the treatment is of utmost important, especially for the non-responders, since in non-responders of some other patient groups (disruptive behaviour) symptoms worsened (increased agression). Given the challenges providing psychotherapy to patients with personality disorders[55] and the empowerment by neurofeedback and enhancement of motivation that it provides[57], neurofeedback still offers a viable supplement to regular treatment. Therefore, the benefits participants could experience with TBV MED BPD outweigh the potential harm.

2. Objectives and Endpoints of the Clinical Investigation

2.1 Primary Objective and Primary Endpoint

To determine whether amygdala-fMRI-BOLD neurofeedback has a specific effect on dysregulated affect in BPD beyond nonspecific benefit. The main hypothesis to be tested is whether downregulation training of amygdala activation with neurofeedback reduces the intensity of negative affect assessed before treatment (T0) as compared to after treatment (T1) and whether the change is greater in the treatment group as compared to the control group.

Primary Endpoint: *Affect intensity* is measured via behavioral sampling using EMA over four days, 9 am to 10 pm, with 12 hourly smartphone prompts (+ jitter to avoid prompt anticipation). EMA data on affect will be assessed with widely used measures that were recently harmonised in a Delphi process with more than 50 EMA experts from the German Center for Mental Health.

2.2 Secondary Objectives and Secondary Endpoints

2.2.1 Main Investigation

A) *Affect intensity* assessed via behavioural sampling (EMA), group difference of change from T0 to T2.
B/C) *Borderline Symptom Severity* change (B: T0 to T1, C: T0 to T2) will be measured with the Zanarini Rating Scale for BPD (ZAN-BPD) and compared between groups. ZAN-BPD is a structured clinician-administered interview and established for assessment of BPD psychopathology in clinical trials[58].
D) *Amygdala response*, group difference of change from T0 to T1. Improvement will be quantified based on the first neurofeedback run (i.e., initial 4 'View'-trials of session number 1) and the last neurofeedback run (i.e., last 4 'View'-trials of session number 4).
E) *Amygdala self-regulation*, group difference of change from T0 to T1. Improved self-regulation of amygdala activity, change from T0 to T1. Improvement will be quantified based on the first neurofeedback run (i.e., initial 4 'Regulate'-trials of session number 1) and the last neurofeedback run (i.e., last 4 'Regulate'-trials of session number 4).
F) *Improvement in quality-adjusted life years (QALY),* group difference of change from T0 to T3. We hypothesize that the application of amygdala-fMRI-BOLD neurofeedback is cost effective compared to the control treatment. All changes in terms of utilization of mental health care, work productivity and utilities were measured from T0 to T3. Especially, we expect a reduction in inpatient treatment days and an improvement in quality-adjusted life years (QALY) in favor of the intervention group. We anticipate gaining insight into the potential health economic benefits of neurofeedback to society.

To measure resource use of health services, productivity loss, and QALYs, both groups fill in the same questionnaires before the intervention group receives the first neurofeedback session, and six months after the last session. The three questionnaires that are provided via individualized online access are: the FIMPsy[59], the WPAI:GH[60], and a preference-weighted generic instrument, the AQoL-6D[61]. We will analyze health care utilization, productivity loss and its associated direct and indirect costs between groups from a societal perspective. We will calculate incremental cost-effectiveness ratios (ICER), defined as the ratio between net total costs and net effects (i.e. the net costs for averting an additional inpatient treatment day and to gain an additional QALY). In addition, we will quantify the average costs of a single fMRI neurofeedback session using micro costing by consulting a specialist. With such costs at hand, we will calculate the net monetary benefit (NMB) of the neurofeedback treatment. To confirm the uncertainty around the ICER, non-parametric bootstrapping is performed and presented in cost-effectiveness diagrams with 95% confidence intervals (sampling uncertainty). Willingness-to-pay thresholds are presented as cost-

effectiveness acceptability curves. Consequences of uncertainty are visualized using value of information (VOI) curves. These analyses should inform stakeholders in health care (i.e. payers – health insurance companies - and service provider) about reimbursement decisions.

2.2.2 Accompanying Research

In sub-studies to the main trial, we investigate following research questions/hypotheses:

- Predictive value of white matter structure for neurofeedback response: Differences in white matter microstructure, as assessed using DTI before the neurofeedback training at V3, will predict the response to neurofeedback training in individuals with borderline personality disorder (BPD), as measured by a reduction in affect intensity from pre-training (T0) to post-training (T1).
- Impact of neurofeedback training on neuroplasticity: Neurofeedback training will induce changes in neuroplasticity, observed as a decrease in mean diffusivity (MD) in DTI measures between pre-training and post-training (V3 and V4), compared to a control group undergoing a yoked feedback condition. These changes are hypothesized to be detectable not only in the amygdala but also in other emotion-regulatory brain structures such as the prefrontal cortex.
- Relationship between white matter structural and functional connectivity: Structural connectivity, as assessed with DTI (using a global fiber tracking approach) will correlate with functional connectivity, particularly between emotion-regulation networks and the amygdala during the fMRI tasks.
- Is response to fMRI-NF moderated by the level of patients' dissociation?
- Is fMRI-NF improving (i.e. lowering) levels of patients' dissociation?
- Criteria for probably not responding to psychotherapy are assessed such as attachment style, paranoid symptoms, younger age, baseline distress, higher baseline non-acceptance of emotional response, to test whether they can successfully be treated with neurofeedback. High risk non-responders identified with the respective tools (attachment style measured with the Relationship Scales Questionnaire (RSQ), paranoid symptoms measured with the Paranoia Checklist (PCL), higher baseline non-acceptance of emotional response measured with the Difficulties in Emotion Regulation Scale (DERS) will be compared with the patients not fulfilling those criteria with regard to change in levels of distress (measured with CGI) and Borderline Symptom Severity change (measured with the Zanarini Rating Scale for BPD (ZAN-BPD) from T0 to T2.

3. Design of the Clinical Investigation

3.1 Overall Clinical Investigation Design

This is a randomized controlled, patient-investigator-biometrician blinded, multi-center trial to assess superiority of fMRI-NF compared to sham-control feedback with indication of BPD. The study is designed to confirm effects of the treatment on affect instability and emotion dysregulation that were previously found to be changed following the treatment. Further aims of the investigation are to assess neurocognitive mechanisms of response to NF, socioeconomic effects, and the influence of pathological states such as dissociation that may influence treatment response.

Comparator/control group: The assumed mechanism of NF is that changing a neural process will change related cognition and behavior. While this model is widely accepted, non-specific effects may mediate NF treatment outcomes as well[17]. The current state of evidence is best represented by a synthesis-model of both NF specific and non-specific factors accounting for psychosocial and placebo mechanisms[18]. To show that amygdala-NF is effective, it is necessary to control for non-specific factors in a RCT design. Participants in the control group are not provided with their own feedback signal. Instead a signal of another participant ('yoked feedback') is presented, which is an established standard in NF trials. Advantages of yoked feedback: a) the matching of the amount of reward received by both groups and b) unforeseen training effects are excluded that could be induced by other, conservative control conditions such as the training of alternative signals (e.g. different brain region)[19]. Although the risk of patient unblinding with non-contingent feedback has been raised and will be monitored in this project, many studies found that participants remained unaware that they had received yoked feedback[19].

Trial design:

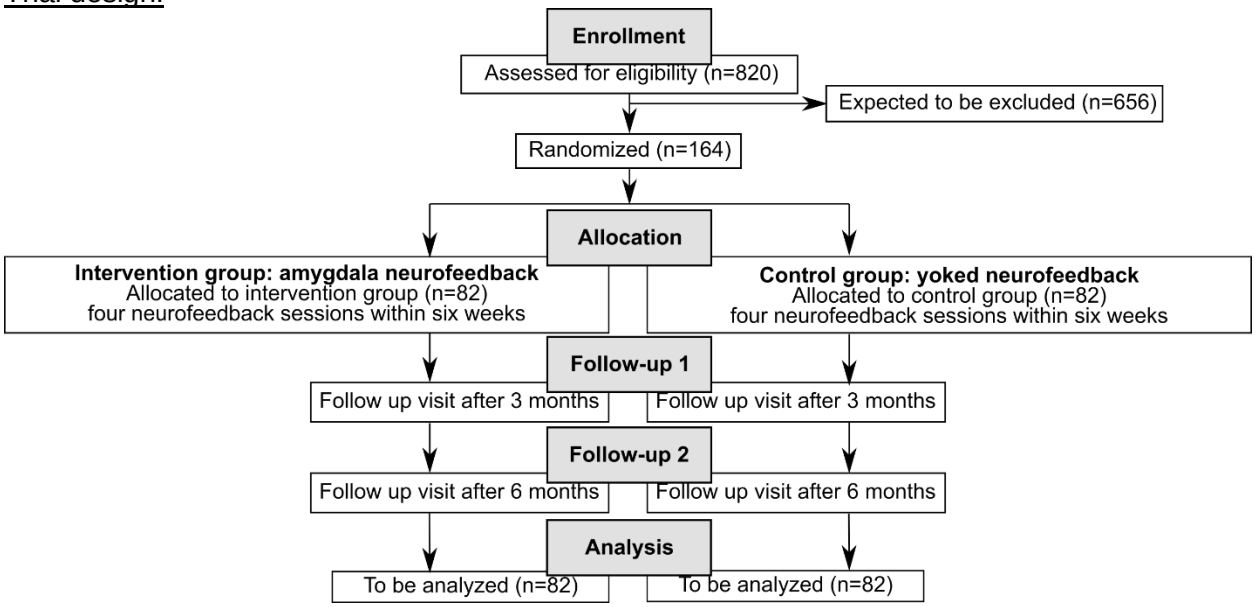


Figure 2. Trial design.

Trial Time Flow:

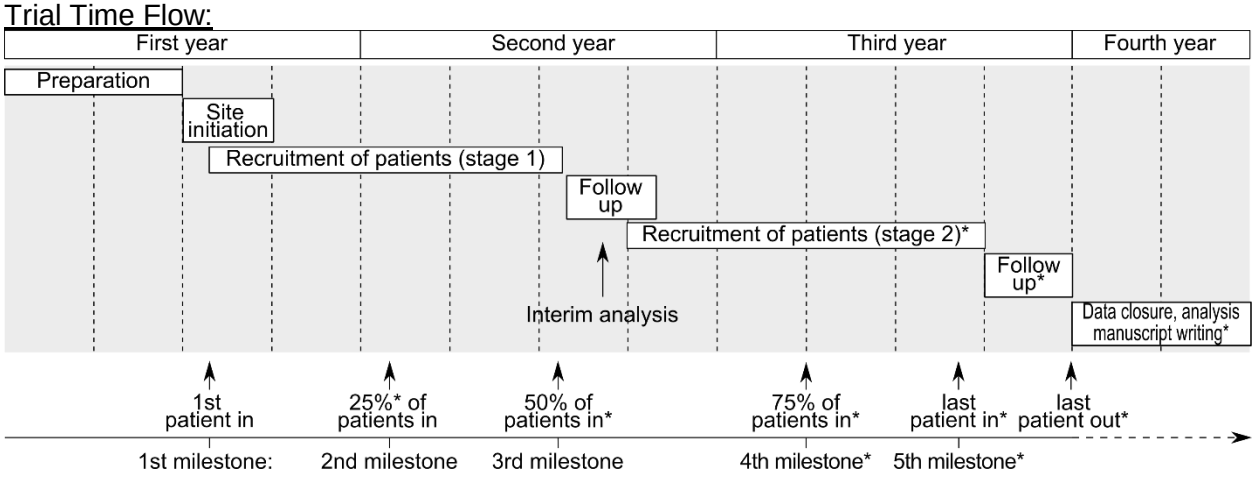


Figure 3. Trial Time Flow. Phases marked with * depend on decision to continue recruitment following interim-analysis.

3.2 Planned Interim Analysis

The interim analysis is scheduled when 82 of the included subjects in the full analysis set have been reached. If the clinical investigation continues without adaptation, the final analysis will be performed after inclusion of 82 further subjects. For details see chapter 9.6.

Trial allocation and (interim-) analysis design

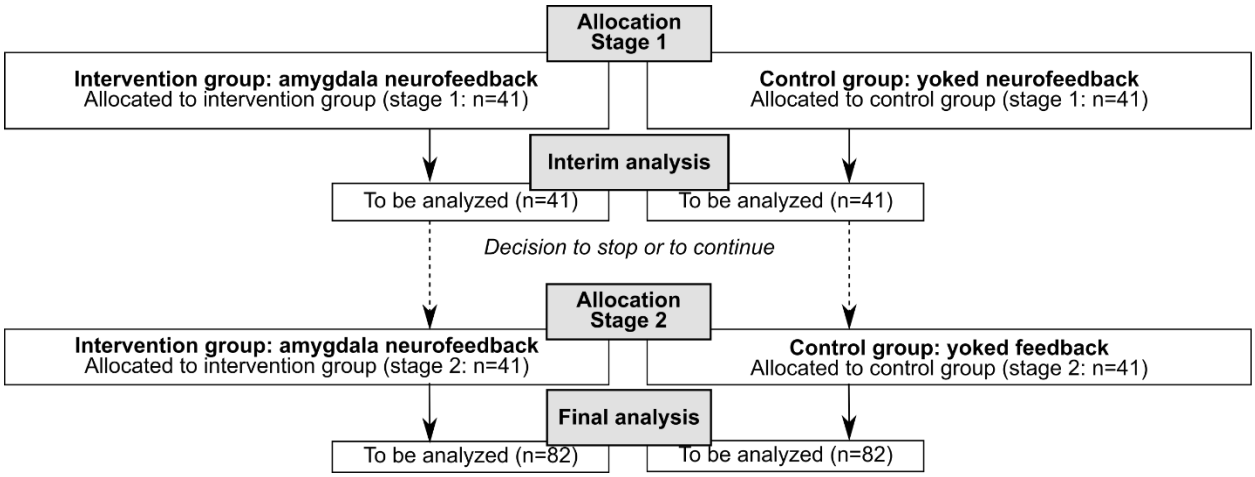


Figure 4. Allocation and analysis design

3.3 Overall Duration of the Clinical Investigation

The clinical investigation will be conducted over a period of approximately 4 years. The duration of the clinical investigation may be extended and additional sites may be added depending on the observed rate of recruitment.

3.4 Duration of Clinical Investigation for each Subject

The investigation consists of:

- one day of Screening,

- a 1 month treatment period,
- a 6-months post-treatment follow-up period.

In total the duration of the clinical investigation for each subject is expected to be 7-8 months.

Patient time flow:

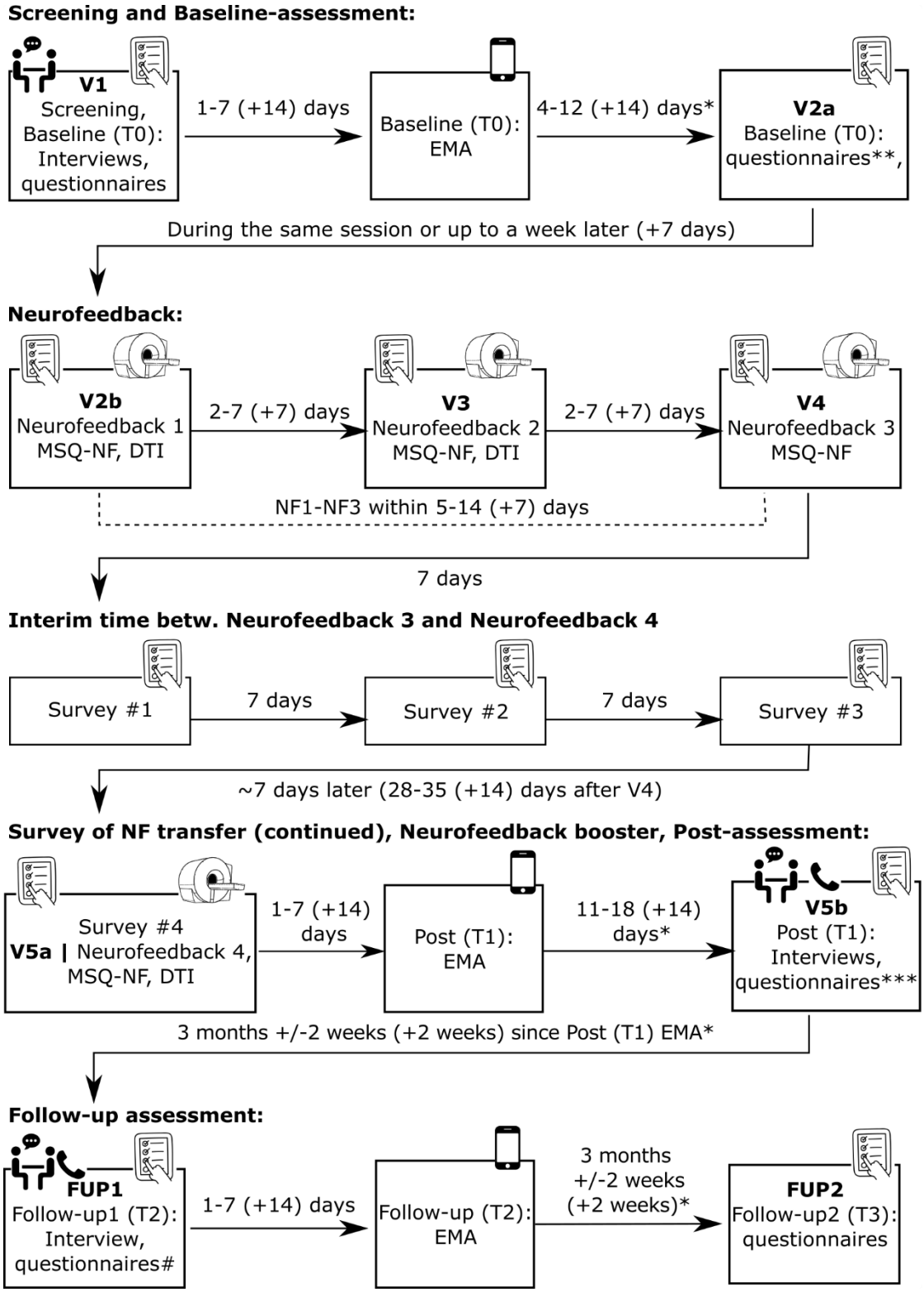


Figure 5. Patient Time Flow. Above the arrows the time periods are given to complete tasks per protocol, e.g. "**1-7** (+14) days" (bold: time period per protocol). Exceeding these time periods is a protocol deviation and should be documented accordingly in the eCRF. The patient can stay in the study as long as the maximum tolerable delay given in brackets is not exceeded e.g. "1-7 (**+14**) days" (bold: maximum tolerable delay). If visit/procedure cannot be completed in time, the subject is to be terminated. **An exemption of this rule is when Neurofeedback visits V3 and/or V4 cannot be conducted according to protocol within the given time**: As long as patients have a valid Neurofeedback visit V2b AND are able to complete the Neurofeedback 4 (Booster-Neurofeedback) V5a visit, they remain in the study. With other words, a lower-than-envisaged training dose is acceptable, as long as the first and the last neurofeedback session can be conducted according to protocol. In case of missed session V3 or V4, V5a has to be scheduled 28-35 (+14) days after the last Neurofeedback visit that was completed according to protocol. Although a lower training dose is acceptable, missed treatment is a protocol deviation. Trial staff should motivate patients to receive the full training dose of 4 neurofeedback sessions whenever possible.
* Count from first day of EMA data sampling
** Online questionnaire to be completed after the last day of EMA data sampling and before fMRI-scan begins. It is possible that subject (begins to fill or) completes online-questionnaires remotely before the V2a on-site visit.
*** Online questionnaires should be completed on same day of interview and must be completed within 7 days following interview. Questionnaires must not be filled during EMA data sampling.
# Online questionnaires should be completed on same day as the interview is taking place. Patient can begin to fill questionnaires 7 days before the interview day.

Figure legend:  = On-site interview,  = interview conducted on-site or remotely  = ePRO questionnaire,  = Ecological Momentary Assessment (EMA),  = MR scan.

3.5 Definition of End of Investigation

The end of clinical investigation is defined as "last subject last visit" (LSLV). In case of an early termination of the investigation (see chapter 7.5), the date of the early termination will be the date for end of investigation.

3.6 Patient Involvement

We consulted with the "Advisory Board of Affected Persons" (*Betroffenenbeirat*) of the Central Institute of Mental Health (CIMH) about the design and recruitment aspects of the project. Main outcomes from the meeting:

- Endpoints can be considered relevant.
- Questionnaires and interviews seem adequate, reasonably focused and concise.
- In case patients terminate participation of the trial early, the investigator should document the reasons.
- Participation should be acknowledged and patients should be informed e.g. by a newsletter about completion status of the trial and the general outcomes. More details could be provided for interested patients via a website. Therefore, it has been decided decided to budget costs for a trial website.
- BB will support the investigators during the recruitment process.

The perspective from the Betroffenenbeirat representatives was helpful to confirm attractiveness to participate in the trial and to confirm adequacy and relevance of measures for the patients' needs. Their reflections on design aspects such as inclusion criteria, public relations and patient information were helpful to conceptualize the study. Subject involvement during trial phase: A

patient review board consisting of 4 patients/affected persons will be formed. Tasks of the board are: participation in PPI training courses, the definition of the board's tasks and goals, support in the development of the homework-part, co-development of informed consent and the patient instructions, involvement in interpretation and dissemination of results, co-authorship on paper.

3.7 Measures to Minimize Bias

3.7.1 Randomization and blinding

Randomization and blinding will be used as primary methods to prevent bias. Participants will be randomized 1:1 to receive either the experimental or the control condition. In line with the CONSORT Statement[62], GCP-compliant randomization software will assure concealed assignment to avoid a potential selection bias on the part of the study members involved in enrollment. Stratified permuted block randomization with trial site as a stratum will be applied. Within each stratum, block sizes will be variable to protect concealed assignment. The protocol conceals group allocation from patients and staff involved in data processing and statistical analysis. The source of feedback will be selected automatically (amygdala or yoked feedback), based on a priori randomization, without revealing group assignment to staff. To minimize the risk to unblind the biostatistician, patient randomization will be managed by the CRO. The dataset transferred to the biostatistician will not include the variable coding for group assignment. The data analysis syntax of the primary endpoint will be written by the biostatistician, but the interim analysis including the variable coding for group assignment will be run by the CRO. Descriptive statistics from interim analysis will be disclosed at the end of the trial.

The randomization list will be kept in safe and confidential custody at the KKS Heidelberg.

The DSMB remains unblinded and will be provided a unblinding list.

3.7.2 Breaking the Blind

3.7.2.1 Unblinding in the end of the trial

At the end of the study and after data verification and database lock, the assigned blinded codes are broken for the final analysis of study data. Detailed instructions on randomization, blinding and breaking the blind are distributed to the respective authorized personnel prior to the start of the study. Patients are informed that they can´t receive any information by the clinical project management or the principal investigator about the treatment they had been administered during the study until the entire study has been completed.

Blinded parties: Patients, investigators, biostatisticians (Kleindienst)

3.7.2.2 Emergency unblinding

Allocation of a patient to treatment vs. sham-control group does not have any consequences for the immediate treatment of patients in case of (serious) adverse events during this trial. Therefore, emergency unblinding is not applicable. If unblinding becomes necessary for regulatory reasons before the end of the trial, the unblinding is possible based on the randomization list kept by the KKS.

4. Subject Selection

4.1 Number of Subjects and Sites

A total of 164 subjects will be enrolled in the clinical investigation, i.e. 82 subjects per treatment group (see chapter 9.9).

The clinical investigation will be multicenter. The clinical investigation will take place at 6 sites in Germany: CIMH Mannheim; Tübingen University, Dept. of Psychiatry; Gießen University, Dept. of Psychiatry; Freiburg University, Dept. of Psychiatry; Hamburg University, Dept. of Psychiatry; Halle University, Dept. of Psychiatry.

If enrollment is delayed, additional sites may be recruited. Screening of subjects for this clinical investigation is competitive, i.e. screening for the clinical investigation will stop at all sites at the same time once a sufficient number of subjects has been recruited. Investigators will be notified about screening completion and will then not be allowed to screen any more subjects. Subjects already in screening at this time will be allowed to continue to randomization if eligible and will be added to the analysis set.

4.2 General Criteria for Subjects' Selection

As there will be no preferences on the selection of gender to be included, it is anticipated that the clinical investigation results will give a representative gender distribution, which should reflect the natural gender distribution in the underlying disease.

4.3 Inclusion Criteria

Subjects meeting all of the following criteria will be considered for enrollment in the clinical investigation:

1. 18-65 years
2. Diagnosis of Borderline Personality Disorder according to DSM-5
3. Insufficient response to ≥2 therapies. The criterion is fulfilled if the patient reports:
    a) 2 or more psychotherapy treatments with 12 or more sessions each OR:
    b) 2 or more psychotherapy treatments with a duration per treatment of at least 12 weeks OR:
    c) a medical history of 2 or more psychopharmaceutic treatments, each over the course of at least 4 weeks OR:
    d) a combination of 2 or more treatments such as:
        i. psychotherapy with 12 or more sessions,
        ii. psychotherapy with a duration of 12 weeks or longer,
        iii. psychopharmaceutic treatment over the course of at least 4 weeks.
4. Sufficient German language skills to give informed consent to the study, to understand questions posed by used instruments, and capable of completing the fMRI tasks
5. Ability of subject to understand character and individual consequences of clinical investigation
6. Written informed consent (must be available before enrollment in the clinical investigation)
7. For women of childbearing potential (WOCBP) adequate contraception (as defined in Appendix 2).

4.4 Exclusion Criteria

Subjects presenting with any of the following criteria will not be included in the clinical investigation:

1. Treatment with benzodiazepines within 7 days prior the initial screening

2. Current moderate or severe alcohol or substance use disorder within 1 month prior the initial screening
3. Meeting the diagnostic criteria for a psychotic disorder or schizophrenia (life-time), as determined by clinical interview at initial screening
4. Current or history of significant neurological condition (such as stroke, traumatic brain injury, space occupying lesions, multiple sclerosis, Parkinson's disease, vascular dementia, transient ischemic attack)
5. Significant visual impairment which might interfere with the performance of investigation procedures
6. Change of treatment (psychopharmacologic, psychological) 2 weeks prior to study participation or before completion of the post-assessment.
7. Treatment with any neurofeedback other than investigational device three months prior to or during the study participation.
8. Unable or unwilling to comply with study procedures, including study prohibitions and restrictions
9. History of claustrophobia or inability to tolerate scanner environment
10. Fulfilling any of the MRI contraindications on the standard site radiography screening questionnaire (e.g. history of surgery involving metal implants)
11. Clinically relevant structural brain abnormality as determined by prior MRI scan
12. Planned medical treatment within the study period that might interfere with the study procedures
13. Participants deemed to be at significant risk of serious violence or suicide based on any one of the following:
    a. Significant risk of committing violent acts, homicide, or suicide based on history, routine psychiatric status examination, or according to the investigator's experience OR
    b. Any suicide attempt in the past 3 months (i.e., actual attempt, interrupted attempt, aborted attempt) prior to screening and during the screening period OR
    c. Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months prior to screening or during the screening period.
14. BMI of 16.5 or lower
15. Participation in other clinical trials or observation period of competing trials, respectively
16. Previous participation in this trial (Re-Screening possible, c.f. Chapter 4.6.2)
17. Pregnancy and lactation
18. Held in an institution by legal or official order
19. Legally incapacitated.

4.5 Lifestyle Considerations

No alcohol, drugs or not-prescribed medications to be consumed 24 hours before an MRI measurement. Patients should try to get sufficient sleep in the night before each MRI measurement. Patients should follow their regular activities during EMA data sampling.

4.6 Subject Assignment

4.6.1 Identification Numbers

All screened subjects receive a screening number. Subjects included in the clinical investigation (all inclusion criteria and none of the exclusion criteria met) are assigned a consecutive subject number.

Each number will be assigned only once. For allocation to a treatment arm see section 3.7.1. No subject will be allowed to participate in this clinical investigation more than once.

4.6.2 Screening Failures

Subjects, who evidently do not meet inclusion criteria or meet exclusion criteria prior to enrollment are considered screening failures. Screening failures will be recorded on the screening list, but will not be provided with a subject number. Minimal information to be obtained from screening failures include screening failure details and eligibility criteria.

Re-screening is also allowed provided that the reasons for screening failure were reversible and have been resolved, based on investigator judgement. A subject is considered a “re-screener” if he/she was not eligible for the clinical investigation initially and is subsequently re-screened, going through the informed consent process for a second time, receiving a new unique number and repeating the screening assessments.

5. Investigational Device

5.1 Description of the Investigational Device

The investigational software in this clinical investigation:

Product Name	Purpose	Manufacturer	Classification	Used Software Versions
TBV MED BPD	Real-time fMRI BOLD-signal tracking in the brain.	BrainInnovation Oxfordlaan, 55 6229EV, Maastricht Niederlande	1	-

For further details regarding the device and its mode of operation please see the Investigator’s Brochure (IB), as well as the Instructions for Use (IFU).

On the effective date of this CIP version, the software is not CE certified as medicinal product with indication BPD.

5.2 Supplies of Investigational Device

The sponsor will provide a laptop with pre-installed investigational software and valid license for the trial period to site.

5.3 Device Accountability and Traceability

Not applicable.

5.4 Use of the Investigational Device

Sponsor will train trial staff how to operate the software. Instructions for Use will be distributed to sites.

5.5 Specific Medical or Surgical Procedure Involved

No specific medical or surgical procedure is performed for use of the investigational device.

5.6 Comparative Devices

No comparator device will be used in this clinical investigation.

6. Clinical Investigation Visits and Investigations / Assessments

This section describes the procedures and tests specific for the clinical investigation required to be performed at specified visits as outlined in the schedule of assessments. Also refer to section 3.4, Figure 5, Patient Time Flow, for more information on timing of visits and procedures. For details on the individual assessments please refer to sections 6.10.

6.1 Screening Visit / Baseline (T0), V1

During the Screening Phase, the following assessments are conducted and recorded in the source documents and the eCRF:

1. Informed consent
2. Suicidality assessment (using C-SSRS)
3. Review of inclusion/exclusion criteria
4. BPD-diagnosis according to DSM-5 (using IPDE)

Not mandatory for screening failures:

5. Medical history (prior and concomitant diseases)
6. Previous and ongoing medication, psychotherapy treatment, neurofeedback treatment
7. Demography (*age, sex/gender: DiMIS Table 2, race/ethnicity: DiMIS Table 1 Item 6d, education: DiMS Table 1 Items 3a,b*)
8. Last menstruation (to assess potential effects of cycle phase on self-regulation and outcomes)

Interviews/assessments conducted during the on-site screening visit:

1. CGI-S (State version)
2. ZAN-BPD
3. FIMPsy (patient self-report via ePRO with investigator assistance if needed)

Interviews and assessments of the screening phase should be collected on the same day as the informed consent is given or within 7 days thereafter.

Questionnaires to be filled during screening visit or later. The questionnaires have to be completed one day before the first scheduled day of EMA sampling. The subjects receive a link to the ePRO platform where they can fill in the online questionnaires on their own electronic device. The subject can pause and save interim entries (by actively clicking the “save” button on the ePRO site), and resume the answering of questionnaires later.

1. BSL-23
2. BDI
3. DERS-36
4. DES
5. SCL-27
6. WPAI:GH

6.2 Baseline Visit (T0) continued, V2a

Cave: Patients are randomized only after EMA data collection was confirmed. Before patients come in for the on-site part of this visit, they accomplish EMA and online questionnaires at home. In the beginning of the on-site part of this visit, the investigator has to confirm that EMA data has been recorded as described below.

The smartphone for EMA data sampling is prepared during the Screening visit. EMA is conducted on four consecutive days including 2 days at the weekend. The first day of EMA sampling should always be a weekday (i.e., Thursday or Friday) so that trial staff is able to check that the recording

is going well and that trial staff is available for patients if any problems and questions come up in the beginning of EMA.

EMA data sampling can begin the day after V1 earliest, but should not begin later than 7 days after V1.

The subjects fill the questionnaires below remotely in the ePRO system during this time: Earliest, they can begin 1 day after EMA data sampling and they have to complete questionnaires 7 days thereafter. Study staff should plan sufficient time in the beginning of Visit V2a to allow the patient to complete questionnaires that may not have been completed at this time. All questionnaires have to be completed before the first MR-scan.

1. AQoL-6D
2. BSL-23
3. DSS-acute
4. PCL
5. RSQ

Before the patient can continue with on-site part of this visit, trial staff needs to confirm whether the patients answered the minimum number of EMA prompts of 50%. **If the minimum number of EMA prompts was not made, the patient cannot be randomized to the trial.**

At the day of MR-scan:

- To exclude any fetotoxic risk of participation in an MR-study, “WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test” (ref. HMA-CTFG Contraception guidance Version 1.2, 2020-06-14). The result of the test is to be documented in the patient source documents.
- If applicable, the day of the last menstruation should be recorded.

Patients receive instructions for the neurofeedback training.V2a should be combined with V2b (Neurofeedback 1) in the same MR-session.

6.3 Neurofeedback 1-3 (V2b, V3, V4)

AE/SAEs are assessed following randomization. The first AE assessment is conducted on V2b when the MR session has been completed. In the following visits, AE/SAE are assessed in the beginning of each visit (to detect AE/SAE since the last visit). Additionally, AE are assessed in the end of each Neurofeedback visit (to detect AEs related to the MR session). Assessment of potential pregnancy with a pregnancy test is mandatory for WOCBP in the beginning of each MR session.

MR safety criteria are checked. Patients are positioned in the MR-tube following guidelines in the Investigator’s Brochure. Patients receive a refresher of neurofeedback instructions. As part of the MR session, technical and anatomical scans are acquired. MR-scans of the neurofeedback visits:

- fMRI neurofeedback (BrainSTEADy training implemented in TBV MED software, in all visits)
- Questionnaire assessment in the end of each visit:
  - DSS-4
  - MSQ-NF
- DTI scans:
  - V1, V4: A series of 4 scans (each 1.5 min) is conducted before and after the Neurofeedback.
  - V3: Two 9-min-scans are conducted after Neurofeedback.

In the end of visit 3, patients are instructed to fill the Survey of NF transfer provided in the next weeks.

6.4 Interim weeks between Neurofeedback 3 (V4) and Neurofeedback 4 (V5a)

Patients receive a weekly email prompt with a link to the Survey of NF transfer presented via the ePRO platform. The prompts are sent 7, 14 and 21 days after Neurofeedback 3. The link should be valid 2 days. Patients should be informed about the importance to fill in the questionnaire.

6.5 Neurofeedback 4, Post-assessment visit (T1), V5a

- The Survey of NF transfer is conducted a last time in the beginning of the visit.
- AE/SAEs are assessed before and after the MR session.
- Assessment of potential pregnancy with a pregnancy test is mandatory for WOCBP in the beginning of each MR session.
- The day of the last menstruation should be assessed, if applicable.
- MR safety criteria are checked.
- Patients receive a refresher of neurofeedback instructions. Patients are positioned in the MR-tube following guidelines in the Investigator's Brochure. As part of the MR session, technical and anatomical scans are acquired.
- fMRI neurofeedback is conducted (BrainSTEADy training implemented in TBV MED software, in all visits)
- DTI scan is conducted (see above)
- Questionnaire assessment in the end of the visit:
    - DSS-4
    - MSQ-NF

EMA is conducted as described above on 4 consecutive days including a weekend. EMA data sampling can begin the day after V5a and should not begin later than 7 days after V5a.

6.6 Post-assessment visit (T1) continued, V5b

One week after the end of EMA data sampling (i.e., 11 days after the beginning of EMA) earliest, but no later than 2 weeks thereafter (i.e., 18 days after the beginning of EMA), clinical interviews are conducted on-site or remotely via phone or via safe internet application:

1. CGI-I (Improvement version)
2. ZAN-BPD
3. If applicable, the day of the last menstruation should be assessed
4. The patients will be asked questions for checking the blind (blind check). An investigator-version and a NF-trainer version of the blind-check questions are to be completed by trial staff.
5. Concluding questionnaire to be filled by patient.

Preferably on the same day as the interview the patient fills in (and completes) questionnaires in the ePRO system. It is also possible that the patient fills the questionnaires before or after the interview. Questionnaires must be completed during this time: One week after EMA data sampling (i.e., 11 days after the beginning of EMA) until 2 weeks after EMA data sampling (i.e., 18 days after the beginning of EMA).

1. BSL-23
2. BDI
3. DERS-36
4. DSS-acute
5. SCL-27

6.7 Follow-up assessment 1 visit (T2), FUP1

FUP1 is to be scheduled 3 months (+/- 2 weeks) after Post-assessment (T1) EMA.

The patient can fill in the questionnaires in the ePRO system one week before the interview and must complete the questionnaires no later than at the day of the interview:

1. BSL-23
2. BDI
3. DERS-36
4. DSS-acute
5. SCL-27

The ZAN-BPD interview is conducted on-site or remotely via phone or via safe internet application. If applicable, the day of the last menstruation should be assessed.

EMA data sampling begins 1-7 days after the interview.

6.8 Follow-up assessment 2 visit (T3)

Subjects receive a link to ePRO platform where they can fill in the online questionnaires on their own electronic device. The subject must complete the questionnaires within 7 days.

1. AQoL-6D
2. BSL-23
3. BDI
4. DERS-36
5. DSS-acute
6. FIMPsy
7. SCL-27
8. WPAI:GH

6.9 Planned Treatment after End of Investigation Participation

After the end of the investigation no further treatment of patients is necessary.

The investigator will continue to observe all subjects (also withdrawals) because of intolerable AEs / SAEs until any findings have been clarified or became stable.

6.10 Assessments

AEs	AEs will be asked for at each contact between the responsible investigator and the subject. Furthermore, new pathological and clinically relevant findings or aggravation of pre-existing symptoms in examinations will be documented as AEs. AEs will be reported with subject ID, start and end date, description, grading, seriousness, relatedness, action taken and outcome
AQoL-6D	The Assessment of Quality of Live Mark 2 instrument (AQoL-6D[51]) is a multi-attribute utility instrument that measures health-related quality of life. The instrument contains of 20 items grouped into five dimensions (illness, independent living, social relationships, physical senses and psychological wellbeing). The instrument provides weighted and unweighted age- (16 to 74 years) and gender-specific norms. Utility scores, i.e. QALYs, are elicited via time-trade off-derived (TTO) formulas51. The questionnaire will be filled in at visit

	V1 and again six months after the last neurofeedback session. The AQoL-6D is used for health economic analyses (sub-project by Höll).
BDI-II	Depressivity is measured with the Beck Depression Inventory (BDI-II[63]), which is a widely established 21-items self-report questionnaire. Items are rated on a scale from 0 to 4, a total score is received by averaging across all items. Higher values indicate higher depressivity
Blind check	An in-house developed questionnaire. Subjects are asked about their belief in what experimental condition they were randomized (i.e., amygdala-feedback or sham-feedback). There is a version for patients and a version for trial staff.
BSL-23	The Borderline Symptom List short version (BSL-23[64]) is an established self-rating questionnaire to assess Borderline symptom severity within a 1-week time frame. It is composed of 23 items. Each item is rated on a scale from 0-4 (0=not at all to 4=very strong/several times a day). Total score is received by averaging across the 23 items. The scale will be administered at visits V1, V5 and FUP.
Concluding questionnaire	An in-house developed, single-page self-report questionnaire asking the patient to rate their experience with the treatment after V5.
C-SSRS	The C-SSRS (https://cssrs.columbia.edu/) is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score but provides some categorical and some severity information specifically for behavior and ideation.
DERS	The Difficulties in Emotion Regulation Scale[65], is a 36-item self-report measure. Items are rated on a scale of 1 (almost never) to five (almost always). Higher scores indicate more difficulty of emotion regulation.
DES	In order to better characterize the sample with respect to dissociation, we will assess trait dissociation at baseline based on the most widely used assessment instrument, i.e. the DES[66] (28 items).
DSS-4	To investigate whether state dissociation during the fMRI-NF might be detrimental to the effect of the fMRI-NF-intervention, a brief assessment of state dissociation (5 items) following each fMRI-NF-session will be administered.
DSS-acute	To investigate whether fMRI-NF is improving patients' dissociation a comprehensive assessment of state dissociation, the DSS-acute[67] (22 items) will be assessed.
FIMPsy	The "Fragebogen zur Inanspruchnahme medizinischer und nicht medizinischer Versorgungsleistungen bei psychischen Erkrankungen" (FimPsy[59]) assesses health care resource use (including outpatient and inpatient medical care, intake of medication, informal care, psychiatric counselling, psychosocial care, social participation, vocational (re-)integration,) in patients with mental disorders over the previous six months. The FimPsy facilitates health economic evaluations by collecting type, frequency or duration of health care utilization.

Medical history and underlying disease history	Clinically significant diseases, surgeries, previous medical procedures, smoking history, use of alcohol and/or drug abuse, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs) taken by the subject within 7 d prior to start of investigational treatment.
MSQ-NF	Mental strategies used by participants for amygdala downregulation during the neurofeedback training will be assessed using Mental Strategies Questionnaire for NeuroFeedback (MSQ-NF). Patients will determine their own mental strategy for every regulation block and fill out the questionnaire at the end of every neurofeedback visit (V2b, V3, V4, V5a) for every distinct mental strategy separately. MSQ-NF allows to characterize strategies across dimensions, and identify the features of successful mental strategies.
[EMA]	Smartphone-based assessment over four days, 9 am to 9 pm, with 12 hourly smartphone prompts. When prompted, subjects will answer up to 15 questions about their emotions and negative events.
IPDE	The International Personality Disorder Exam (IPDE) is a clinician-administered semi-structured interview used to assess personality disorders as defined in the DSM-5 and ICD-11. The BPD subsection will be used to assess for the presence of severity of symptoms related to BPD. It will be administered during the diagnostic interview.
Negative affect intensity (based on EMA)	The primary endpoint is based on the EMA scale measuring negative affect.
PCL	The Paranoia Checklist[68] (PCL; 18 items) measuring the extent of paranoid symptoms, will be assessed for prediction of potential non-response to therapy.
RSQ	The Relationship Scales Questionnaire[69] was developed as a continuous measure of adult attachment. The RSQ contains 30 short statements on a 5-point scale ranging from "not at all like me" to "very much like me", participants rate the extent to which each statement best describes their characteristic style in close relationships.
Survey of NF transfer	Short questionnaire to ask patients whether they used self-regulation strategies learned during neurofeedback in daily life and how effective they were.
SCID	The Structured Clinical Interview for DSM-5 is a semi-structured clinician-administered interview for the assessment of psychiatric diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders Version 5.
SCL-27	The SCL-27 is designed to screen for psychological complaints in patients with leading physical symptoms. The subscales depressive, dysthymic, vegetative, agoraphobic, sociophobic symptoms and symptoms of mistrust are formed, as well as a global severity index (GSI-27).
WPAI-GH	The General Health (GH) version of the Work Productivity and Activity Impairment Questionnaire (WPAI-GH[50]) is a questionnaire designed to assess presenteeism and absenteeism due to health problems and work or activity impairments. The WPAI:GH consists of six questions, which elicit the amount of productivity loss to society over the past seven days. The questionnaire will be filled in at visit V1 and again six

	months after the last neurofeedback session. The WPAI-GP is used for health economic analyses (sub-project by Höll).
ZAN-BPD	Symptom severity will be assessed with the Zanarini Rating Scale for BPD[58] (ZAN-BPD). ZAN-BPD is a structured clinical interview administered by trained staff, who are blinded with respect to group allocation. The questions are adapted from the Diagnostic Interview for DSM-5 Personality Disorder to reflect a 1-week time frame. Each criterion is rated on a scale from 0-4, yielding a total score of 0 to 36.

7. Discontinuation and Early Termination

Any subject can withdraw from the treatment or the clinical investigation verbally or in writing at any time without personal disadvantages and without having to give a reason. However, the investigator should make a reasonable effort to ascertain possible reasons, while fully respecting the subject's rights. Specifically, the subject must not be coerced or unduly influenced to continue participation. Any given reason should be specified in the subjects file and in the CRF.

The investigator can also discontinue the investigational treatment after considering the risk-to-benefit ratio, if he / she no longer considers the treatment justifiable. The date of and the primary reason for withdrawal (one primary reason must be determined), as well as the observations available at the time of withdrawal are to be documented on the CRF. In all subjects who discontinue the clinical investigation prematurely, a withdrawal examination at least with respect to the primary endpoint should be carried out. The subject must be asked to consent to this last examination. The withdrawal examination must be specified in the CRF.

For details concerning sample and statistical considerations see 9.1.

7.1 Temporary Discontinuation from Treatment

Temporary treatment discontinuation at the discretion of the investigator is defined as one or more applications of the investigational device not performed.

Temporary treatment discontinuation may be considered by the investigator because of

- AEs/SAEs
- Unexpected unavailability or malfunction of the MR scanner
- Unexpected unavailability or malfunction of other equipment that is critical for proper function of the investigational device and that cannot be replaced in a timely manner

The usage of the investigational device may be resumed under close and appropriate clinical and/or laboratory monitoring if according to the investigator’s medical judgment the concerned event is unlikely to be related to the investigational device and provided that eligibility criteria for the clinical investigation are still met. For all temporary treatment discontinuations, duration must be recorded by the investigator on the appropriate pages of the e-CRF. See section 13.5 for recommended treatment continuation in case of unavailability/malfunction.

7.2 Permanent Discontinuation from Treatment

Permanent treatment discontinuation is any treatment discontinuation associated with the investigator’s or the subject’s definitive decision not to re-expose the subject to the investigational device. The following criteria will lead to a permanent discontinuation from investigational treatment:

- Subject’s request, i.e. withdrawal of consent for treatment,
- Loss to follow up,

- Death,
- Use of illicit drugs, prohibited concomitant medications,
- Intolerable AEs such as critical suicidal ideation, suicide attempt, psychotic state
- Lack of subject's compliance
- Existing or intended pregnancy or lactation. If a female subject becomes pregnant, she will be followed up until birth or termination of the pregnancy.
- Any additional diagnosis due to which, in the investigator's opinion, participation in the clinical investigation may pose a risk for the subject or that may interfere with CIP adherence,
- Significant structural brain abnormality observed during MRI scan
- Subject did not meet one of the in-/exclusion criteria (coming to light after inclusion): Treatment with benzodiazepines within 7 days prior to the initial screening, current or history of significant neurological condition, fulfilling any MRI contraindication

Even if the treatment is discontinued, the subjects may remain in the clinical investigation and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the schedule of assessments and section 6. Consent for further data collection should be documented in the patient file.

7.3 Discontinuation from the Clinical Investigation

In addition to death, the following incidents will lead to discontinuation of a subject from the clinical investigation:

- Loss to follow up
- Withdrawal of consent
- Lack of compliance

7.3.1 Withdrawal of Consent

Subjects may withdraw their consent to participation in the clinical investigation at any time without the need to justify the decision. If a subject wants to withdraw his/her consent, the investigator should explain the difference between treatment discontinuation and withdrawal from participation in the clinical investigation, including the options for continued follow-up after treatment discontinuation (see section 7.2). The decision of the subject must be documented in the source data. In case the subject still wants to withdraw from participation in the clinical investigation, an early treatment discontinuation visit should be conducted as outlined in the schedule of assessments and section 6, if possible.

7.3.2 Loss to Follow-Up

Subjects will be considered lost to follow-up if they fail to show up for visits of the clinical investigation and cannot be contacted by the site. Site personnel is expected to make diligent attempts to contact subjects who did not show up for a scheduled visit or were otherwise not available. These contact attempts should be documented in the subject's medical record.

7.4 Temporary Halt

A temporary halt of a clinical investigation is defined as an unforeseen interruption not provided in the clinical investigation plan but with the intention to resume it. If the reason for the temporary halt may have a negative effect on benefit-risk assessment, re-start is possible only after approval of a substantial modification.

7.5 Early Termination of the Clinical Investigation

Early termination is defined as the premature end of a clinical investigation before the conditions specified in the CIP are met.

The following reasons or events may result in an early termination:

- New findings on the investigational device leads to doubt as to the benefit-risk ratio;
- Subject enrollment is insufficient;
- DSMB recommends termination of the entire clinical investigation or single treatment arms.

An early end of the clinical investigation due to early inclusion of the total number of subjects is not considered an early termination. In the event of premature discontinuation of the clinical investigation for any reason whatsoever, the regulatory authorities should be informed according to applicable regulatory requirements. In case of an early termination of the clinical investigation, the date of early termination will be the date of end of trial.

When the clinical investigation is terminated, all materials related to the clinical investigation (CRFs: empty, completed or partially completed; emergency envelopes etc.) must be returned to the sponsor. The laptop with the investigational software installed must be returned to the sponsor.

7.6 Premature Closure of a Site

Premature closure of a single site by the sponsor may be considered for the following reasons:

- The investigator failed to recruit any subjects even though he/she had received the laptop with the investigational software, means and information necessary to perform the clinical investigation and had reasonable time to do so.
- Non-compliance with ISO 14155:2020(E), any provision of the clinical investigation plan or breach of the applicable laws and regulations of the investigator, sub-investigator or delegated staff.

In the event of premature closure for any reason whatsoever, the regulatory authorities must be informed according to applicable regulatory requirements. When a site is closed, all materials related to the clinical investigation (CRFs: empty, completed or partially completed; emergency envelopes etc.) must be returned to the sponsor. The laptop with the investigational software installed must be returned to the sponsor.

8. Adverse Events

8.1 Definitions

8.1.1 Adverse Event

According to the ISO 14155:2020(E) 3.2 and the Regulation (EU) 2017/745 Art. 2 (57) an adverse event (AE) means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, **in subjects, users or other persons,** in the context of a clinical investigation, whether or not related to the investigational device and whether anticipated or unanticipated.

This definition includes events related to the investigational medical device or the comparator and the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

An AE may be:

- New symptoms/ medical conditions,
- New diagnosis,
- Changes of laboratory parameters,

  The criteria that should be considered when determining whether an abnormal test finding should be reported as adverse event are as follows:

  - Test result is associated with accompanying symptoms, and/or
  - Test result require diagnostic testing or medical/surgical intervention, and/or
  - Test result lead to a discontinuation from the clinical investigation, significant additional concomitant drug treatment, or other therapy, and/or
  - Test result is considered clinically relevant at the discretion of the investigator or sponsor.
- Intercurrent diseases and accidents,
- Worsening of medical conditions/ diseases existing before start of the clinical investigation,
- Recurrence of disease,
- Increase of frequency or intensity of episodic diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical investigation plan and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the clinical investigation. In the latter case the condition should be reported as medical history.

AEs are classified as "non-serious" or "serious".

8.1.2 Serious Adverse Event

In accordance with ISO 14155:2020(E) 3.45 and the Regulation (EU) 2017/745 Art. 2 (58) serious adverse event (SAE) means any adverse event that led to any of the following:

(a) death,

(b) serious deterioration in the health of the subject, that resulted in any of the following:

(i) life-threatening illness or injury,

(ii) permanent impairment of a body structure or a body function,

(iii) hospitalization or prolongation of subject hospitalization,

(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

(v) chronic disease,

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

(c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

(d) Not applicable (Note that this option is only to be selected in case of reportable device deficiencies that did not lead to an SAE.).

8.1.3 Adverse Events of Special Interests

Not applicable

8.1.4 Device Deficiency

According to the EN ISO 14155:2020 3.19 and the MDR Art. 2 (59) a device deficiency (DD) means any inadequacy in the identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

This definition includes device deficiencies related to the investigational device or the comparator.

8.2 Expectedness / Anticipatedness

The classification of expectedness / anticipatedness should be performed by the sponsor according to the following definition:

Expected / anticipated:	an AE which by its nature, incidence, severity or outcome has been identified in the Investigator Brochure (IB).
Unexpected / unanticipated:	an unexpected / unanticipated event is one which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis.

In this clinical investigation IB will be used for determination of the expectedness / anticipatedness.

8.3 Characteristics of Adverse Events

8.3.1 Grading of AEs

The investigator should assess the intensity as follows:

Mild:	signs and symptoms which can be easily tolerated. Symptoms can be ignored or disappear when the subject is distracted.
Moderate:	symptoms cause discomfort but are tolerable, they cannot be ignored and affect normal activity.
Severe:	symptoms strongly affect normal activity.

If an AE shows an undulating course of intensity, it must be documented only once with predominant or medically most appropriate intensity.

Clarification of the difference in meaning between "serious" and "severe": The terms “serious” and “severe” are not synonymous. The term “severe” should be used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache). This is not the same as “serious”, which is based on the existence of at least one of the above-mentioned seriousness criteria.

8.3.2 Causal Relatedness

The **relatedness** between the AE and all potential causes will be assessed. The potential causes are:

- investigational device,
- comparator (sham-neurofeedback),
- medical procedure,
- underlying disease,
- other.

The classification of relatedness should correspond to one of the following criteria:

Causal relatedness: The adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relatedness with investigational device use / application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on.
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation / exposure) and reintroduction of its use (or increase of the level of activation / exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness / clinical condition or / and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

Probable: The relatedness with the use of the investigational device or comparator, or the relatedness with procedures, seems relevant and / or the event cannot be reasonably explained by another cause.

Possible: The relatedness with the use of the investigational device or comparator, or the relatedness with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness / clinical condition or / and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Not related: Relatedness to the device, comparator or procedures can be excluded when:

- the event has no temporal relatedness with the use of the investigational device, or the procedures related to application of the investigational device;

- the adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation / exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation / exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness / clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

The classification of relatedness will be carried out by both the responsible investigator and the sponsor.

8.3.3 Outcome of AEs

All subjects who have reportable AEs must be monitored to determine the outcome. The clinical course of the AE will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a stable condition. This also holds for ongoing AEs/SAEs of withdrawn subjects.

The outcome of an AE at the time of the last observation will be classified as:

Recovered / resolved:	All signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation,
Ongoing:	Signs and symptoms of an AE are mostly unchanged or worsened at the time of the last interrogation,
Recovered / resolved with sequel:	Actual signs and symptoms of an AE disappeared but there are sequels related to the AE,
Death:	Resulting in death. If there are more than one adverse event only the adverse event leading to death (related) will be characterized as ‘fatal‘,

8.3.4 Countermeasures

The term “**countermeasures**” refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. The following categories will be used to classify the countermeasures taken for adverse events:

No	No countermeasures / treatment performed
Yes	Newly-prescribed medication or other countermeasures, e.g. an operative procedure

8.4 Period of Observation and Documentation

AEs will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the subjects to the medical staff at any time during the study or observed at any of the clinical investigation visit.

The observational period begins with the randomization of the patient to the trial (V2a, following confirmed EMA assessment) and ends with the last visit of the clinical investigation, i.e. Follow-up Visit 2 (FUP2). Thereafter, the investigator does not need to actively monitor subjects for adverse events. However, if the investigator becomes aware of a serious adverse event with a suspected causal relatedness to the investigational device or the medical procedure that occurred after the end of the observational period he or she shall report the SAE without undue delay to the Sponsor, as long as the clinical investigation is still ongoing. These events are also to be documented in the eCRF.

AEs will be documented in the subject file and in the eCRF. If applicable, all medical diagnoses or symptoms occurring prior to the beginning of the period of observation and documentation will be recorded in the eCRF as medical history.

The following general rules apply to the documentation of the AEs and SAEs: The start date of an SAE must not be earlier than that of the corresponding AE. The end date of a SAE is typically the same as that of AE. The end date of the SAE must not be later than the end date of the corresponding AE. Due to limited regulatory standard outcome values, the outcome of AEs and SAEs that are ongoing at the time of death is documented as “ongoing”.

All SAEs and their relevance for the benefit-risk assessment of the clinical investigation will be evaluated continuously during the clinical investigation and for the final report. All SAEs will be documented in the eCRF and in the ‘SAE form’ (see section 8.5.1).

8.5 Investigator’s Vigilance related Reporting Obligations

8.5.1 Reporting of Serious Adverse Events

All SAEs and any device deficiencies must be reported by the investigator to the PV department of KKS Heidelberg **immediately, but not later than 24 hours after the SAE / DD becomes known** using the ‘SAE/DD form’. The initial report must be as complete as possible including details of the SAE / DD and an assessment of the causal relatedness between the event and the investigational device / medical procedure.

The reporting will be performed by faxing or e-mailing (in case of technical issues) a completed ‘SAE/DD form’ to the PV department of KKS Heidelberg,

fax number: +49 (0)6221/56 33725

or e-mail: pharmakovigilanz.KKS@med.uni-heidelberg.de

8.6 Sponsor’s Vigilance related Reporting Obligations

8.6.1 Sponsor’s Assessment (Second Assessment)

All SAEs and DD will be subject to a **second assessment** by Sponsor’s designated persons, who will be independent from the reporting investigator.

The second assessor will fill out a ‘Second Assessment Sheet’ for each SAE and each DD and send it back per fax or e-mail to the PV department of KKS Heidelberg within 48 hours,

fax number: +49 (0)6221/56 33725

or e-mail: pharmakovigilanz.KKS@med.uni-heidelberg.de

The ‘Second Assessment Sheet’ will contain the following information:

- assessment of relatedness between SAE / DD and investigational device and medical procedure,
- assessment of relatedness between SAE / DD and underlying disease (indication),
- assessment of expectedness / anticipatedness of SAE / DD (derived from IB),
- statement if the Risk Benefit Assessment for the clinical investigation did change as a result of SAE / DD.

8.6.2 Expedited Reporting to the National Competent Authority

The sponsor shall report to the competent authorities:

- any SAE that has a causal relatedness with the investigational device or the medical procedure or where such causal relatedness is reasonably possible,
- DD that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate,
- and any new findings in relation to any event referred to in points above.

These SAEs / DDs which indicate an imminent risk of death serious injury, or serious illness and that requires prompt remedial action for other patients, users or other persons or a new finding to it: Immediately, **but not later than 2 calendar days after awareness** by sponsor of a new reportable event or of new information in relation with an already reported event. This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.

Any other SAEs / DDs or a new finding / update to it: Immediately, **but not later than 7 calendar days following the date of awareness** by the sponsor of the new reportable event or of new information in relation with an already reported event.

The reporting format is described on the appropriate homepages of authorities.

8.6.3 Periodic Reporting to the German Competent Authority (BfArM)

The sponsor shall report all SAEs (independent on causal relatedness) and all DD exclusively to the German competent authority (BfArM) in a summarized form quarterly.

The quarterly safety reports consist of the following three parts:

- summary assessment of SAEs and DDs,
- table “complication rates”,
- statement of DSMB.

The templates are provided on the homepage of BfArM.

9. Statistical Procedures

9.1 Definition of Population to be analyzed in the Clinical Investigation

The primary analysis will be performed for the full analysis set (FAS) which comprises all subjects with valid informed consent randomized into the clinical investigation. In this set, every subject is analyzed according to the group randomized into (i.e. intention to treat, ITT).

The per-protocol set will comprise all subjects in the FAS who were treated according to the randomized treatment, as specified in the study protocol. Specifically, subjects have to be eligible according to in- and exclusion criteria. Before the clinical investigation team is unblinded, rules for selecting the per-protocol set will be selected by at least the sponsor and biometrician, who remains blinded at that stage.

The safety set will comprise all subjects who have received the investigational device at least once, and will allocate the subjects to the treatment they actually received, regardless of randomization.

Reasons for missing values (e.g., death of subject, withdrawals, missed assessments), and reasons for premature end of treatment, intercurrent events, reasons for screening failure, and protocol deviations will be recorded.

9.2 Analysis Variables

The primary and secondary endpoints have been specified in detail in sections 2.1 and 2.2.

9.3 General Considerations

The primary analysis will be performed on all subject data at the time the clinical investigation ends. The trial will be conducted within the framework of a sequential design according to Bauer & Köhne[71] with one scheduled interim analysis. All analyses will be carried out using validated statistical software, in particular SAS™.

9.4 Primary Analysis

The primary analysis will be performed by testing the hypothesis whether downregulation training of amygdala activation with neurofeedback reduces the intensity of negative affect assessed before treatment (T0) as compared to after treatment (T1). This hypothesis will be tested at the one-sided overall significance level α of 0.025. The primary endpoint will be analyzed on the full analysis set in stage 1 after 82 participants (n1=41 per group) have reached this endpoint according to the ITT principle. The effect of the intervention with respect to the primary outcome will be tested from the time*condition interaction of a mixed linear model with the mean score of negative affect as dependent variable, time as within-subject factor, condition (amygdala-NF vs control) as between-subject factor, trial site as a random factor, and sex as a cofactor. If the p-value pertaining to the primary outcome in stage 1 (p1) exceeds the critical threshold of $\alpha 0=0.3$ in stage 1 the trial will be stopped for futility, i.e., without rejection of the null hypothesis. If $p1 \leq \alpha 1$ (with $\alpha 1=0.0131$ according to Bauer & Köhne, 1994, p. 1031) the null hypothesis (H0) can be rejected at stage 1 and the trial is terminated. If $\alpha 1 < p1 \leq \alpha 0$ the trial will be continued (stage 2) with an additional sample size of n2=41 patients per group. If the trial enters the second stage, the null hypothesis is rejected at the final analysis if the product of the stage-wise p-values p1p2 falls below the critical boundary of $c\alpha = 0.0038$.

9.5 Secondary Analyses

Secondary endpoints A), B) and C) will be analysed analogously to the primary endpoint, i.e. from the time*condition interaction of a mixed linear model. Amygdala response (secondary endpoint D) and changes in amygdala self-regulation (secondary endpoint E) will be using mass-univariate GLM and region of interest analysis. Neural response will be quantified by fitting the hemodynamic response function to the amygdala BOLD-signal time course. Resulting values will be statistically analysed using analysis of variance. Secondary endpoint F) (health care utilization) will be include analyses of productivity loss and its associated direct and indirect costs between groups from a societal perspective. Statistical analyses will be performed strictly according to the ITT principle. Missing data will be imputed with the last observation carried forward (LOCF) method, a conservative approach strengthening the null-hypotheses of equal costs and effects between intervention and control condition. Cost data are mostly highly right-skewed. Therefore, we will apply generalized linear models (GLM) with gamma distribution and identity link function to estimate differences in health care costs between groups. We will perform a crude model containing randomization group as explanatory variable and an adjusted model containing randomization group (study site), and baseline costs as explanatory variables. As the time horizon of the study is one year, we will not discount costs and outcomes.

For the cost-utility analysis, the outcome is quality-adjusted life years (QALY). QALYs are commonly used aggregate measures of quality and quantity of life and are used to compare the cost-effectiveness of a broad range of health care interventions. We will calculate QALY for V1 and T3 using the multi-attribute utility instrument Assessment of Quality of Life (AQoL)-6D. Unfortunately, there are currently no German value sets with preference weights for the AQoL-6D. Thus, we will use the established value sets and norms from Australia and the cross-walks for the EQ-5D-5L version to elicit QALYs. We will calculate incremental cost-effectiveness ratios (ICER), defined as the ratio between net total costs and net effects To satisfy the condition of statistical uncertainty around the ICER, we will perform non-parametric bootstrapping with 1,000 to 5,000 replications, which will be plotted on cost-effectiveness planes. Likewise, we will calculate bootstrapped 95% confidence intervals (95%CI) around the ICER. Since willingness-to-pay thresholds are usually unknown, we will calculate the incremental (net) monetary benefit (NMB) of the neurofeedback treatment. While the NMB approach is a function of willingness-to-pay thresholds, we will use different thresholds and illustrate them as cost-effectiveness acceptability curves. Consequences of uncertainty are visualized using value of information (VOI) curves.

Safety analyses will be based on AEs, SAEs, and potential deterioration in the ZAN-scale.

9.6 Interim Analyses

One scheduled interim analysis will be carried out on the primary endpoint at the end of stage 1, i.e. after 82 participants (n1=41 per group) have reached the primary endpoint according to the ITT principle. If the p-value pertaining to the primary outcome in stage 1 (p1) exceeds the critical threshold of $\alpha 0=0.3$ in stage 1 the trial will be stopped for futility, i.e., without rejection of the null hypothesis. If $p1 \leq \alpha 1$ (with $\alpha 1=0.0131$ according to Bauer & Köhne, 1994, p. 1031) the null hypothesis (H0) can be rejected at stage 1 and the trial is terminated. If $\alpha 1 < p1 \leq \alpha 0$ the trial will be continued with an additional sample size of n2=41 patients per group (stage 2). The interim analysis will be carried out by unblinded statisticians at the KKS Heidelberg. The results will be communicated to the DSMB. Otherwise, the results will not be disseminated inside or outside the clinical investigation team. The KKS will communicate the decision to STOP or to CONTINUE directly to the sponsor.

For pragmatic reasons (in particular to guarantee feasibility of recruitment within the scheduled time) no further interim analyses are planned.

9.7 Sensitivity Analyses

In addition to the intent-to-treat analyses all analyses will be carried out per protocol. In the event of deviations with regard to significance the assessment of statistical significance will be based on the intent-to-treat analyses.

9.8 Subgroup Analyses

On a descriptive level, analyses of the primary endpoint will be carried out for both men and women. Because the sample is relatively small, we anticipate that the case numbers for the gender diverse subgroup and for other races/ethnicities than Caucasian will be too small to allow for reliable subgroup analyses.

9.9 Sample Size / Power Calculation

Power calculations were carried out to determine the sample size needed for achieving an overall power of $1-\beta \geq 0.90$ for the primary outcome. This power analysis is based on the improvements (i.e. pre-post differences of the mean negative affect) and the pooled standard deviation of these improvements as observed in our pilot data[12]. Mean improvements were 0.37±0.52 in the group with amygdala-NF and 0.03±0.44 in the control group. This translates to a between-group difference in the improvements of 0.34 and a pooled standard deviation of 0.46, which corresponds to a standardized mean difference (SMD) of $\delta_1=0.74$. Despite the lack of established minimally relevant difference, SMDs above 0.50 are likely highly relevant because negative affect assessed in real life conditions is crucial for individuals with BPD and closely relates to dysfunctional and self-harming behaviors. The utility of an add-on intervention that can be combined with traditional treatment is particularly high. As suggested by the International Committee of Harmonization (ICH) E9 guideline, sensitivity analyses were considered when determining the sample sizes n_1 and n_2 (i.e. the n's per group at stages 1 and 2 of the sequential trial). To this end, the following scenarios were investigated. Scenario (S1) based on the point estimates according to the pilot data analyses, i.e. an absolute group difference (AGD) of 0.34 in the improvement of the mean negative affect and a pre-to-post correlation (r=0.82) required for specifying the correlation matrix in the power analysis were complemented by scenarios (Sa-Sc) based on more conservative, albeit realistic values for r and the AGD. For correlation r, the lower end of the 95% confidence interval (i.e. r=0.73) was considered, while sensitivity analyses alternatively considered an AGD of 0.23 (instead of 0.34), which corresponds to a medium SMD of 0.50, which is both plausible according to the pilot data and still presents a clinically meaningful difference. Furthermore, as suggested by Pilz et al.[72], we set a constraint for the minimal conditional power of 0.70 for stage 2 and have split n_1 and n_2 to minimize the expected total sample size. These conditions were required for all scenarios considered under H_1 (i.e. S1, Sa-Sc). Accordingly, $n_1=41$ plus (possibly) $n_2=41$ participants per group are needed to achieve an overall power of 90% in all of these scenarios. Accordingly, the maximum total sample size is 164.

10. Data Management

For more details refer to the corresponding data management plan (DMP). All data management activities will be conducted according to the current SOPs.

10.1 Data Collection and Handling

In this clinical investigation the clinical data management system MARVIN by EvidentIQ Germany is used for data collection by using an electronic CRF (eCRF) with remote data entry (RDE).

All entries in the CRF must be verifiable by source documents. There must be no data that are inconsistent between eCRF and source documents. In addition, source documents must reflect that the subject has been enrolled in this clinical investigation and must include all medical information necessary for appropriate medical care outside of the clinical investigation.

All CIP-required information collected during the clinical investigation must be entered into the eCRF by the investigator or a designated representative. There must not be subject identifying data in the eCRF. Data corrections must always be justified. Data entry should be completed within 7 days after the respective investigational procedure (e.g., an examination). Any pending data entries have to be completed immediately after the final examination. Missing data should be explained. Completeness and correctness of all data entries in the eCRF have to be confirmed by dated electronic signatures of the responsible investigator.

10.2 Data Cleaning and Quality Checks

Data entries will be checked for plausibility and consistency. The checks are defined in the clinical investigation specific data validation plan (DVP). In case of implausibilities, 'warnings' will be generated during data entry (edit checks). The responsible investigator or a designated representative must then either correct the entered data or confirm its correctness by giving an appropriate explanation. The responsible data manager will check all explanations and resolves the warnings if the explanation is appropriate. The responsible monitor may raise electronic questions (monitor queries) to the responsible investigator as well. The investigator or a designated representative should answer queries within 7 days. The responsible monitor will verify the answer and will resolve the query if the answer is appropriate. A similar query flow can be used by the data manager (DM query).

All missing data or inconsistencies have to be clarified by the responsible investigator prior to database lock. If no further corrections in the database are required it will be declared as locked and used for statistical analysis.

11. Archiving and Storage

11.1 Essential Records and Source Data

The sponsor will archive the Trial Master File (TMF), CRFs, and reports. The investigator will archive the Investigator Site File (ISF) as well as source data. Records and source data will be stored for at least 10 years after the end of the clinical investigation.

Any change of data ownership shall be documented. All data shall be made available to relevant authorities on request.

11.2 Collection, Storage and Future Use of Biological Samples and Corresponding Data

Not applicable

12. Regulatory, Ethical and Oversight Considerations

12.1 Compliance Statement

This clinical investigation will be conducted in compliance with the clinical investigation plan and in accordance with the following regulatory requirements:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
- ISO 14155:2020(E),
- Applicable laws and regulations

12.2 Data Protection and Subject Privacy

Data obtained during the clinical investigation will be handled pursuant to the EU General Data Protection Regulation (GDPR) and national regulatory requirements.

To ensure confidentiality of records and personal data, only pseudonymized data will be transferred to the sponsor by using a subject identification number instead of the subject's name. The code is only available at the site and must not be forwarded to the sponsor. In case a subject's records will be forwarded e.g. for SAE processing or adjudication committees, personal data identifying the subject will be redacted by the site prior to forwarding. Access to the subject's files and clinical data is strictly limited. Data specific for the clinical investigation generated at the site need to be available for inspection on request by the local participating investigators, the sponsor's representatives, by the IRB / IEC and the regulatory authorities. A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs / IECs and subjects will be informed as appropriate.

Data transferred directly to the sponsor will be kept on in-house servers of the Central Institute of Mental Health where security measures are in place to prevent unauthorized access from outside the institute. Access to data directories will be limited to trial staff who is required to access the data to fulfill their tasks. An automatic back-up system saves data for 6 weeks to restore data after loss.

Sites will inform sponsor about a potential data privacy breach in connection with the clinical investigation immediately when it is brought to their attention.

12.3 Approval of the Clinical Investigation

This clinical investigation will be initiated only after all required legal documentation has been reviewed and approved by the responsible IRB / IEC and the regulatory authority has been notified according to national and international regulations. The same applies for the implementation of changes introduced through modifications.

12.4 Subject Information and Informed Consent

Before being enrolled in the clinical investigation, the subject must consent to participate after being fully informed by an investigator about the nature, importance, risks and individual consequences of the clinical investigation and his/her right, to terminate participation at any time. The subject should also have the opportunity to consult the investigator, or a physician of the investigating team about the details of the clinical investigation. The investigator shall emphasize that subjects are completely free to participation or to withdraw later on at any time, without suffering consequences for future care and without the need to justify (see section 7.3.1).

Each subject will be informed that his/her source records may be reviewed by the local investigators, the monitor of the clinical investigation, a quality assurance auditor or authority inspector, and the IRB/EC in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

After reading the informed consent document, subject and physician conducting the informed consent discussion must sign and personally date the informed consent form. A copy of the signed informed consent document must be given to the subject; the original will be filed by the investigator. A copy of the information about insurance must be given to the subject.

The information process must be documented in the source records.

Written subject information must be in a language understandable to the subject and must specify who informed the subject.

If the subject is unable to write, oral presentation and explanation of the content of the informed consent form and of the data protection information must take place in the presence of an impartial witness. The witness and the physician conducting the informed consent discussions must also sign and personally date the consent document. The witness must not be in any way dependent on the sponsor of the clinical investigation, the site or any member of the investigating team (e.g. an employee at the site).

The subjects will be informed as soon as possible if new information may influence his/her decision to participate in the clinical investigation. The communication of this information should be documented.

12.5 Committee Structure

12.5.1 Data Safety Monitoring Board (DSMB)

The tasks of the DSMB are to ensure the ethical conduct of the clinical investigation and protecting the rights and welfare of the subjects.

A DSMB made up of independent experts will be set up. It consists or 3 physicians who are not involved in the conduct of the clinical investigation. The task of the DSMB is to oversee the safety of the subjects in the clinical investigation by periodically assessing the safety and efficacy of the investigational therapy, and to monitor the integrity and validity of the data collected and the conduct of the clinical investigation. The DSMB will meet on a regular basis (approx. 1x per year). After reviewing the data on conduct of the clinical investigation (recruitment, CIP adherence / protocol deviations) and safety issues, the DSMB will make recommendations to the Steering Committee (SC) on the further conduct of the clinical investigation (modification, continuation, closure).

For further details see charter.

12.6 Steering Committee (SC)

The steering committee is comprised of the coordinating investigator and his supporting co-investigators, i.e. clinical experts not directly involved in the clinical investigation and the responsible biometrician. The steering committee is responsible for the scientific integrity of the clinical investigation plan, the quality of the clinical investigation conducts as well as for the quality of the final clinical investigation report. The Steering committee will decide on the recommendations made by the DSMB.

12.7 Insurance

The insurance was taken out at HDI Global SE (insurance number: 57 010321 03010/03739).

13. Quality Control and Quality Assurance

13.1 Quality Assurance

A risk-based approach is used for quality management of the clinical investigation. It is initiated by the assessment of critical data and processes for subject protection and reliability of the results as well as identification and assessment of associated risks. The rationale and strategies for risk management during conduct of the clinical investigation including monitoring approaches, vendor management and other processes focusing on areas of greatest risk will be documented. Continuous risk review and assessment may lead to adjustments in conduct, design or monitoring approaches of the clinical investigation. A quality assurance audit/inspection of this clinical investigation may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities (see section 13.4).

13.2 Monitoring

Following a risk-based approach, a combination of monitoring techniques (central and on -site visits) will be used to monitor the clinical investigation.

As the monitoring strategy will consider current aspects of risk-based quality management, frequency of monitoring activities per site will vary depending on recruitment and general performance, e.g. quality of documentation.

The monitor will ensure that the clinical investigation is conducted according to the protocol and applicable regulatory requirements by reviewing essential records, source documents and entries into the CRFs (see section 0). The monitor will document the visits in a report for the sponsor. The site will be provided with a follow-up letter about the findings and the necessary actions to be taken. Details of monitoring will be defined in the monitoring plan.

In case of critical findings during monitoring or an audit, the site might be closed prematurely by the sponsor (see section 7.6).

13.3 Source Documents

In accordance with regulatory requirements, the investigator should maintain adequate source documents and investigational records including all observations / data pertinent to the investigation on each subject. Source data as well as reported data should follow the "ALCOA principles", i.e. should be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). All data reported on the eCRF must be consistent with and verifiable by the source data except for following "direct entries":

- In- and exclusion criteria (yes/no checkboxes), excluding: psychiatric diagnoses listed in eligibility criteria, suicidality, fulfilling any of the MRI contraindications

The current medical history of the subject may not be sufficient to confirm eligibility for the clinical investigation so that the investigator may need to request records on previous medical history and test results. In case of incompliance, any corrective action e.g. repeated instructions must be documented in the subject's medical records, too.

13.3.1 Direct Access to Source Documents

According to ISO 14155:2020(E), the investigator(s) / institution(s) must provide direct access to source data / documents for monitoring related to the clinical investigation, audits and inspections by regulatory authorities. Via the written informed consent each subject has agreed to grant monitors and auditors related to the clinical investigation and inspectors from regulatory authorities direct access to his/her original medical records (see section 12.4).

In case of electronic medical records, the monitor's / auditor's / inspector's access must be restricted to the subjects. If this is not possible the files have to be reviewed in the presence of site staff. The electronic medical record should have an accessible audit trail.

13.4 Audits and Inspections

Representatives of the sponsor may visit the site at any time during or after completion of the clinical investigation to audit compliance with applicable regulatory requirements and sponsor's policies. Similarly, officials of the responsible authorities may carry out inspections either as part of a national GCP compliance program or to review the results of the clinical investigation in support of a regulatory submission. Both audits and inspections will require access to all records of the clinical investigation and source documents (see section 13.3.1). The investigator and site personnel must be available for consultation during site audits / inspections.

The investigator should immediately notify the sponsor if he/she becomes aware of an upcoming inspection.

13.5 Deviations from the CIP (Protocol Deviations)

Definition, categorization and examples of protocol deviations (PD) are described in the PD Log specific for the clinical investigation and the applicable SOPs.

Figure 6 provides a decision tree how to deal with missed or interrupted MR-scans. Whenever the regular schedule is left (i.e., 'no'-arm is true), a PD has to be documented. If the indicated time intervals are exceeded, the subject has to be discontinued (early discontinuation).

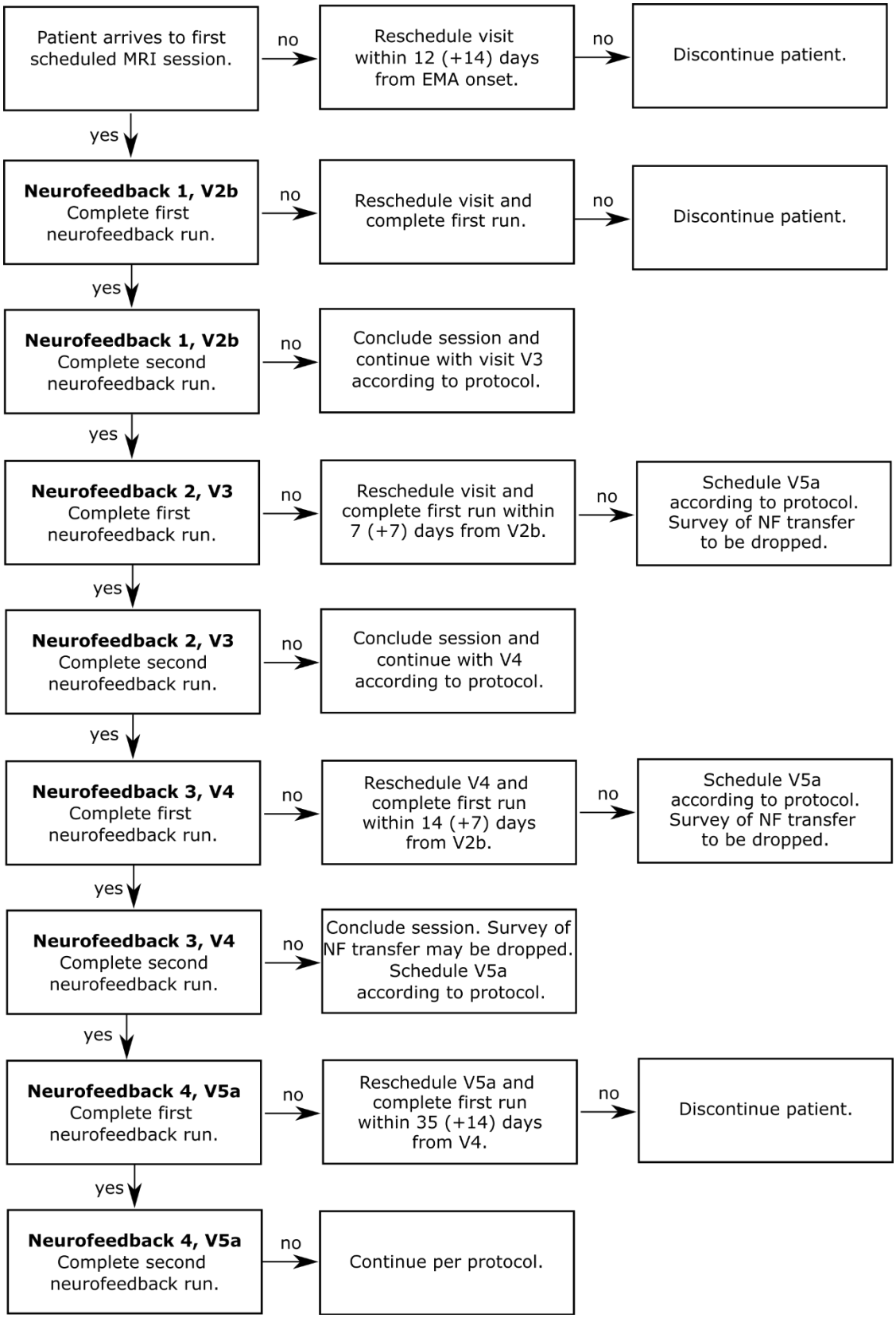


Figure 6. Decision-tree of missed/interrupted MR-visits. If rescheduling of a session is demanded, the investigator needs to make sure that the visits are done in line with the period as defined above. C.f. section 3.4 Figure 5, Patient Time Flow.

14. Administrative Agreements

14.1 Financing of the Clinical Investigation

This research is funded by federal funding agency German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), PA 3107/4-1 and SCHM 1526/26-1, project #502833016. Access to core facilities for Magentic Resonance Imaging (MRI) and technical services, including provision of servers, computers and licenses for analysis software is partly funded by DFG and the sponsor, Central Insitute of Mental Health.

14.2 Financial Disclosure

Investigators will provide the sponsor with accurate financial information in accordance with local regulations allowing the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the conduct of the clinical investigation. The investigator agrees to update this information in case of significant changes.

14.3 Publication Policy / Dissemination of Data of the Clinical Investigation

A summary of the clinical investigation data will be written after all subjects have completed the clinical investigation. The sponsor will submit a summary of the final results of the clinical investigation within 12 months after the regular completion or 3 months after early termination or temporary halt of the clinical investigation. The rights of the investigator and the sponsor regarding publication of the results of the clinical investigation are described in the investigator contract. In general, no results of the clinical investigation should be published prior to finalization of the summary.

The results of this trial will be published as an original article in a peer-reviewed medical journal. As far as preprints are allowed by the target journals, the manuscripts will be submitted to a preprint server such as bioRxiv or medRxiv before submission to the journal.

We expect following types and numbers of publications:

Primary publications:

- 1 paper of the study protocol
- 1 main clinical trial results report presenting clinical efficacy results of primary and secondary outcomes
- 1 paper presenting neuroimaging results
- 1 paper describing the published dataset

Secondary publications:

- Papers from sub-projects and secondary data analysis

Authorship will be defined according to the International Committee of Medical Journal Editors (ICMJ, https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). Below persons qualify for authorship in primary and secondary publications, as long as they will have met all four ICMJ criteria at time of manuscript submission:

- Steering committee members
- Up to one staff of recruiting sites per paper, additionally to SC-members
- Representatives from KKS Heidelberg (Clinical/project manager), biostatistician (NN)
- PRB members

- For papers from sub-projects: authors of the sub-project abstract and additional staff involved in the sub-project.

One representative of each center will be included on each primary and secondary paper. The project leaders will lead primary publications and may assign first and senior author position between them. Authorships of secondary publications and order of authorship of all publications is to be discussed in the steering committee. The project leaders may appoint co-authors listed above as (equally contributing) first/senior authors if they think that this is justified by the quality and/or effort of the contribution.

Other researchers that contribute significantly to secondary publications may be listed as authors as well.

The results of this trial will be published with open access. The study procedures will be described in depth to warrant reproducibility of trial methods and data analysis. The study protocol and other non-proprietary, unprotected documents will be published with open access, as long as publication of materials does not predate the privacy of trial participants and trial staff. Study materials such as scripts to present experimental stimuli, experimental stimuli themselves and questionnaire templates will be published with open access as long as they are not IP/patent protected.

14.4 Registration of the Clinical Investigation

Prior to the beginning of the clinical phase the study was registered at http://www.clinicaltrials.gov.

14.5 Declaration regarding Data Sharing

Individual participant data (IPDs) will be made available, as far as legally possible. IPDs (including metadata such as data dictionaries) that underlie results concerning primary or secondary endpoints reported in a published scientific article will be shared on demand after deidentification. Furthermore, the following documents may be made available: Study Protocol, Statistical Analysis Plan or Informed Consent Form.

Data will be published on the open data repository “heiDATA” with restricted access, where it will be citable with a DOI. HeiDATA is an institutional repository for Open Research Data from Heidelberg University. It is managed by the Competence Centre for Research Data, a joint institution of the University Library and the Computing Centre. Data from participants who do not consent for upload will not be shared on heiDATA. Access to the dataset on heiDATA will be embargoed until the primary publication of the clinical trial results is accepted for publication.

15. References

Regulations and norms referred to in this CIP:

(1) WMA Declaration of Helsinki – Ethical Principles for Medical Research involving Human Subjects; Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.
(2) ISO 14155:2020, Clinical investigation of medical devices for human subjects — Good clinical practice. Third Edition, 2020-07
(3) Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 78/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC; OJ L 117, 5.5.2017, p. 1–175; Current consolidated version: 20/03/2023.
(4) EMEA/CHMP/EWP/5872/03 Corr: Guideline on Data Monitoring Committees. Effective date 2006-01-01.
(5) Medical Device Law Implementation Act of 28 April 2020 (Federal Law Gazette [BGBl.]) Part I p. 960, last amended by Article 3f of the Act of 28 June 2022 (Federal Law Gazette I p. 938).
(6) Civil Code in the version promulgated on 2 January 2002 (Federal Law Gazette [Bundesgesetzblatt] I page 42, 2909; 2003 I page 738), last amended by Article 1 of the Act of 10 August 2021 (Federal Law Gazette I p. 3515).
(7) Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Text with EEA relevance); OJ L 119, 4.5.2016, p. 1–88; Current consolidated version: 04/05/2016.
(8) Betäubungsmittelgesetz (narcotic act) in der Fassung der Bekanntmachung vom 1. März 1994 (BGBl. I S. 358), das zuletzt durch Artikel 2 des Gesetzes vom 26. Juli 2023 (BGBl. 2023 I Nr. 204) geändert worden ist.
(9) Strahlenschutzgesetz (radiation protection act) vom 27. Juni 2017 (BGBl. I S. 1966), das zuletzt durch die Bekanntmachung vom 3. Januar 2022 (BGBl. I S. 15) geändert worden ist.
(10) Clinical Trial Facilitation Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials; Version 1.1; 2020-09-21.

References in text:

1. Tomko, R. L., Trull, T. J., Wood, P. K. & Sher, K. J. Characteristics of Borderline Personality Disorder in a Community Sample: Comorbidity, Treatment Utilization, and General Functioning. *Journal of Personality Disorders* **28**, 734–750 (2014).
2. Black, D. W., Blum, N., Pfohl, B. & Hale, N. Suicidal behavior in borderline personality disorder: prevalence, risk factors, prediction, and prevention. *J. Pers. Disord.* **18**, 226–239 (2004).
3. Storebø, O. J. *et al.* Psychological therapies for people with borderline personality disorder. *Cochrane Database of Systematic Reviews* **5**, (2020).
4. Jerschke, S., Meixner, K., Richter, H. & Bohus, M. Zur Behandlungsgeschichte und Versorgungssituation von Patientinnen mit Borderline- Persönlichkeitsstörung in der Bundesrepublik Deutschland1,2. *Fortschr Neurol Psychiatr* **66**, 545–552 (1998).
5. Wagner, T. *et al.* Societal cost-of-illness in patients with borderline personality disorder one year before, during and after dialectical behavior therapy in routine outpatient care. *Behav Res Ther* **61**, 12–22 (2014).

6. Ebner-Priemer, U. W. *et al.* Unraveling affective dysregulation in borderline personality disorder: A theoretical model and empirical evidence. *Journal of Abnormal Psychology* **124**, 186–198 (2015).
7. Reitz, S. *et al.* Stress regulation and incision in borderline personality disorder--a pilot study modeling cutting behavior. *J. Pers. Disord.* **26**, 605–615 (2012).
8. Schulze, L., Schmahl, C. & Niedtfeld, I. Neural Correlates of Disturbed Emotion Processing in Borderline Personality Disorder: A Multimodal Meta-Analysis. *Biological Psychiatry* **79**, 97–106 (2016).
9. Thibault, R. T., Lifshitz, M. & Raz, A. The self-regulating brain and neurofeedback: Experimental science and clinical promise. *Cortex* **74**, 247–261 (2016).
10. Linhartová, P. *et al.* fMRI neurofeedback in emotion regulation: A literature review. *NeuroImage* **193**, 75–92 (2019).
11. Paret, C. *et al.* Alterations of amygdala-prefrontal connectivity with real-time fMRI neurofeedback in BPD patients. *Social Cognitive and Affective Neuroscience* **11**, 952–960 (2016).
12. Zaehringer, J. *et al.* Improved emotion regulation after neurofeedback: A single-arm trial in patients with borderline personality disorder. *NeuroImage: Clinical* **24**, 102032–102032 (2019).
13. Nicholson, A. A. *et al.* The neurobiology of emotion regulation in posttraumatic stress disorder: Amygdala downregulation via real-time fMRI neurofeedback. *Hum Brain Mapp* **38**, 541–560 (2017).
14. Zotev, V. *et al.* Real-time fMRI neurofeedback training of the amygdala activity with simultaneous EEG in veterans with combat-related PTSD. *Neuroimage Clin* **19**, 106–121 (2018).
15. Young, K. D. *et al.* Randomized Clinical Trial of Real-Time fMRI Amygdala Neurofeedback for Major Depressive Disorder: Effects on Symptoms and Autobiographical Memory Recall. *Am J Psychiatry* **174**, 748–755 (2017).
16. Goldway, N. *et al.* Feasibility and utility of amygdala neurofeedback. *Neurosci Biobehav Rev* **138**, 104694 (2022).
17. Thibault, R. T., Lifshitz, M. & Raz, A. Neurofeedback or neuroplacebo? *Brain* **140**, 862–864 (2017).
18. Ros, T. *et al.* Consensus on the reporting and experimental design of clinical and cognitive-behavioural neurofeedback studies (CRED-nf checklist). *Brain* **143**, 1674–1685 (2020).
19. Sorger, B., Scharnowski, F., Linden, D. E. J., Hampson, M. & Young, K. D. Control freaks: towards optimal selection of control conditions for fMRI neurofeedback studies. *Neuroimage* **186**, 256–265 (2019).
20. Paret, C. *et al.* Down-regulation of amygdala activation with real-time fMRI neurofeedback in a healthy female sample. *Front Behav Neurosci* **8**, 299 (2014).
21. Keynan, J. N. *et al.* Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. *Nat Hum Behav* **3**, 63–73 (2019).
22. Wagner, T. *et al.* The societal cost of treatment-seeking patients with borderline personality disorder in Germany. *Eur Arch Psychiatry Clin Neurosci* **272**, 741–752 (2022).
23. Jacobi, F., Grafiadeli, R., Volkmann, H. & Schneider, I. [Disease burden of borderline personality disorder: cost of illness, somatic comorbidity and mortality]. *Nervenarzt* **92**, 660–669 (2021).
24. Silbersweig, D. *et al.* Failure of Frontolimbic Inhibitory Function in the Context of Negative Emotion in Borderline Personality Disorder. *American Journal of Psychiatry* **164**, 1832–1841 (2007).
25. New, A. S. *et al.* Amygdala–Prefrontal Disconnection in Borderline Personality Disorder. *Neuropsychopharmacol* **32**, 1629–1640 (2007).

26. Minzenberg, M. J., Fan, J., New, A. S., Tang, C. Y. & Siever, L. J. Frontolimbic structural changes in borderline personality disorder. *Journal of Psychiatric Research* **42**, 727–733 (2008).
27. Grottaroli, M. *et al.* Microstructural white matter alterations in borderline personality disorder: A minireview. *Journal of Affective Disorders* **264**, 249–255 (2020).
28. Sagarwala, R. & Nasrallah, H. A. White matter pathology in patients with borderline personality disorder: A review of controlled DTI studies. *Annals of Clinical Psychiatry* **32**, (2020).
29. Rüsch, N. *et al.* Reduced interhemispheric structural connectivity between anterior cingulate cortices in borderline personality disorder. *Psychiatry Research: Neuroimaging* **181**, 151–154 (2010).
30. Rüsch, N. *et al.* Inferior frontal white matter microstructure and patterns of psychopathology in women with borderline personality disorder and comorbid attention-deficit hyperactivity disorder. *NeuroImage* **35**, 738–747 (2007).
31. Whalley, H. C. *et al.* White matter integrity and its association with affective and interpersonal symptoms in borderline personality disorder. *NeuroImage: Clinical* **7**, 476–481 (2015).
32. Vandekerckhove, M., Berens, A., Wang, Y. L., Quirin, M. & De Mey, J. Alterations in the fronto-limbic network and corpus callosum in borderline-personality disorder. *Brain and Cognition* **138**, 103596 (2020).
33. Maier-Hein, K. H. *et al.* Disorder-Specific White Matter Alterations in Adolescent Borderline Personality Disorder. *Biological Psychiatry* **75**, 81–88 (2014).
34. Carrasco, J. L. *et al.* Microstructural white matter damage at orbitofrontal areas in borderline personality disorder. *Journal of Affective Disorders* **139**, 149–153 (2012).
35. Gan, J. *et al.* Abnormal white matter structural connectivity in treatment-naïve young adults with borderline personality disorder. *Acta Psychiatr Scand* **134**, 494–503 (2016).
36. Nenadić, I., Katzmann, I., Besteher, B., Langbein, K. & Güllmar, D. Diffusion tensor imaging in borderline personality disorder showing prefrontal white matter alterations. *Comprehensive Psychiatry* **101**, 152172 (2020).
37. Ninomiya, T. *et al.* Reduced white matter integrity in borderline personality disorder: A diffusion tensor imaging study. *Journal of Affective Disorders* **225**, 723–732 (2018).
38. Baczkowski, B. M. *et al.* Deficient amygdala–prefrontal intrinsic connectivity after effortful emotion regulation in borderline personality disorder. *Eur Arch Psychiatry Clin Neurosci* **267**, 551–565 (2017).
39. Silvers, J. A. *et al.* Affective lability and difficulties with regulation are differentially associated with amygdala and prefrontal response in women with Borderline Personality Disorder. *Psychiatry Research: Neuroimaging* **254**, 74–82 (2016).
40. Kamphausen, S. *et al.* Medial prefrontal dysfunction and prolonged amygdala response during instructed fear processing in borderline personality disorder. *The World Journal of Biological Psychiatry* **14**, 307–318 (2013).
41. Brodt, S. *et al.* Fast track to the neocortex: A memory engram in the posterior parietal cortex. *Science* **362**, 1045–1048 (2018).
42. Paret, C. *et al.* fMRI neurofeedback of amygdala response to aversive stimuli enhances prefrontal–limbic brain connectivity. *NeuroImage* **125**, 182–188 (2016).
43. Sampaio-Baptista, C. *et al.* fMRI neurofeedback in the motor system elicits bidirectional changes in activity and in white matter structure in the adult human brain. *Cell Reports* **37**, 109890 (2021).
44. Tavor, I., Botvinik-Nezer, R., Bernstein-Eliav, M., Tsarfaty, G. & Assaf, Y. Short-term plasticity following motor sequence learning revealed by diffusion magnetic resonance imaging. *Hum Brain Mapp* **41**, 442–452 (2020).
45. Sagi, Y. *et al.* Learning in the Fast Lane: New Insights into Neuroplasticity. *Neuron* **73**, 1195–1203 (2012).

46. Kleindienst, N. *et al.* Dissociation predicts poor response to Dialectial Behavioral Therapy in female patients with Borderline Personality Disorder. *J Pers Disord* **25**, 432–447 (2011).
47. Kleindienst, N. *et al.* State dissociation moderates response to dialectical behavior therapy for posttraumatic stress disorder in women with and without borderline personality disorder. *European Journal of Psychotraumatology* **7**, 30375 (2016).
48. Spitzer, C., Barnow, S., Freyberger, H. J. & Grabe, H. J. Dissociation predicts symptom-related treatment outcome in short-term inpatient psychotherapy. *Aust N Z J Psychiatry* **41**, 682–687 (2007).
49. Kleindienst, Nikolaus. Dissociation jeopardizes successful exposure-based treatment of posttraumatic stress-disorder. (2016).
50. Ebner-Priemer, U. W. *et al.* Emotional learning during dissociative states in borderline personality disorder. *J Psychiatry Neurosci* **34**, 214–222 (2009).
51. Woodbridge, J., Reis, S., Townsend, M. L., Hobby, L. & Grenyer, B. F. S. Searching in the dark: Shining a light on some predictors of non-response to psychotherapy for borderline personality disorder. *PLoS ONE* **16**, e0255055 (2021).
52. Landes, S. J., Chalker, S. A. & Comtois, K. A. Predicting dropout in outpatient dialectical behavior therapy with patients with borderline personality disorder receiving psychiatric disability. *Borderline Personal Disord Emot Dysregul* **3**, 9 (2016).
53. DGPPN e. V. (Hrsg.) für die Leitliniengruppe. S3-Leitlinie Borderline-Persönlichkeitsstörung. Version 1.0 vom 14.11.2022 verfügbar unter: https://www.awmf.org/leitlinien.
54. Schmahl, C., Niedtfeld, I. & Herpertz, S. C. [Borderline personality : Alterations to brain structure and function through psychotherapy]. *Nervenarzt* **89**, 1232–1236 (2018).
55. Babaskina, L., Afanasyeva, N., Semyonkina, M., Myasnyankina, O. & Sushko, N. Effectiveness of Neurofeedback Training for Patients with Personality Disorders: A Systematic Review. *Iran J Psychiatry* **18**, 352–361 (2023).
56. Hall, K. & Moran, P. Borderline personality disorder: an update for neurologists. *Pract Neurol* **19**, 483–491 (2019).
57. Donantueno, C., Yger, P., Cabestaing, F. & Jardri, R. fMRI-based neurofeedback strategies and the way forward to treating phasic psychiatric symptoms. *Front Neurosci* **17**, 1275229 (2023).
58. Zanarini, M. C. *et al.* Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD): a continuous measure of DSM-IV borderline psychopathology. *J. Pers. Disord.* **17**, 233–242 (2003).
59. Grupp, H., König, H.-H., Riedel-Heller, S. & Konnopka, A. FIMPsy – Fragebogen zur Inanspruchnahme medizinischer und nicht medizinischer Versorgungsleistungen bei psychischen Erkrankungen: Entwicklung und Verwendung. *Psychiat Prax* **45**, 87–94 (2018).
60. Reilly, M. C., Zbrozek, A. S. & Dukes, E. M. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* **4**, 353–365 (1993).
61. Richardson, J., Atherton Day, N., Peacock, S. & Iezzi, A. Measurement of the Quality of Life for Economic Evaluation and the Assessment of Quality of Life (AQoL) Mark 2 Instrument. *Aust Econ Rev* **37**, 62–88 (2004).
62. Schulz, K. F., Altman, D. G., Moher, D., & CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med* **8**, 18 (2010).
63. Hautzinger, M., Keller, F. & Kühner, C. *BDI-II Beck Depressions-Inventar Revision*. (Hogrefe Verlag, 2009).
64. Wolf, M. *et al.* [Short version of the borderline symptom list (BSL-23): development and psychometric evaluation]. *Psychother Psychosom Med Psychol* **59**, 321–324 (2009).
65. Gratz, K. L. & Roemer, L. Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale. *Journal of Psychopathology & Behavioral Assessment* **26**, 41–54 (2004).
66. Carlson, E. B. *et al.* Validity of the Dissociative Experiences Scale in screening for multiple personality disorder: a multicenter study. *Am J Psychiatry* **150**, 1030–1036 (1993).

67. Stiglmayr, C. E., Braakmann, D., Haaf, B., Stieglitz, R.-D. & Bohus, M. [Development and characteristics of Dissociation-Tension-Scale acute (DSS-Akute)]. *Psychother Psychosom Med Psychol* **53**, 287–294 (2003).
68. Lincoln, T. PCL. Paranoia Checklist - deutsche Fassung [Verfahrensdokumentation und Fragebogen]. (2017).
69. Steffankowski, A. *et al.* Psychometrische Überprüfung einer deutschsprachigen Version des Relationship Scales Questionaire (RSQ). in *Störungsspezifische Therapieansätze - Konzepte und Ergebnisse. Bassler, M. (Hrsg.)* 320–342 (Psychosozial, Gießen, 2001).
70. Raven, J. C. *Raven´s Progressive Matrices Und Vocabulary Scales: Standard Progressive Matrices*. (Hogrefe, Göttingen, Germany, 2009).
71. Bauer, P. & Köhne, K. Evaluation of experiments with adaptive interim analyses. *Biometrics* **50**, 1029–1041 (1994).
72. Pilz, M., Kunzmann, K., Herrmann, C., Rauch, G. & Kieser, M. Optimal planning of adaptive two-stage designs. *Stat Med* **40**, 3196–3213 (2021).

Appendix 1: List of Technical and Functional Features of the Investigational Device

Description below is based on document BPD-CE-REC-Clinical-Evaluation-Plan-SW-TBV-Med-BPD_20240709 received from BrainInnovation.

TBV MED BPD contains the following data processing and visualization functionality:

- Reading of EPI slices into working memory
- 3D motion correction (report of within-run motion)
- 3D spatial smoothing
- Incremental statistical analysis (RLS GLM)
- Drift removal via design matrix (confound predictors)
- Incremental event-related averaging
- Thresholding, clustering and color-coding of resulting statistical maps
- Creation of anatomical projects within TBV MED BPD (including brain extraction, B1 inhomogeneity correction)
- Advanced visualizations in volume (Native, MNI) space
- Connectivity Feedback, i.e. Windowed Pearson and Partial Correlation
  Export to Files (RTP, ERT, BTC, Neurofeedback values) enabling link to external stimulation software and different feedback types (visual, auditory, tactile) and feedback displays
- Visualization of export and computation time for each volume:
  - Shorter than one TR
  - TBV MED BPD shows a warning/error message when time limit is exceeded during the scanning

Restrictions:

- No support of plugins
- No Surface Space available
- Operating system: Windows 10 (64-bit)

TBV MED BPD can be used with the following MRI scanner:

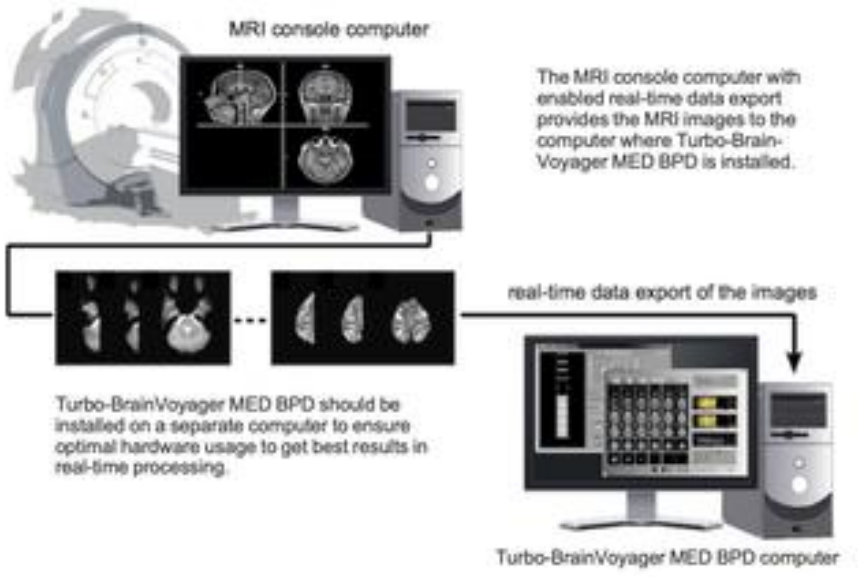
- Manufacturer: Siemens
- Model: Prisma (Fit)
- Static magnetic field (B0) strength: 3T
- Restrictions to specific software versions of the scanners (minimum VB17): syngo MR E11
- Image file type: restriction to DICOM

Further specifications:

- Structural sequences
  - T1-weighted (MPRAGE / ADNI) for Anatomy Creation
  - Standard resolution: 1mm3 isotropic
- Functional sequences
  - T2*-weighted
- Data from other sequences, such as a localizer and gradient field mapping, can be acquired before starting NF
- For each approved sequence an example dataset has to be provided
- Given a baseline level *bl*, the feedback value *fb* for the current time point (without/prior to averaging) with value *val* is calculated within a neurofeedback trial simply as follows: fb = (val - bl) / bl * 100. This results in a percent signal change (PSC) value that can be used for neurofeedback, e.g. by filling a thermometer display (see below). Note that if the detrending time course (default) option is used, the input values to the neurofeedback calculation are already (GLM detrended) PSC values. In this case, the equation simplifies to: fb = (val - bl).

Installation

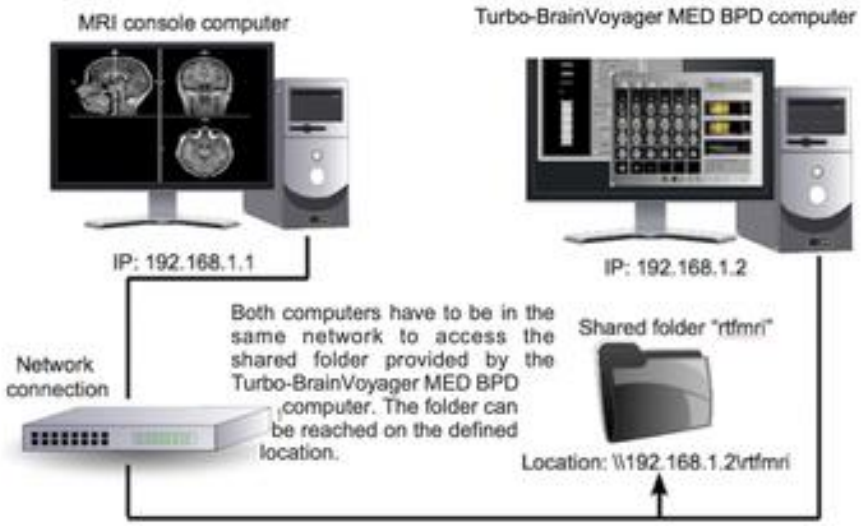
The setup of TBV MED BPD in the scanner environment consist mainly of two parts: Enabling the real-time data export of the MRI images and the access to this exported data from another computer running TBV MED BPD.



As shown in Figure 2 above, the MRI images are exported in real-time from the MRI console computer to the TBV MED BPD computer. On the TBV MED BPD computer all images will be read and processed from a specified directory called "watch folder" in TBV MED BPD. It is essential that the MRI console computer exports the images to a shared folder provided by the TBV MED BPD computer. Otherwise the real-time export could be decelerated because of multiple network queries that are necessary to read the MRI images. To ensure a fast and reliable

data transmission and processing the user needs to verify that all computers that are not necessary for the fMRI experiment are excluded from the network or turned off. The more computers are in the network the more likely it becomes that a prolonged (i.e. non real-time) transmission time occurs. It is recommended to set the power plan of the operating system (if available) to maximum performance. This ensures that the whole processing of the MRI images including online reconstruction from *k*-space to image space can be realized as fast as possible.

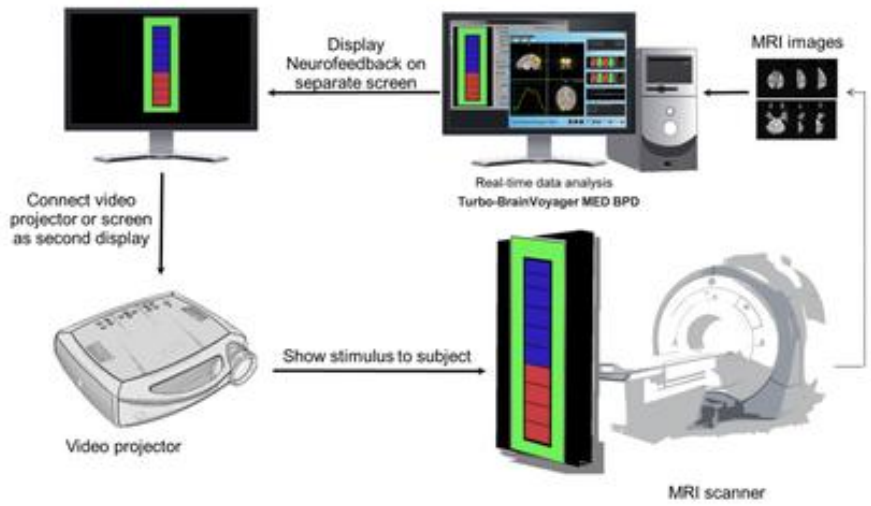
A minimum to use a computer for TBV MED BPD that possesses a minimum of 8GB of working memory, powerful processor and good OpenGL capable graphics card is recommended. While TBV MED BPD is a highly efficient program, the usage of latest PC hardware should be favored.



An example network structure is shown in Figure 3. The shared folder is provided by the TBV MED BPD computer and can be reached via its host name or IP. After setting up the connection one can define the settings and parameters in the TBV MED BPD Settings dialog.

Setup for Neurofeedback

TBV MED BPD supports the advanced real-time application of neurofeedback. The feedback will be conveyed to the subject during the experiment. A conceptional overview of a typical neurofeedback setup is shown in the picture below.



In most cases a video projector is used to convey a visual feedback to the subject in the scanner (but auditory or tactile information has also been used with TBV MED BPD). While TBV MED BPD supports custom feedback visualizations by exporting ROI data in real-time to disk, one can in many cases simply use the in-built neurofeedback dialog to produce feedback visualizations. The neurofeedback dialog allows to select the data from one or more ROIs as the source of feedback information for a subject during an ongoing measurement.

Update procedure

Updated TBV MED BPD versions can be downloaded from the Brain Innovation servers and installed by the IT or MRI technician in admin mode.

Remote maintenance

User support will be provided via an online helpdesk and by telephone.

Specification of Control Parameters for Real-Time Analysis

In order to run successfully, Turbo-BrainVoyager MED BPD (TBV MED BPD) needs to know several pieces of information about the local environment. The most important information is the location of the data, i.e. the location where the incoming scanned slices are to be expected. In order to find the data, the program looks in the MasterTBV file. The user can edit the master file directly or more conveniently using the MasterTBV File dialog.

The MasterTBV file provides the highest level of control by pointing to a "TBV Watch Directory". This directory may contain TBV MED BPD settings files, which provide the next level of control, containing information about a particular run in a particular session. A TBV MED BPD settings file is stored in JSON format with extension ".tbvj" and contains information about the expected data coming from the scanner as well as settings controlling real-time analysis and visualization. There are also "MTBV settings files", which specify analyses across multiple runs within a session. The user can edit a TBV MED BPD file directly or more conveniently using the TBV MED BPD Settings File dialog.

Appendix 2: Contraceptive and Barrier Guidance

Definition of women of childbearing potential (WOCBP):

For the purpose of this clinical investigation, a woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Birth control methods which may be considered as highly effective:

For the purpose of this clinical investigation, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable[1]
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomized partner[1,2]
- sexual abstinence[3]

Acceptable birth control methods which may NOT be considered as highly effective:

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[4]
- cap, diaphragm or sponge with spermicide[4]

[1] Contraception methods that are considered to have low user dependency.

[2] Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the subject and that the vasectomized partner has received medical assessment of the surgical success.

[3] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the investigational treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical investigation and the preferred and usual lifestyle of the subject

[4] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

Pregnancy information:

All menarchal females should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the clinical investigation. It is important to be sensitive in introducing this issue, as understanding and comprehension of sexual activity, pregnancy and contraception is influenced by age, socio (educational) economic and familial background. Therefore consultation, monitoring and questioning regarding potential sexual contacts with the subject are to be performed at every visit by investigators familiar with the subject. The consultations should consider the socio-economic, cultural factors and religious beliefs of the subject. The investigator should discuss possible birth control methods and the management of the pregnancy test results with the subject.

Appendix 2: Informed Consent and Recruitment Process

No special arrangements or processes necessary, ref. chapter 12.4.

Appendix 3: Provisions regarding Exceptional Circumstances

Not applicable