SleepExpert: a behavioral treatment program for insomnia in patients with psychiatric disorders

Ethic Commission of the Canton of Bern Number: 2020-01897

Document Date: 26.05.2021

Clinical Study Protocol

SleepExpert: a behavioral treatment program for insomnia in patients with psychiatric disorders

Study Type:	Clinical trial with Medical Device
Study Categorisation:	Risk category A according to HRA
Study Registration:	Intended Registry: Swiss National Clinical Trial Portal and clinicaltrials.gov
Study Identifier:	SleepExpert Pilot
Sponsor-Investigator:	Prof. Dr. Christoph Nissen UPD Bern Chefarzt, Stv. Ärztlicher Direktor Bolligenstrasse 111 CH-3000 Bern christoph.nissen@upd.ch
Investigational Product:	Internet-based self-help program ("SleepExpert" Web Application), European CE marking for medical devices: approved (released on 01.10.2018) and valid for five years
Protocol Version and Date:	Version 4 – 26.05.2021

PROTOCOL SIGNATURE FORM

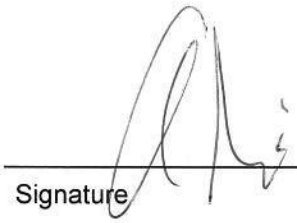
Study number	SleepExpert Pilot
Study Title	SleepExpert: a behavioural treatment program for insomnia in patients with psychiatric disorders

The Sponsor-Investigator has approved the protocol version 4 dated 26.05.2021, and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ISO 14155 norm and the local legally applicable requirements.

Sponsor-Investigator:
Name: Prof. Dr. Christoph Nissen

Bern, 09.06.2021

Place/Date



Signature

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Local Principal Investigator at study site*:

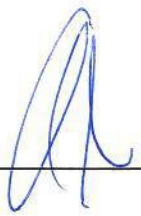
I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ISO 14155 norm and the local legally applicable requirements.

Site	Universitäre Psychiatrische Dienste Bern, UPD
Principal investigator	Prof. Dr. Christoph Nissen

Bern, 09.06.2021

Place/Date

Signature



STUDY SYNOPSIS

Sponsor-Investigator:	Prof. Dr. Christoph Nissen
Study Title:	SleepExpert: a behavioural treatment program for insomnia in patients with psychiatric disorders
Short Title / Study ID:	SleepExpert Pilot
Protocol Version and Date:	Version 4 – 26/05/2021
Trial registration:	intended: clinicaltrials.gov & Swiss National Clinical Trial Portal
Study category and Rationale:	Risk category A according to HRA. The Medical Device has a CE mark.(see below for further explanations)
Clinical Phase:	Medical Device Study Risk category A, Phase of development I
Background and Rationale:	Mental disorders are highly prevalent, undertreated, and associated with substantial disability and reduced quality of life (Demyttenaere et al., 2004). One third of patients with mental disorders comorbidly suffer from insomnia disorder according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013, S. 5). Following current European and American practice guidelines for adult patients, cognitive behavioral therapy for insomnia (CBT-I) is the first line treatment (Qaseem et al., 2016; Riemann et al., 2017). Various adaptations of CBT-I for different target groups and settings have been developed. One of them is Brief Behavioral Treatment for Insomnia (BBT-I), consisting of four sessions centering of bedtime restriction (Troxel et al., 2012). This demonstrates that brief versions of CBT-I can be similarly effective as the complete program. The intervention "SleepExpert" is based on BBT-I as a brief version of CBT-I, the first-line treatment for insomnia according to current guidelines. There has been a feasibility study, however this study was uncontrolled. In the proposed project, we aim to compare treatment as usual (TAU) plus SleepExpert to TAU plus sleep monitoring in a pilot randomized controlled trial. The objective is to target sleep to improve mental health and to investigate the efficacy of SleepExpert for the improvement of sleep and mental health.
Objective(s):	The primary objective is to assess whether there is a significantly greater reduction in self-assessed insomnia severity (as measured by the Insomnia Severity Index, ISI) across six months (interaction effect Group and Timepoint) in patients in the Tau plus SleepExpert group, compared to patients in the TAU plus sleep monitoring group. The secondary objective is to assess whether there is a significantly greater improvement in general mental health (Brief Symptom Inventory) across six months (interaction effect Group and Timepoint) in patients in the TAU plus SleepExpert group, compared to patients in the TAU plus sleep monitoring group.
Outcome(s):	The primary outcome will be insomnia severity measured with the Insomnia Severity Index (ISI) (Bastien et al., 2001). The ISI will be administered before the intervention (T0) and one, two, 12, and 26 weeks after the start of the intervention
Study design:	This project is a prospective randomized controlled clinical pilot trial with a cluster-crossover design involving two groups: An interventional group (TAU, plus SleepExpert) and a control group (TAU plus sleep monitoring).

Inclusion / Exclusion criteria:	Inclusion criteria: - Age 18 years or older - Documented diagnosis of acute insomnia, i.e. insomnia criteria according to ICD-10 for at least 2 weeks (Ellis, Gehrman, Espie, Riemann, & Perlis, 2012) - Insomnia Severity Index (ISI) total score > 7, equivalent to relevant insomnia (Gagnon, Bélanger, Ivers, & Morin, 2013) - Inpatient in one of the two participating psychiatric wards in the UPD Bern - Ability to understand the aims and procedures of the study - Willingness to participate and ability to provide written informed consent Exclusion criteria: - Incabability of judgement - Inability to participate in a low-threshold behavioral treatment program, e.g. due to severe cognitive impairment or high symptom severity precluding participation (e.g., severe catatonic symptoms, massive hallucinations, acute endangerment to self or others, involuntary commitment). Note that the named symptoms will lead to exclusion only if they lead to inability to give informed consent or an inability to participate in the program. Excluded patients will be re-assessed regularly and included if symptoms improve and participation is possible at a later point in time.
Measurements and procedures:	Patients will first be screened and assessed for eligibility. Eligible patients who signed the informed consent form will undergo a first assessment (T0) and then participate in the intervention. Additional assessments will be made one, two, 12, and 26 weeks after the start of the intervention.
Study Product / Intervention:	TAU plus "SleepExpert" behavioral treatment program for insomnia (face-to-face combined with a web application)
Control Intervention (if applicable):	Treatment as Usual (TAU) plus sleep monitoring
Number of Participants with Rationale:	Assuming an alpha error level of 0.05 (two-sided) and a power of 0.8, a total sample size of n=60 will be sufficient to detect a medium effect (Cohen's d=0.65).This is a pilot trial with the primary aim of collecting qualitative experience and preliminary efficacy data.
Study Duration:	Two years
Study Schedule:	Month Year of First-Participant-In (planned): August 2021 Month Year of Last-Participant-Out (planned): January 2024

Investigator(s):	Prof. Dr. Christoph Nissen (Sponsor-Investogator) Institution: UPD Bern Position: Chefarzt, Stv. Ärztlicher Direktor Address: Bolligenstrasse 111, 3000 Bern Mail: christoph.nissen@upd.ch Dr. phil. Elisabeth Hertenstein (Sub-Investigator) Institution: UPD Bern Position: Psychologist Address: Bolligenstrasse 111, 3000 Bern Mail: elisabeth.hertenstein@upd.ch
Study Centre(s):	Single-centre Universitäre Psychiatrische Dienste Bern
Statistical Considerations:	Our primary analysis will be a linear mixed model with the following co-variables: fixed intervention effect (TAU plus SleepExpert versus TAU plus sleep monitoring), fixed baseline ISI score effect, random patient effect (multiple ISI scores during follow-up), random cluster effect. Depending on model fit, we may need to simplify the model.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ISO EN 14155 norm as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
ASR	Annual Safety Report
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use
ISO	International Organisation for Standardisation
ITT	Intention to treat
MD	Medical Device
MedDO	Medical Device Ordinance *(in German: MepV, in French: ODim)*
PI	Principal Investigator
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Study Plan

Table 1. Patient schedule

	screening	T0	T1 (week1)	T2 (week2)	T3 (week12)	T4 (week 26)	debriefing***
Time point (days)	at or after admission to ward until T 0	0	7±2	14±2	84±7	182±7	
Eligibility screen	x						
Informed consent	x (signature 24 hours or more after first information)						
Medical History	x						
Insomnia Severity Index	x	x	x	x	x	x	
Brief Symptom Inventory		x		x		x	
Beck Depression Inventory		x		x		x	
Visual analogue scales*		x	x	x	x	x	
Daily sleep Diary**			x	x	x	x	
Medication status	x	x	x	x	x	x	
TAU plus SleepExpert							
TAU plus sleep monitoring***							
Adverse Events		x	x	x	x	x	

* self-constructed visual analogue scales will be used to measure subjective sleep quality, mood, concentration, and tiredness

** the sleep diary will be used continuously throughout the study period (baseline until T4)

*** debriefing: All patients, i.e. the TAU plus sleep monitoring and TAU plus SleepExpert group will have an individual appointment with a sleep expert (physician or psychologist) after completion of the study, i.e. after 6 months, in which the gathered information (sleep diaries and actigraphy data) will be discussed and individualized further diagnostics and treatments, if needed, will be initiated.

1.2 Sponsor, Sponsor-Investigator

Name: Prof. Dr. Christoph Nissen
Institution: UPD Bern
Position: Chefarzt, Stv. Ärztlicher Direktor
Address: Bolligenstrasse 111, 3000 Bern
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1.3 Principal Investigator

Name: Prof. Dr. Christoph Nissen
Institution: UPD Bern
Position: Chefarzt, Stv. Ärztlicher Direktor
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1.4 Statistician ("Biostatistician")

Mattia Branca, PhD
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1.5 Laboratory

Not applicable

1.6 Monitoring institution

Clinical Trial Unit – CTU, Mittelstrasse 43 | CH-3012 Bern

1.7 Data Safety Monitoring Committee

A DSMC is not needed because the study doesn't come along with great risks.

1.8 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

Intended registry: clinicaltrials.gov & Swiss National Clinical Trial Portal

2.2 Categorisation of study

The psychotherapeutic protocol used in this study (Cognitive Behavioral Therapy for Insomnia) is non-invasive. Comparable therapeutic protocols have been thoroughly investigated in patients with insomnia without adverse events. Sleep restriction as used in this therapy may be associated with temporary daytime sleepiness. No long-lasting or serious adverse effects of these psychotherapies are known. In addition, multiple previous studies have shown that Cognitive Behavioral Therapy for insomnia is also feasible as an online application. The new aspect of this study is a change of the target group: instead of patients with insomnia only, the intervention will be applied in patients with insomnia and mental disorders (both disorder groups are category F in the ICD-10). We have no reason to assume that the psychotherapeutic protocol is associated with unexpected risks in this target group. The internet-based self-help program platform developed by Prof. Thomas Berger, University of Bern, that will be used in this study has received a CE mark in 2018 that is valid for 5 years. All examinations and interventions in this study are in accordance with current safety standards and the risk associated with a participation in this study is regarded as minimal. Thus, this study belongs to category A.

2.3 Competent Ethics Committee (CEC)

The Sponsor-Investigator ensures that approval from an appropriately constituted Competent Ethics Committee (CEC; Kantonale Ethikkommission (KEK) Bern) is sought for the clinical study.

The Sponsor-Investigator further ensures that no changes will be made to the protocol or in research activities without his prior approval and, in case of significant changes according to ClinO Art.29, CEC approval. Exempt from this requirement are measures, which have to be taken immediately in order to protect the study participants. Any safety or protective measures that have to be taken during the conduct of the clinical trial due to unanticipated risks to humans will be reported to the CEC within 7 days. Amendments will be reported according to section 2.10 and intermediary reports (annual safety reports) will be forwarded to the CECs yearly.

Premature study end or interruption of the study will be reported within 15 days. The regular end of the study will be reported to the CECs within 90 days and the final study report shall be submitted within one year after study end.

2.4 Competent Authorities (CA)

Approval from Swissmedics is not necessary because this is a category A study.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the European Regulation on medical devices 2017/745 and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

The investigators of this study have no intellectual, financial, proprietary or other conflict of interest related to the proposed study.

2.7 Patient Information and Informed Consent

The investigators will explain the following to each potential participant:

- The nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail
- That participation in the study is voluntary and that he/she may withdraw from the study at any time
- That withdrawal of consent only will terminate study related treatment and investigations, but not affect subsequent medical assistance and treatment
- That the participant's medical records may be examined by authorised individuals other than their treating physician

During the informed consent procedure, the candidate will have the opportunity to ask questions concerning the study and he or she will receive a patient information sheet and a consent form describing the study. The patient information sheet will provide all the information necessary for the candidate to make an informed decision about study participation.

The candidate should read and consider the patient information and be given at least 24 hours to consider study participation.

When willing to take part in the study, the candidate will sign and date the informed consent form. The investigator having discussed the study with the participant must also sign and date the form. The signed form will be retained as part of the study records, and a copy will be given to the participant.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study specific procedure.

Asymmetric information of patients on wards randomized to the control- vs. intervention-arm will be performed because patients in the control-arm have no opportunity to receive the treatment and thus information about SleepExpert may be demotivating. All patients, including those in the control arm, will receive treatment as usual, i.e. psychiatric treatment following the current standard clinical practice according to clinical guidelines. Whether or not SleepExpert has an additional benefit is the research question of the proposed trial, but is not yet clear. Thus, it is ethical to not give SleepExpert to the patients in the control arm and to not inform them about the intervention.

2.8 Participant privacy and confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured using unique subject identification code numbers to correspond to treatment data in any computer files.

The investigators affirm and uphold the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

For study related monitoring, audits, EC review and CA inspections, the investigator will provide direct access to source data and source documents including parts of patients' medical record relevant to the study (e.g. medical history) to authorised representatives of the Sponsor-Investigator, the CA, or a CEC.

2.9 Early termination of the study

Based on general expertise regarding the significance of the accumulating data, or other important reasons such as accumulating external evidence, quality concerns etc. the Sponsor-Investigator may terminate the study at any time. Termination will be in accordance with relevant regulatory, scientific, and ethical principles.

Premature study end or interruption of the study will be reported to the CEC to chapter 2.3.

2.10 Protocol amendments

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety, and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the Sponsor-Investigator and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Mental disorders are highly prevalent, undertreated, and associated with substantial disability and reduced quality of life (Demyttenaere et al., 2004). The 12 months prevalence of any mental disorder is 12% in Europe, whereby anxiety disorders and mood disorders are the most prevalent (Demyttenaere et al., 2004). One third of patients with mental disorders comorbidly suffer from insomnia disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria (American Psychiatric Association, 2013, S. 5), i.e. persistent sleep disturbances and associated daytime impairments for at least three months (Seow et al., 2018). The prevalence of acute insomnia symptoms (< 3 months) is up to 68% in patients with mental disorders (Seow et al., 2018). Having comorbid acute or chronic insomnia is associated with significantly higher impairment compared to having a mental disorder without insomnia (Seow et al., 2018). As opposed to early lines of research aiming at the identification of disorder-specific patterns of sleep disturbance (e.g., early morning awakening as a marker of depression), recent work demonstrates that disruptions of sleep continuity (insomnia) represent a highly prevalent and trans-diagnostic problem in a wide range of mental disorders including anxiety disorders, affective disorders, schizophrenia, substance use disorders, eating disorders, borderline personality disorder and autism spectrum disorders (Baglioni et al., 2016).

Following current European and American practice guidelines for adult patients, cognitive behavioral therapy for insomnia (CBT-I) is the first line treatment (Qaseem et al., 2016; Riemann et al., 2017).

CBT-I is a treatment package including psychoeducation, restriction of time in bed, relaxation, and cognitive restructuring. Implementation of bedtime restriction is the best predictor for therapeutic success of CBT-I (Harvey, Inglis, & Espie, 2002), and bedtime restriction is also efficacious as a stand-alone treatment for insomnia (Miller et al., 2014). The major mechanism of action of bedtime restriction is an increase of homeostatic sleep pressure, thereby shortening sleep-onset latency and increasing sleep depth.

Various adaptations of CBT-I for different target groups and settings have been developed. One of them is Brief Behavioral Treatment for Insomnia (BBT-I), consisting of four sessions centering of bedtime restriction (Troxel, Germain, & Buysse, 2012). This demonstrates that brief versions of CBT-I can be similarly effective as the complete program.

In addition to shortening the program as in BBT-I, another promising approach for improving the implementation and dissemination of CBT-I is internet-assisted treatment using online programs or apps. This approach seems well feasible and effective in patients with insomnia without comorbidity (Seyffert et al., 2016). CBT-I and BBT-I have primarily been conceptualized and thoroughly evaluated for patients with primary insomnia, somatic comorbidity or minor psychiatric comorbidity (Trauer, Qian, Doyle, Rajaratnam, & Cunnington, 2015). A large number of trials has shown that in these patient groups, CBT-I and BBT-I improve insomnia with large effect sizes and can also improve comorbid mental symptoms such as mild depression with small to medium effect sizes (Ballesio et al., 2018). Both CBT-I and BBT-I, however, are insufficiently researched in patients with severe psychiatric disorders and symptoms including psychosis, severe addiction, borderline personality disorder and suicidality. These patients are rarely included because most trials are conducted in outpatient settings. Only a minority of studies have been conducted in psychiatric wards (Sheaves et al., 2016), and insomnia in this patient group is still frequently treated pharmacologically. According to current guidelines, however, CBT-I is also the first-line treatment for patients with insomnia and comorbid severe mental disorders (Riemann et al., 2017). Pharmacological treatment should only be considered if CBT-I is not available or not effective (Qaseem et al., 2016; Riemann et al., 2017). The reason is that the most thoroughly evaluated medication for insomnia, benzodiazepines and benzodiazepine receptor agonists, are not suitable for long-term treatment due to tolerance, dependency, and adverse effects such as cognitive impairment (Wilt et al., 2016). Together, the evidence for efficacy as a prerequisite for dissemination and implementation of CBT-I in patients with severe mental disorders, including those in an acute crisis, is insufficient.

The overarching objective of the proposed project is to target sleep to improve mental health. The specific aim is to investigate the efficacy of SleepExpert, a pragmatic behavioral treatment program for insomnia, in patients with severe mental disorders on psychiatric wards.

3.2 Investigational Product (treatment, device) and Indication

SleepExpert 1.0 is the first version of an online Program to treat Insomnia. The internet-based self-help platform used for the implementation of CBT-I in this study has been developed by the University of Bern (Prof. Dr. Thomas Berger), has been used successfully in previous trials (Krieger et al., 2019) and has received a CE mark in 2018.

The device is intended for patients with mental disorders and insomnia who are treated for mental disorders in a hospital or an outpatient unit.

A CE Declaration of Conformity will be submitted with this ethics application.

No parts of the device are in contact with body tissues or fluids, it is an online application. No specific training is needed to operate the application.

3.3 Preclinical Evidence

Not applicable, device does not need Swissmedic notification.

3.4 Clinical Evidence to Date

There is no available clinical research data to date on exactly this product (SleepExpert). However, the therapeutic content that is used in this study is based on Cognitive Behavioral Therapy for insomnia (CBT-I). This intervention has been found to be highly effective and without lasting adverse effects in many studies and is recommended for the treatment of insomnia in current clinical guidelines (Qaseem et al., 2016; Riemann et al., 2017). A meta-analysis of randomized controlled trials has shown that CBT-I is also effective and without adverse effects when delivered online (Seyffert et al., 2016).

3.5 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

In this study, SleepExpert will be applied in three steps, namely i) a face-to-face group session held by a psychologist or physician, ii) self-management with coaching by nurses, and iii) self-management without systematic support. This form of administration has been developed to adapt CBT-I, the gold standard treatment for insomnia, to the needs of patients with severe mental disorders and insomnia. Patients with severe mental disorders, especially those hospitalized on psychiatric wards in an acute crisis, often suffer from cognitive impairments and motivational problems that make it impossible to implement CBT-I as usual. The gradual adaptation of support from face-to-face therapy to self-management is supposed to make CBT-I accessible for this specific patient group.

3.6 Explanation for choice of comparator (or placebo)

SleepExpert, an app-assissted treatment program with a face-to-face component, will be embedded into routine clinical care (treatment-as-usual, TAU). The comparison group in this trial will receive inpatient psychiatric treatment-as-usual (TAU) plus sleep monitoring. TAU comprises standard clinical care, including intensive daily contacts with health care providers on the wards, medical treatment, pharmacotherapy, psychotherapy in individual and group setting, nurse support, additional therapies such as music or ergotherapy and social support, informed by current guidelines for the respective disorder and adapted to individual needs. Of note, no change to any aspects of TAU will be made. Sleep monitoring will consist of daily sleep diary entries with the help of a smartphone app. In contrast to the SleepExpert version, the sleep monitoring version will not give any feedback or advice concerning sleep behavior. Patients in the control group will receive TAU plus sleep monitoring, whereas patients in the experimental group will receive TAU plus SleepExpert. We chose TAU, and not an active placebo control, as a comparator for the following reasons: Placebo control groups are mostly used to control for unspecific effects of attention by health professionals or contact with other patients. In our trial, patients in the TAU group will also get an extensive level of daily attention by health professionals and will also have the possibility to get to know other patients with similar problems. SleepExpert will be associated with a minimal amount of added therapist attention and contact time. Thus, an active control group is not necessary to control for these context aspects. Moreover, participants in an active control group would likely notice that they receive a "dummy treatment" that is unlikely to improve their sleep. This would reduce motivation to participate, may increase the dropout rate and reduce vaildity. Due to the inpatient and selected setting, TAU, in this study, can be well controlled and described and will be comparable across groups.

3.7 Risks / Benefits

The study will potentially be associated with direct advantages for the participating patients and indirect / potential advantages for the treatment of sleep disorders in patients with mental disorders in the case of positive results. No health related or other ethical problems are expected for the participants. Thus, the benefits of the study are supposed to outweigh the risks.

3.8 Justification of choice of study population

Patients with mental disorders and insomnia have been chosen because insomnia is highly prevalent in patients with mental disorders and the goal of this study is to improve treatment options for insomnia in this group. No vulnerable participants will be included into the study. Minors and patients incapable of judgement or under tutelage for health issues will be excluded from participation in the study. During the screening procedures, it will be made sure that patients understand the purpose and content of the study, potential risks and benefits, and that patients are able to comply with the study procedures (participation in group session, handling of web application). Patients who do not fulfil these criteria will be excluded from participation.

4. STUDY OBJECTIVES

4.1 Overall Objective

The main hypothesis is to investigate whether SleepExpert improves insomnia and general mental health in patients with severe mental disorders.

4.2 Primary Objective

The primary objective is to assess whether there is a significantly greater reduction in self-assessed insomnia severity (as measured by the Insomnia Severity Index, ISI) across six months (interaction effect Group and Timepoint) in patients in the Tau plus SleepExpert group, compared to patients in the TAU plus sleep monitoring group.

4.3 Secondary Objectives

The secondary objective is to assess whether there is a significantly greater improvement in general mental health (Brief Symptom Inventory) across six months (interaction effect Group and Timepoint) in patients in the TAU plus SleepExpert group, compared to patients in the TAU plus sleep monitoring group.

4.4 Exploratory objectives

Exploratory objectives include the effect of TAU plus SleepExpert versus TAU plus SleepMonitoring on the following parameters:

- Severity of depressive symptoms (Beck Depression Inventory, BDI)
- mood, tiredness, concentration, and subjective sleep quality (self-construced visual analogue scales)
- Daytime sleepiness (Epworth Sleepiness Scale)
- Medication
- Hospitalization

4.5 Safety Objectives

The study aims to assess short- and long-term safety of SleepExpert and its tolerability in terms of incidence of sleep- and mental-health related side effects and use of sleep medication.

5. STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome will be insomnia severity measured with the Insomnia Severity Index (ISI) (Bastien et al., 2001). The ISI will be administered before the intervention (T0) and one, two, 12, and 26 weeks after the start of the intervention.

5.2 Secondary Outcomes

The secondary outcome will be general mental health measured with the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983). The BSI will be administered before the intervention (T0) and one, two, 12, and 26 weeks after the start of the intervention.

5.3 Exploratory Outcomes

Exploratory outcomes will be the severity of depressive symptoms (Beck Depression Inventory, BDI) (Beck et al., 1988), self-constructed visual analogue scales measuring mood, tiredness, concentration and subjective sleep quality, daytime sleepiness (Lapin et al., 2018), medication (self-reported) and hospitalization (self-reported number of inpatient stays within the follow-up period). Timepoints when the different exploratory outcomes will be administered can be found in table 1 (section 9.1).

5.4 Safety Outcomes

At T0, T1, T2, T3, and T4, participants will be asked about significant negative life events in order to assess possible adverse effects of the treatment. AEs will be categorized concerning the type of the reaction, severity, relatedness to the intervention, action taken and outcome (Raisch, Troutman, Sather, & Fudala, 2001).

6. STUDY DESIGN

6.1 General study design and justification of design

This project is a prospective randomized controlled clinical pilot trial with a cluster-crossover design

involving two groups: An interventional group (TAU, plus SleepExpert) and a control group (TAU plus sleep monitoring).

Two different wards in the trial site (UPD Bern) will constitute the clusters. The study is conceptualized with a crossover, i.e. clusters (wards) will first be randomized to one of the groups for a duration of 4 months. After a washout-phase of two months, they will then be allocated to the other group for another 4 months. The order (TAU plus SleepExpert first vs. TAU plus sleep monitoring first) will be randomly allocated in a 1:1 fashion.

A total of 60 patients will be included. Patients will be assessed before the intervention (T0) and at the following time-points after the start of the intervention: 1 week (T1), 2 weeks (T2), 12 weeks (T3) and 26 weeks (T4).

6.2 Methods of minimising bias

6.2.1 Randomization

Wards will be randomly assigned to one of the two treatment conditions (cluster-randomization). A random list will be generated via the website random.org.
Randomization, data acquisition, data entry, and data analysis will be performed by staff members that are blinded regarding the treatment condition.

6.2.2 Blinding procedures

Study participants and care providers cannot be blinded because they will notice whether they receive / deliver an actual treatment or a monitoring control. Due to the crossover cluster design (randomization of wards to either TAU plus sleep monitoring or TAU plus SleepExpert), patients who are on the same ward at the same time will not get in contact with patients who are in the other arm. Thus, contamination due to exchange between patients will be reduced as far as possible. There will be two different participant information sheets, one for patients in the SleepExpert group and one for patients in the control group. Patients in the control group will not be informed about the SleepExpert treatment program - they will only be informed about the sleep monitoring they will receive.

Outcome assessors (interviewers) and data analysts will be blinded. In the respective documents and database entries, patients will be identified with a code. The key for assigning the codes to patients will not be known to the interviewers and data analysts.

6.2.3 Other methods of minimising bias

- The primary applicant is a staff member at the sleep clinic of the University Psychiatric Services Bern. The resources at this established, specialized sleep clinic will ensure that included patients are carefully diagnosed, i.e. that only patients fulfilling the defined eligibility criteria will be included. This ensures generalizability of the results to the intended population.
- Study attrition and reasons for dropout will be carefully documented throughout the study period.
- An intention to treat analysis will be provided since a per-protocol analysis may result in biased effects if many patients drop out due to (perceived) inefficacy.
- The outcome measures are widely used, valid, and reliable measures that have been recommended by experts for the research assessment of insomnia (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006).
- Therapists will be experienced, well-trained, and supervised.
- The trial will be registered in a publicly accessible database before recruitment of the first subject. Hypotheses and the analysis plan will be made publicly available. This precludes that the analysis plan is changed after inspection of the data ("fishing for significances").

6.3 Unblinding Procedures (Code break)

The code will only be broken if it is necessary in order to avert an immediate risk to the health of the person concerned or to guarantee the rights of the person or a legal basis exists for breaking the code. In this study, blinding of care providers and patients is not possible and will not be performed. Care providers on the wards will always be aware whether or not their patients received SleepExpert and data regarding the participation in the study intervention will be documented according to Good Clinical Practice. Thus, it is unlikely that circumstances under which the code has to be broken will occur.

7. STUDY POPULATION

7.1 Eligibility criteria

Minimal exclusion criteria will be defined with the aim of improving care for a broad population of patients with severe mental disorders and with the aim of maximizing generalizability and external validity.

Inclusion criteria:

- Age 18 years or older
- Documented diagnosis of acute insomnia, i.e. insomnia criteria according to ICD-10 for at least 2 weeks (Ellis et al., 2012)
- Insomnia Severity Index (ISI) total score > 7, equivalent to relevant insomnia (Gagnon et al., 2013)
- Inpatient in one of the two participating psychiatric wards in the UPD Bern
- Ability to understand the aims and procedures of the study
- Willingness to participate and ability to provide written informed consent

Exclusion criteria:

- Incabability of judgement
- Inability to participate in a low-threshold behavioral treatment program, e.g. due to severe cognitive impairment or high symptom severity precluding participation (e.g., severe catatonic symptoms, massive hallucinations, acute endangerment to self or others, involuntary commitment). Note that the named symptoms will lead to exclusion only if they lead to inability to give informed consent or an inability to participate in the program. Excluded patients will be re-assessed regularly and included if symptoms improve and participation is possible at a later point in time.

7.2 Recruitment and screening

During the enrolment phase, all patients admitted to the participating wards of the UPD Bern will be screened in person. The screening will consist of a few questions regarding sleep, implemented into the routine clinical interview at enrolment, and filling in the insomnia severity index (Gagnon et al., 2013). The clinical interview as well as the questionnaire (insomnia severity index) are part of the clinical routine in our hospital and not specific for this study. Eligible patients will be contacted by study staff, informed about the study, and invited to participate. For further information about the study a flyer containing the most important details will be given to the participants. The screening and enrolment process will be standardized across the wards to minimize the risk of selection bias.

Each patient in the clinic fills in a general consent form at admission, stating whether or not they agree to be approached for information about ongoing studies. Only patients who gave their written general consent will be contacted. There will be two different study information documents with attached consent forms, one for the active study phase where TAU plus SleepExpert is running, and one for the control phase where TAU plus sleep monitoring is running. Since patients are not randomized on an individual basis, but clusters (wards) are randomized, patients who are screened for the project in a phase where TAU plus sleep monitoring is running on their ward cannot be randomized to TAU plus SleepExpert. In these phases, it may be demotivating for patients to be informed about the SleepExpert treatment, because it is not available for them. Thus, we decided to give them extensive relevant information about the project they can participate in (sleep monitoring) and only basic information about the use of their data within a clinical trial.

7.3 Assignment to study groups

The two clusters (UPD wards) will be assigned to one of the following two study sequences – while one cluster will follow the first sequence, the other one will follow the second sequence. Which ward will follow which study sequence will be randomly assigned.

- TAU plus SleepExpert first for 4 months; fade-out for one month; wash-out for one month; TAU plus sleep monitoring for 4 months
- TAU plus sleep monitoring for 4 months; fade-out for one month, wash-out for one month; TAU plus SleepExpert for 4 months

During the TAU plus SleepExpert and TAU plus sleep monitoring phases, patients will be actively recruited. During the fade-our phases, no active recruitment will take place, but already recruited patients will be able to complete their treatment. During the wash-out phase, no recruitment and no study-related treatment will take place.

Depending at which stage of the study the ward stands at the time point when a subject is admitted to the ward, her or she will either receive TAU plus SleepExpert or TAU plus sleep monitoring, or, if admitted during the wash-out phase, the subject will not be able to participate in the trial.

7.4 Criteria for withdrawal / discontinuation of participants

Participants will be withdrawn from the study immediately if there are any concerns about the participants' safety. Participants can also choose to withdraw from the study at any time, and are not required to provide their reason for withdrawing from the study. Coded data acquired before withdrawal will be analyzed.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment / medical device)

8.1.1 Experimental Intervention (treatment / medical device)

General information

Both groups will receive psychiatric inpatient treatment-as-usual (TAU). TAU will be provided according to current treatment guidelines for the respective mental disorders. Within the trial period, TAU will be delivered as usual in the respective hospitals. No restrictions with regard to pharmacotherapy, psychotherapy, or any other inpatient therapy or subsequent outpatient care will result from participation in the SleepExpert trial.

TAU will consist of the following interventions: daily visit by a physician or psychologist, if necessary individualized pharmacological treatment according to current guidelines, individualized disorder-specific psychotherapy according to current guidelines, daily contact with a psychiatric nurse, ergo therapy, and other group therapies according to a personalized schedule (e.g. music therapy, art therapy, relaxation therapy, etc.). The duration of the inpatient stay will be adapted to the progress of the individual patient and will vary from participant to participant. The duration of the stay is typically between one to eight weeks, exceptions are possible.

The TAU plus SleepExpert group will receive a specific treatment for insomnia. This treatment will consist of the following three phases:

1) a face-to-face treatment initiation guided by a medical doctor/ psychologist in a group format (1 hour),

2) self-managed implementation of behavioral changes assisted by an online application ("Become your own SleepExpert") and coached by nurses (two individual contacts per week of about 5 min duration), and

3) self-management by the patients assisted by the same online application after discharge from the hospital.

The treatment initiation will be a psycho-educative group session held by a physician or psychologist. During this group session, basic information about sleep regulation will be provided, including the two components i) homeostatic build-up of sleep pressure as a function of prior wake time, and ii) relevance of individual circadian sleep-wake preferences. At the end of the group session, an individual sleep window (duration of bed time and timing) will be worked out with every patient. In most patients, the time in bed is shortened and 'lights-off' is delayed compared to the previous behavior with the aim of increasing sleep pressure and moving sleep time into a physiological time frame. The background is that patients with insomnia often increase their time in bed in order to catch more sleep - which, however, is actually detrimental for sleep quality. The online application will be introduced in this group therapy session. In the second phase of the treatment program, nurses will regularly meet with the patients to discuss their sleep behavior. Patients will be assisted in keeping or, if necessary, adapting their prescribed sleep window, and will receive advice, motivation and assistance in using the application. Patients will learn how to use the application in order to document and adjust their sleep behavior. In the third phase (defined as starting from discharge from the psychiatric ward), patients will use the online application in self-management to keep optimizing their sleep behavior. All patients, i.e. the TAU plus sleep monitoring and TAU plus SleepExpert group will have an individual appointment with a sleep expert (physician or psychologist) after completion of the study, i.e. after 6 months, in which the gathered information (sleep diaries) will be discussed and individualized further diagnostics and treatments, if needed, will be initiated.

Online application

The online application 'Become your own SleepExpert' is currently developed in cooperation with Prof.

Thomas Berger, University of Bern. Prof. Berger has a longstanding experience in the field of internet- and app-based prevention and treatments of mental problems and disorders. His publication record includes a multitude of studies investigating the efficacy of online treatments for different mental health problems and disorders, including anxiety, depression, insomnia, adjustment problems and self-criticism (e.g., Krieger et al., 2019; Moser et al., 2019; Schuster et al., 2019; Weisel et al., 2019).

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

Patients in the control group will receive the same TAU as the experimental group (see 8.1.1).

In addition, patients in the control group (TAU plus sleep monitoring) receive a smartphone app (sleep monitoring). No further interventions will be provided through this app.

8.1.3 Packaging, Labelling and Supply (re-supply)

Not applicable.

8.1.4 Storage Conditions

Not applicable.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention and Control Intervention

This chapter can also be merged with chapter 8.1.1.

8.2.2 Control Intervention

This chapter can also be merged with chapter 8.1.2.

8.3 Dose / Device modifications

Not applicable.

8.4 Compliance with study intervention

Adherence will be monitored using subjective patient data from the SleepExpert application. In the application, patients will log their bed times and rise times as well as subjective sleep times.

Treatment contamination (i.e., patients in the TAU plus sleep monitoring group learning about details of the SleepExpert intervention) will be prevented by cluster randomization of wards. One entire ward will be randomized to one of the conditions. The other ward will receive the remaining condition (preventing that both wards get the same condition). Patients in the control group will not get in close contact with patients in the intervention group. Additional measures to increase adherence include a start of the intervention in the inpatient setting along with individual coaching by nurses and a helpdesk that can be called in case of problems with the program. Please note that no further extensive contacts are planned to increase generalizability of the program after completion of the study.

8.5 Data Collection and Follow-up for withdrawn participants

If a patient withdraws consent for further study participation, the data collected up to the time point of withdrawal will be included in the study and no further data will be collected. The data of withdrawn participants will not be anonymized but will remain coded after analysis of the data set.

For participants who discontinue the study intervention but do not withdraw from participation in the study, study visits and data collection will continue in the same way as for non-withdrawn participants.

8.6 Trial specific preventive measures

No specific preventive measures will be taken in this trial. There will be no restrictions to treatment or daily life related to this trial.

8.7 Concomitant Interventions (treatments)

All concomitant treatments / interventions are permitted and will be recorded in the CRF. The aim of this trial is to implement SleepExpert into the clinical routine care for patients with severe mental disorders, thus no artificial / trial-specific restrictions will be applied. Careful documentation of concomitant treatment will prevent biasing of the results.

8.8 Medical Device Accountability

Not applicable, patients will use the trial-specific web applications from their own devices.

8.9 Return or Destruction of Medical Device

Not applicable.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

The overall planned study duration is 2.5 years. Patients will first be screened and assessed for eligibility. Eligible patients who signed the informed consent form will undergo a first assessment (T0) and then participate in the intervention. Additional assessments will be made one, two, 12, and 26 weeks after the start of the intervention. A plan of each patients' schedule within the study is outlined in table 1 which is illustrated in chapter 1.1.

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

The ISI is a valid, reliable and change-sensitive self-rating questionnaire that is widely used as an outcome measure in clinical trials in insomnia research (Buysse et al., 2006). It ranges from 0 to 28 with higher values indicating more severe problems. A self-rating questionnaire in contrast to objective sleep measures such as polysomnography or actigraphy is reasonable and widely accepted for measuring insomnia severity because insomnia is defined on the basis of subjective sleep dissatisfaction (American Psychiatric Association, 2013; Medicine, 2014; Organization, 2004) and objective measures often deviate from this perception (Harvey and Tang, 2012). An advantage of the ISI, compared to a sleep diary, is that it combines different aspects of insomnia such as sleep onset difficulties, sleep maintenance difficulties, and daytime impairment in one summary score. For more information, see chapter 5.1.

9.2.2 Assessment of secondary outcomes

The BSI is a brief version of the Symptom Checklist 90 (SCL-90) (Derogatis et al., 1976). It shows high correlation with the long version and has a good test-retest reliability (Derogatis and Melisaratos, 1983). We chose the BSI because it is an efficient measure of general mental health. In our sample, patients will suffer from different mental disorders including but not limited to depression, psychosis, anxiety and substance abuse. In addition, we expect that many patients suffer from more than one mental disorder (comorbidity). A general measure, beyond the severity of specific disorders, is thus needed to picture changes in general mental health. For more information, see chapter 5.2

9.2.3 Assessment of exploratory outcomes

Exploratory outcomes will be the severity of depressive symptoms (Beck Depression Inventory, BDI) (Beck et al., 1988), self-constructed visual analogue scales measuring mood, tiredness, concentration and subjective sleep quality, daytime sleepiness (Lapin et al., 2018), medication (self-reported) and hospitalization (self-reported number of inpatient stays within the follow-up period).

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For all mentioned questionnaires, the primary metric will be the total score of the respective questionnaire. We will also perform additional analyses to compare the number of patients with response and remission between the two trial groups. Following Morin et al., response is defined as an improvement of > 7 points on the ISI (Morin et al., 2011). Remission is defined as an ISI score of < 8.

9.2.4 Assessment of safety outcomes

9.2.4.1 *Adverse events*

At T0, T1, T2, T3, and T4, participants will be asked about significant negative life events in order to assess possible adverse effects of the treatment. AEs will be categorized concerning the type of the reaction, severity, relatedness to the intervention, action taken, and outcome (Raisch et al., 2001).

9.2.4.2 *Laboratory parameters*

Not applicable. No laboratory parameters will be assessed in this study.

9.2.4.3 *Vital signs*

Not applicable. No vital signs will be assessed in this study.

9.2.5 Assessments in participants who prematurely stop the study

For participants who discontinue the study intervention but do not withdraw from participation in the study, study visits and data collection will continue in the same way as for non-withdrawn participants.

Dropouts before start of treatment (i.e. non-starters) will be replaced by recruitment of new participants.

Patients who started the intervention but who were prematurely withdrawn from the study will not be replaced by newly enrolled patients.

9.3 Procedures at each visit

The following visits will be conducted: screening, T0, T1, T2, T3 and T4.

9.3.1 Screening

The screening will be performed on the day patients are admitted to the participating wards. All patients admitted to these respective wards will be screened. The screening will consist in a brief clinical interview and filling in the Insomnia Severity Index. In the clinical interview, patients will briefly be asked about their sleep problems and their medical history by a trained physician. The aim is to determine whether the diagnostic criteria for acute insomnia are fulfilled and whether any exclusion criteria are fulfilled. Patients need a total score > 7 on the Insomnia Severity Index to be included. For details regarding this questionnaire, please see chapter 5.

9.3.2 Timepoints T0 to T4

Time point T0 (day 0):

- Insomnia Severity Index
- Brief Symptom Inventory
- Beck Depression Inventory
- Visual analogue scales (subjective sleep quality, mood, concentration, and tiredness)
- Sleep diary will be handed out
- medication status
- adverse events

Time point T1 (day 7±2):

- Insomnia Severity Index
- Visual analogue scales (subjective sleep quality, mood, concentration, and tiredness)
- sleep diary will be checked
- medication status
- adverse events

Time point T2 (day 14±2):

- Insomnia Severity Index
- Brief Symptom Inventory
- Beck Depression Inventory
- Visual analogue scales (subjective sleep quality, mood, concentration, and tiredness)
- sleep diary will be checked
- medication status
- adverse events

Time point T3 (day 84±7):

- Insomnia Severity Index
- Visual analogue scales (subjective sleep quality, mood, concentration, and tiredness)

- sleep diary will be checked
- medication status
- adverse events

Time point T4 (day 182±7):

- Insomnia Severity Index
- Brief Symptom Inventory
- Beck Depression Inventory
- Visual analogue scales (subjective sleep quality, mood, concentration, and tiredness)
- sleep diary will be checked
- medication status
- adverse events

For details regarding the mentioned questionnaires, please see chapter 5.

10. SAFETY

10.1 Drug studies

Not applicable

10.2 Medical Device Category C studies

Not applicable

10.3 Medical Device Category A studies

Device deficiencies and all **adverse events (AE)** including all **serious adverse events (SAE)** are collected, fully investigated, and documented in the source document and appropriate case report form (CRF) during the entire study period, i.e. from patient's informed consent until the last protocol-specific procedure. Documentation includes dates of event, treatment, resolution, assessment of seriousness, and causal relationship to device and/or study procedure [ISO 14155, 6.4.1.].

10.3.1 Foreseeable adverse events and anticipated adverse device effects

Potential adverse events are transitional worsening of the sleep disorder and / or the mental disorder, daytime tiredness and daytime sleepiness. No SAE that could be related to the investigational device or study procedures are expected during this clinical trial.

10.3.2 Definition and Assessment of safety related events

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

This includes events related to the investigational device or the comparator and to the procedures involved. For users or other persons this is restricted to events related to the investigational medical device.

Adverse Device Effect (ADE):

Adverse event related to the use of an investigational medical device [ISO 14155: 3.1].

This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Event (SAE) [European regulation on medical devices 2017/745, art. 58]:

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) hospitalisation or prolongation of patient hospitalisation,
  (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,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

These are submitted to the EC via BASEC within 7 days (see below chapter 10.2.3). A planned hospitalisation for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

Device deficiency:

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance,

such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

Device deficiency with SAE potential:

Device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

Health hazards that require measures:

Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants SAE [ClinO Art. 37].

Causal Relationship of SAE [MEDDEV 2.7/3 revision 3, May 2015]:

A causal relationship towards the medical device or study procedure should be rated as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Unlikely:** The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

Device deficiencies that might have led to an SAE are always related to the medical device.

10.3.3 Reporting of Safety related events

Reporting to Sponsor-Investigator:

All SAEs, device deficiencies and health hazards that require measures are reported to the Sponsor-Investigator within 24 hours upon becoming aware of the event. Device deficiencies are assessed regarding their potential to lead to an SAE.

Pregnancies

Reporting of pregnancy is not necessary in this study.

Reporting to Authorities:

The sponsor-investigator will apply to the notification requirements specified in Art. 15 of the MedDO of 17 October 2011 (SR 812.213).

The sponsor investigator will report to the Ethics Committee via BASEC **device deficiencies** that could have led to serious adverse events if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate within 7 days [ClinO Art. 42].

Health hazards that require measures are reported to the Ethics Committee via BASEC within 2 days [ClinO Art. 37].

Periodic safety reporting:

A yearly safety update-report is submitted by the Investigator to the Ethics Committee via BASEC.

A report is submitted to Swissmedic by the Sponsor-Investigator, as defined in Art. 15a,b of the MedDO of 17 October 2011 (SR 812.213).

10.4 Assessment, notification and reporting on the use of radiation sources

Not applicable.

11. STATISTICAL METHODS

11.1 Hypothesis

Hypothesis: SleepExpert improves insomnia and general mental health in patients with severe mental disorders.

Primary objective: To assess whether there is a significantly greater reduction in self-assessed insomnia severity (as measured by the Insomnia Severity Index, ISI) across six months (interaction Group x Time) in patients in the Tau plus SleepExpert group, compared to patients in the TAU plus sleep monitoring group.

Secondary objective: To assess whether there is a significantly greater improvement in general mental health (Brief Symptom Inventory) across six months (interaction Group x Time) in patients in the TAU plus SleepExpert group, compared to patients in the TAU plus sleep monitoring group.

Exploratory objectives: Additional objectives include the effect of TAU plus SleepExpert versus TAU plus SleepMonitoring on the following parameters:

- severity of depressive symptoms (Beck Depression Inventory, BDI)
- mood, tiredness, concentration, and subjective sleep quality (self-construced visual analogue scales)
- daytime sleepiness (Epworth Sleepiness Scale)
- medication
- hospitalization

11.2 Determination of Sample Size

A power analysis was conducted with G-Power (Faul, Erdfelder, Lang, & Buchner, 2007). Assuming an alpha error level of 0.05 (two-sided) and a power of 0.8, a total sample size of n=60 will be sufficient to detect a medium effect (Cohen's d=0.65). This is a pilot trial with the primary aim of collecting qualitative experience and preliminary efficacy data. A large confirmatory trial will be conducted if the results of this pilot trial are encouraging.

11.3 Statistical criteria of termination of trial

no statistical criteria for termination of trial have been formulated.

11.4 Planned Analyses

At the start of recruitment, a statistical analysis plan (SAP) will be written. The plan determines all necessary data preparation steps (e.g. additional validations, generation of new variables), definitions (e.g. analysis sets), and statistical analyses (e.g. models, outputs such as tables and graphs).

11.4.1 Datasets to be analysed, analysis populations

All analyses will be done on the as-treated analysis considering the cross-over design.

11.4.2 Primary Analysis

The primary outcome, i.e. the four overall scores of the ISI of all follow-up time-points will be analyzed with a mixed effects linear model. The model will take into account the hierarchical structure of the data: multiple ISI scores per patient and clusters (cross-over). Because of the complexity of the data and the small number of clusters we assume that we will not be able to introduce random effects for patients and clusters. However, our first approach will still be a linear mixed model with the following co-variables: fixed intervention effect (TAU plus SleepExpert versus TAU plus sleep monitoring), fixed baseline ISI score effect, random patient effect (multiple ISI scores during follow-up), random cluster effect. Depending on model fit, we may need to simplify the model and modify the random effects. This model is pre-specified and the rationale for switching will be made explicit. The analysis will be made after all data has been collected by one of the principal investigators.

11.4.3 Secondary Analyses

Continuous outcomes (Brief Symptom Inventory, Beck Depression Inventory) will also be analyzed by a mixed effects linear model using the same procedure used to estimate the primary outcome. Binary outcome data will be analysed using mixed effect logistic regression with odds-ratio as the effect measure. The number of hospitalizations will be also analyzed by a mixed effects model. Interim analyses

No planned interim analysis

11.4.4 Safety analysis

The frequency of occurrence of adverse events of different categories will be analysed using descriptive statistics and compared between the two groups using Chi square tests.

11.4.5 Deviation(s) from the original statistical plan

The SAP is a version-controlled document which allows to track all changes to the statistical analysis. Any post-hoc changes will be transparently reported in all publications.

11.5 Handling of missing data and drop-outs

Dropouts before start of treatment (i.e. non-starters) will be replaced by recruitment of new participants. Multiple imputation will be used in case data are not available for more than 5-10% of the sample.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

The investigator will maintain appropriate medical and research records for this trial. The records will be kept in compliance with ISO14155 and meeting regulatory and institutional requirements for confidentiality. The principal investigator, sub-investigators, and clinical research nurses or coordinators will have access to the records. The principal investigator will permit authorized representatives of the Sponsor and the CEC to examine clinical records for the purposes of inspections, quality control, quality assurance, and evaluation of study safety and progress.

12.1.1 Case Report Forms

Data is recorded in paper CRFs as source documents. ECRFs will be given as an option for direct anonymized data entry from participants for follow-up time points when they are not patients on the wards anymore. The eCRFs will be created and stored on the database RedCap which is a database recommended from the Clinical Trial Unit Bern. Data entry from the source paper CRFs to eCRFs should only be performed by authorised personnel and data should be consistent with the available source documents. When this is not the case, a detailed explanation of the discrepancies should be provided. The principal investigator should ensure the accuracy, completeness, and timeliness of the data reported and sign off the completed eCRFs. In order to reflect the current patient status throughout the study, eCRFs will be kept up to date. This means that eCRFs should be completed no later than two weeks after a participant's visit and that data entry not should be delayed unnecessarily.

12.1.2 Specification of source documents

Source documents for each study participant, including original study related documents, treatment and medical history, must be available at the sites.

When hospital medical records are electronic, key-data should be printed and filed as certified copies in the patient binders of the investigator site file. A certified copy is a copy of the original record that has been verified, i.e. by a dated signature, to have the same information, including data that describe the context, content, and structure, as the original.

Any change or correction to a source document should be dated, signed (by identifiable initials), and if necessary explained. The change should under no circumstances obscure the original entry.

All data captured in the eCRF should be itemised on a source data location list, which will be stored in the investigator site file at each study site. This list should reflect the work flow at the study site, clearly indicating the source data location corresponding to each eCRF entry. If several sources are possible for one eCRF entry, the priority order of these must be specified in the list.

12.1.3 Record keeping / archiving

All study data (written and electronic) and in particular the investigator site file (ISF), must be retained for a period of at least 10 years from the completion or premature termination of the trial. The Investigator should take measures to prevent accidental or premature destruction of these documents.

12.2 Data management

Data of all subjects will be coded and data analysis will be performed using these codes only. Unblinding of subject-specific data is possible after consent has been given by the subjects and the project leader. The code will only be broken if it is necessary in order to avert an immediate risk to the health of the person concerned or to guarantee the rights of the person (e.g. in revoking the consent) or a legal basis exists for breaking the code. Range checks for data values will be performed to exclude data entry errors.

Project data will be handled with uttermost discretion and only be accessible to authorized personnel who will have access to data for study purposes (e.g. data analysis) for the whole study duration. Only the investigators and Ethics Commission are allowed to have inspections on the original data, and will be allowed direct access to source documents will be permitted for purposes of monitoring, audits or inspections.

12.3 Data Management System

Our technical implementation for data management uses the database RedCap which is recommended from the Clinical Trial Unit Bern. he sponsor-investigator is responsible and will ensure correct and conscientious use of the data management system, and will monitor the data management. The system is tested before the start of data collection in consultation with the institution's IT experts.

12.4 Data security, access and back-up

Access to parts of the data will be granted only to individuals that require it to conduct the research. For instance, only individuals that need to contact or communicate with participants have access to the participant's identity and contact details. Researchers that do statistical analysis of the study cohort get only access to pseudonyms. Access is granted through personal accounts, usually the CampusID by the University of Bern. Exchange of data is strictly channeled through a system that tracks all changes and prevents permanent deletion of files by researches. The system provides a full audit trail and centralized access control. Data processing is done on personal computers/laptops and institutional servers. The personal devices are protected against theft/loss by a full system encryption (BitLocker).

12.4.1 Analysis and archiving

Before final analysis, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time is recorded in archive tables.

The study database with all archive tables will be securely stored by UPD Bern. The Sponsor also archives the Trial Master File and the final report for at least 10 years.

In accordance to Data Protection Directive of the UPD Bern and the SAMW-guidelines for creating biological databases, all study data will be archived for a minimum of 10 years after study termination or premature study termination. In case of paper form, data will be archived in lockable drawers at the research facility (Research Dept. of the Translational Research Center, University Hospital of Psychiatry, Bolligenstr. 111, CH-3000 Bern 60.). In case of digital data, the raw data, derived data, code, meta-data, and all history will be exported from the version control system and archived for 10 years at the University of Bern on an archival system that stores two copies of the data in two geographically distinct locations. At the end of the project, researchers are asked to remove study data from their devices and local servers. Raw data, code, and all intermediate data can be restored and/or transferred in its entirety or partially.

12.4.2 Electronic and central data validation

Data edit checks will be implemented into the EDC system, limiting entries to appropriate, realistic values (e.g. not allowing future dates, missing values etc.). Furthermore, selected data points are cross-checked for plausibility with previously entered data for each individual participant.

Before database lock each PI will validate the collected data from his site with his signature.

12.5 Monitoring

On-site will be part of the quality control activities implemented for this study. Monitoring will be performed according to a separate monitoring plan.

For the purposes of monitoring, the PI at the site will provide the monitor with access to study documentation, patient records, facilities and any other resources necessary. During on-site monitoring visits, the PI or his designee will support the monitor in his/her activities and answer questions arising. Questions and queries arising during central data monitoring will be handled in a timely manner.

All involved parties will keep participant data strictly confidential.

12.6 Audits and Inspections

No site audits by the sponsor are planned for this study, but the sponsor reserves the right to perform such an audit should it be considered necessary.

In case of an audit or an inspection, the auditors / the inspectors will get access to study documentation, patient records, facilities and any other resource deemed related to the study by the authority. Before, during and after the audit or inspection, the investigator will support the auditors/inspectors in their activities and answer any questions arising.

All involved parties will keep participant data strictly confidential.

12.7 Confidentiality, Data Protection

The principal investigator safeguards the confidentiality of participating patients' data, ensuring that no patient information containing identifying data will leave the study site.

Direct access to source documents and other study related records at the participating study sites will be permitted for purposes of monitoring, audits and inspections. The monitoring institution (i.e. CTU Bern) and the CEC will have access to all information necessary to accomplish their tasks.

12.8 Storage of biological material and related health data

Not applicable.

13. PUBLICATION AND DISSEMINATION POLICY

Trial results will be published in a peer-reviewed journal and presented at national and international conferences. The principal investigator has all rights for publication and will have ultimate authority over all publication activities.

14. FUNDING AND SUPPORT

14.1 Funding

The project is financed with intramural money of the UPD Bern. External funding by the Velux Foundation has been applied for.

14.2 Other Support

Not applicable.

15. INSURANCE

Not applicable (study category A).

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17. APPENDICES

ICH: (NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

Please consider well with adding documents here that are very frequently changing, they may be mentioned as separately provided documents and listed here.

Except for medical devices, the section headings can be renamed accordingly.

1. IMP: IB or SPC

2. Medical Devices: IB (according to ISO 14155)

3. Medical Devices: Assurance of producer

4. Medical Devices: List of norms (vollständig eingehaltene, teilweise eingehaltene)

5. Radiolabelled products: Strahlenschutzverordnung

6. e.g. List of study sites / PIs

List of countries or centres where data will be collected or reference to where list of study sites can be obtained

7. Other

e.g. Specific protocols (e.g. MRI)

e.g. Case Report Form (e.g. CRF)

e.g. Patient Information and informed consent

Model of consent form and other related documentation given to participants and authorised surrogates and additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

e.g. Other material to patients

Model of consent form and other related documentation given to participants and authorised surrogates and additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable