Federal State Autonomous Educational Institution of Higher Education
I.M. SECHENOV FIRST MOSCOW STATE MEDICAL UNIVERSITY
of the Ministry of Healthcare of the Russian Federation
(Sechenovskiy University)

Study protocol

« Effectiveness and Cost-Effectivenessof Internet-Based CognitiveBehavioral Therapy for Insomnia in Clinical Settings»

Speciality: 14.01.11 Nervous diseases
(Code and name of medical speciality)

IPC codes A61B 5/16 (Diagnosis; Psycho-physical tests);

Scientific supervisor and primary investigator: Ph.D, M.D., associate professor of the Chair of neurology, i.m. Sechenov First Moscow State medical university M.G. Poluektov

1. BACKGROUND

The burden of Chronic insomnia (CI) is high, with point prevalence ranging between 6% and 10% (2–4). Apart from deterioration in the quality of life of each patient, their families, and friends, CI imposes also a non-negligible social and economic burden. This burden includes resources used for treatment, as well as reduced or lost work productivity. CI impacts labor by means of time, efficiency, and results in productive work activities losses and may even lead to loss of employment. The treatment of choice is a multicomponent treatment, cognitive-behavioral therapy for insomnia (CBT-I). CBT-I consists of sleep restriction, stimulus control, various relaxation techniques, sleep hygiene education, and cognitive restructuring of maladaptive beliefs and concerns about sleep.Nevertheless, time-consuming treatment courses and the lack of trained CBT-I clinicians cause difficulties in the implementation of these methods. Thus, developing innovative automatized and remote methods of performing CBT-I, such as internet-delivered CBT-I (iCBT-I), is of significant relevance. A meta-analysis reports a large within-group effect size for iCBT-I (Hedges's g = 0.86) for self-reported insomnia severity (16). This effect size was not found to be significantly different then effect sizes in individual or group CBT-I. A number of studies have shown the efficacy of iCBT-I in comparison with control groups receiving less active treatments (i.e., wait-list, sleep education, etc.) as summarized in several meta-analyses.

Internet-based CBT-I (Sleepsy©) consists of interactive educational material divided into eight modules and explaining homeostatic and circadian mechanisms of human sleep

regulation, the pathogenesis of CI, and its daytime consequences. In this study we aim to confirm effectiveness of this method in the clinical sample in moscow university clinic.

Both pharmacotherapy, CBT-I (or BBT-I) and their combinations produce treatment response only in 60-67% of patients and remission only in 42-55%. A reasonable way to improve the clinical effectiveness is determining the target group of patients that benefits most of iCBT-I. Some studies have shown that efficacy of CBT-I is related to the severity of maladaptive cognitions and behavior. As there is not much knowledge about predictors of iCBT-I treatment efficacy, in this trial, we will deliberately analyze psychometric, anamnectic and sleep characteristics which may act as predictors of CBT-I, which may also be relevant in iCBT-I. Specifying predictors of effectiveness of iCBT-I will give the opportunity to develop more individualized therapeutic decision-making procedure and will be important for economic reasons. In the longer term, obtaining of portrait for patient who benefit from iCBT-I will give us cues to understanding insomnia in whole and its subtypes.

It would be the first implementation of on-line behavioral treatment for insomnia in Russia and the first attempt to develop online materials for chronic insomnia treatment which would simplify the insomnia treatment improve patient adherence. In view of a huge demand of specialists in CBT-I development and approbation of this program will fill this gap in clinical practice. All the participants will have access to care as usual (CAU), which let us reconstruct real clinical situation along the whole course of the study. To our knowledge, this is one of the first studies considering iCBT-I in clinical settings.

1.2. PREVIOUS CLINICAL APPLICATION

Structure of the investigated treatment course Internet-based CBT-I (Sleepsy©) is based on the already established program iSLEEP – internet-based self-help against insomnia that was already tested in previous study in Bern Universitz, Switherland. Short-term effectiveness of iCBT-I was high with effect size from median to large. The longest follow-up period in the studies of iCBT-I was 3 years. After this period there was no difference in the primarz outcomes between intervention and control group, but participants of intervention group used sleep aids significantky less than control. Moreover, there were no adverse events throughout the follow-up

Since the overwhelming majority of iCBT-I randomized controlled trials (RCTs) were conducted in research settings with recruitment via internet and advertisement, it is unclear if the promising results from efficacy studies can be transferred to routine clinical practice. For this study participants will be recruited from the doctor's office to ensure proper diagnostics and exclusion of other diseases affecting depth and length of sleep. It may be that patients, referred to iCBT-I directly from doctor's office, have active and more severe sleep complaints, and therefore are more motivated to benefit from the treatment

2. Aim of the study

Aims:

1. to investigate clinical effectiveness and cost-effectiveness of the internet-based CBT-I program Sleepsy in comparison with care as usual (CAU) among patients with CI recruited from clinical settings.

2. to investigate predictors of treatment outcome by analysis of baseline characteristics.

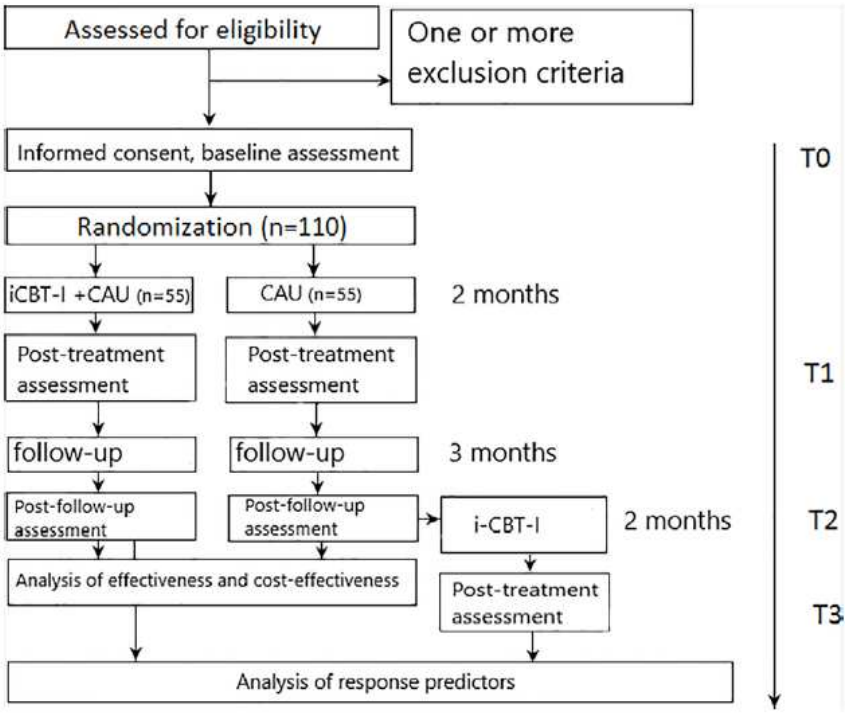
Tasks:
– Baseline assessment of recruited participants;
– Randomization;
– Treatment of intervention group by means of iCBT-I course;
– Post-treatment assessment of all participants;
– Follow-up assessment of all participants;
– Comparison of primary and secondary outcomes in intervention and control groups;
– Treatment of control group by means of iCBT-I course;
– Post-treatment assessment of control group participants;
– Statistical analysis of response predictors.

Hypothesis

- iCBT-I is more effective and cost-effective than CAU in clinical settings
- The analysis will help us identify the typical sleep pattern and obtain psychological portrait of those who benefits from behavioral treatment

3. STUDY DESIGN

a) The proposed study is a multicenter parallel-group add-on superiority RCT comparing an active treatment condition (iCBT-I plus CAU) to CAU alone.



After signing the IC form, participants will receive an e-mail with the link to the Qualtrics Survey Software (Qualtrics, Provo, UT, USA), where they complete baseline assessment and receive the individual allocation code. On completion of baseline measures, subjects will be automatically assigned by the randomization function of Qualtrics Survey Software to either iCBT-I plus CAU or CAU group using single block randomization. Neither participants nor referring specialist nor the research team have foreknowledge and/or control over randomization andthe allocation procedure. Following randomization, the participants will receive an automated email regarding their group allocation and a description of future steps. In case they were allocated to the treatment group, their individual code will provide an access to the iCBT-I program.

Participants in the control group will get access to the iCBT-I program after the 5-month follow-up (3 months after post-assessment) provided they completed the follow-up assessment and still fulfill eligibility criteria. In this group, an additional assessment will be conducted eight weeks after providing access to the CBT-I program to enlarge the sample for the analysis of outcome predictors.

The research team, except the trial coordinator, will be blind to allocation. Coding allocation form, along with the participant's real name and address noted in the IC form, will be stored in the password-protected computer of the trial coordinator. Participants will not be blind to treatment allocation and will receive information about their randomization outcome via email. Questionnaires and sleep diaries will be completed entirely online under the participant's individual code.

3.1.OUTCOMES

3.1.1. The primary endpoint of the present study is the change of Insomnia Severity Index (ISI) from pre- to post-treatment and at follow-up.

3.1.2. Secondary outcomes

1) Subjective Sleep Characteristics will find reflection in the sleep diary in such variables as sleep onset latency (SOL), total sleep time (TST), sleep efficiency (SE), calculated as TST/time in bed × 100, wake after sleep onset (WASO), and number of awakenings. In order to obtain these data we will ask control group participants to fill in online sleep diary in Qualtrics for one week starting at time-point T0 (after randomization), T1 and T2. iCBT-I + CAU group participants will fill it only at time-point T2 since online sleep diary is integrated into the iCBT-I program and we can use its data for the treatment and post-treatment period.

2) Severity of Insomnia. ISI is important not only as primary measure of treatment effect but also as possible outcome predictor and response criterion. To evaluate it, we will use baseline ISI score and ISI score at the other timepoints. The response criterion is determined as decrease of the ISI score of more than 7 points compared to baseline.

3) Daytime symptoms of insomnia are often represented by sense of fatigue, sleepiness, and headaches. The fatigue severity will be evaluated by the Fatigue

Severity Scale (FSS), a disorder nonspecific 7-item scale which measures the severity of fatigue and its effect on a person's activities and lifestyle. Short-form survey (SF-12) version 1.0 is a non-specific scale assessing quality of life by means of eight subscales (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health). Sleepiness as one of the most often reported symptoms of CI will be evaluated by the Epworth Sleepiness Scale (ESS)

4) Anxiety and depressive symptoms will be assessed with the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI-II). Both of them comprise 21-question with a 4-point Likert scale and ranging answers from 0 to 3, yielding a total score ranging from 0 to 63. A BAI total score higher than 25 corresponds to severe anxiety, and a BDI cutoff higher than 28 indicates severe depression.

5) Behavioral Perpetuating Factors. One of the leading perpetuating factors of insomnia is poor sleep habits that can be assessed by the Sleep Hygiene Index, a 13-question questionnaire, yielding a total score ranging from 13 to 65. We have translated it into Russian according to a forward and backward translation procedure.

6) Cognitive Perpetuating Factors will be assessed by the Sleep Locus of Control Questionnaire (SLC) and Dysfunctional Beliefs and Attitudes About Sleep Scale (DBAS). Both questionnaires were validated in Russian.

7) Description of personal characteristics may play an important role in predicting treatment outcome. For this purpose, we intend to use the Personality Inventory for DSM-5 faceted brief form (PID-5-FBF) 100-item self-report inventory designed to assess the 25 pathological personality trait facets and the five domains based on the dimensional trait model (DSM-5 Section III). For translation the questionnaire we used forward and backward translation procedure.

8) In order to evaluate the cost-effectiveness of iCBT-I, we will collect information concerning healthcare consumption and productivity losses for the study period using the Trimbos Questionnaire for Costs associated with Psychiatric illness (TiC-P) consisting of two parts. The first part consists of 14 questions on the volume of health care uptake including names, dosage, and frequency of use of medications for insomnia treatment; the second part is represented by the Short Form-Health and Labor Questionnaire (SF-HLQ), an instrument to collect data on productivity losses (presenteeism and absenteeism) due to health problems. For the proposed study questionnaire was translated into Russian.

9) During the intervention, we will assess adherence by recording of the number of completed modules, total time spent on the iCBTI website, time spent on each module, number of completed sleep diaries and usage of the support. Time spent on the website will be measured by means login/logout data and by keeping an activity journal.

10) In order to analyze such important outcome predictor as patients beliefs about the expected treatment success and to evaluate between-group difference with regard to this factor, we include in baseline assessment one adapted question of Credibility/Expectancy Questionnaire: “At this point, how successfully do you think this treatment will be in reducing your insomnia symptoms?” at scale from 1 to 9.

11) User Satisfaction. After completion of the iCBT-I course participants will be requested to fill in feedback questionnaire developed for this study. It includes 5-point Likert scale, from 1 (very poor/not at all useful) to 5 (very, good/very useful) on questions about satisfaction or dissatisfaction with the treatment, and open questions about possible negative effects of the intervention if any: deterioration of insomnia symptoms, adverse effects, novel symptoms; and about improvement suggestions, what participants like most, if they would recommend it to a friend with insomnia.

12) The System Usability Scale (SUS) is the 10-item non-specific questionnaire used to collect a user’s subjective rating of a product’s (products, websites, applications, hardware, or software) usability and learnability. Each item is scored on a scale of 0 (“strongly Disagree”) to 5 (“strongly Agree”).

13) General information will be requested at baseline: age, sex, education, social status, duration of CI, sleep aids if any.

3.2. ASSESSMENT POINTS

Assessments will take place at weeks 0 (T0 - baseline), 8 (T1 - post-treatment), and 20 (T2 - follow-up) for both groups and additionally at week 28 (T3 - post-treatment) for the control group participants who will complete the follow-up assessment and subsequently offered the iCBT-I program.

(T0) Baseline assessment at Qualtrix: general questions, ISI, BDI, BAI, SF-12, FSS, ESS, SHI, DBAS, LCS, TiC-P, PID, success expectancy. Sleep diary data (SOL, TST, SE, WASO, number of awakenings and sleep quality) will be derived from Sleepsy for iCBT-I + CAU group and from Qualtrics for CAU group

(T1) Post-treatment: ISI, BDI, BAI, SF-12, FSS, ESS, SHI, DBAS, LCS, TiC-P. Sleep diary data (SOL, TST, SE, WASO, number of awakenings and sleep quality) will be derived from Sleepsy for iCBT-I + CAU group and from Qualtrics for CAU group. Additionally iCBT-I + CAU will answer the questions of SUS and user satisfaction

(T2) follow-up: ISI, BDI, BAI, SF-12, FSS, ESS, SHI, DBAS, LCS, TiC-P. Sleep diary data (SOL, TST, SE, WASO, number of awakenings and sleep quality) will be derived from Sleepsy for CAU group and from Qualtrics for iCBT-I + CAU group.

(T3) post-treatment for CAU group: ISI, BDI, BAI, SF-12, FSS, ESS, SHI, DBAS, LCS, TiC-P, SUS and user satisfaction. Sleep diary data (SOL, TST, SE, WASO, number of

awakenings and sleep quality) will be derived from Sleepsy for iCBT-I + CAU group and from Qualtrics for CAU group.

No payment for the participants will be provided

4. INTERVENTION.

Internet-based CBT-I (Sleepsy©) consists of interactive educational material divided into eight modules and explaining homeostatic and circadian mechanisms of human sleep regulation, the pathogenesis of CI, and its daytime consequences. Information is presented in the form of short 10-min videos.

Module 1: Introduction into the program structure and motivation for the program (statement that CBT-I is the treatment of choice for insomnia). Introduction of a sleep diary.
Module 2: Psychoeducation: Information about sleep regulation and sleep hygiene.
Module 3: Sleep Restriction: Stepwise reduction of time in bed (to min. 6 h) to increase sleep pressure based on the sleep diary that patients fill in since the beginning of module 1. If sleep efficiency is above 85%, participants can increase time in bed for 15 min.
Module 4: Sleep hygiene and stimulus control: Information on sleep-inhibiting substances, sleep-wake-rhythm, evening rituals, physical exercise, etc., as well as information on the principle of stimulus control with the aim of re-associating the bed with sleep.
Module 5: Progressive Muscle Relaxation (PMR) based on Jacobson with audio tape and written instruction to download.
Module 6: Cognitive restructuring: Identifying, reexamining and changing dysfunctional thoughts about sleep and the consequences of insomnia.
Module 7: Relapse prevention: what to do to prevent sleep disorders or when the sleep disturbances come back, when to seek medical help and what are the conditions of safe pharmacotherapy for insomnia.
Module 8: Repetition and end.

The program includes a sleep diary in which participants insert data on their bedtime and waketime, sleep latency, total sleep time, and night awakenings. The data entered into the sleep diary are then presented in form of graphs. Furthermore, various exercises serve to put what is learnt into practice. Participants have time to repeat, deepen and apply modules, exercises and examples in their everyday life at their own pace, i.e., the participants are free to choose when and how often they process the modules and whether they process them in one piece or in several stages. Patients will get behavioral instructions based on their questionnaires, sleep diary, and answers in the interactive part of the program. A sleep window will be proposed depending on the preferred wake-up time and average total sleep time over the last 7 days. If the sleep diary indicates a sleep efficiency of 85% or higher for the previous week, the participant will be encouraged to add 15 min to the sleep window. If it does not reach the 85%, recommended sleep window will be decreased based on the preferred wake-up time and average total sleep time over the period of observation. If the sleep efficiency falls between 80% and 85% sleep window will remain stable otherwise (sleep efficiency > 85%) it can be extended by 15 min. All material will be delivered through the internet program and expected to be elaborated by the patients themselves but with the opportunity to contact a psychologist or somnologist within the program (guidance on request) in a secured environment

The program was elaborated by M.G.Poluektov, M.D., Ph.D., associate professor, Sechenov university. M.D., D. R.V.Buzunov, M.D., Ph.D. P.V. Pchelina.

Owner and producer of iCBT-I course “Sleepsy” is LLC Technomarkt, Medical license № ЛО-77-01-015518 22.01.2018.

4.1. CONCURRENT THERAPY

Both groups will have access to CAU. Interventions that are part of CAU may be assigned within the first visit to a referring doctor or at any point of the study on a next doctor visit. All concurrently applied treatments will be assessed repeatedly by selfreport.

4.2.1. RESTRICTER CONCURRENT THERAPY

not applicable

5. SAMPLE SIZE.

110 patients with CI will be recruited through referrals from health care practitioners, i.e., neurologists specialized in somnology.

6. RECRUITMENT CENTRES

Sleep medicine department, University clinic 3, Sechenov First Moscow State Medical University, Moscow). Rossolimo, 11/1, Moscow, Russia. Phone: 8-499-248-69-68

Expected number of participants – 40

Stavropol regional clinical sleep centre. Dzerjinskogo, 2/1 – 7, Stavropol region, Stavropol. Phone: 8 (865) 293 07 09

Expected number of participants – 15

Outpatient clinic of GAUZ "Kuzbass clinical hospital for veterans” Fiftieth anniversary of October, 10, Kemerovo, Kuzbass. Phone: 8 (3842) 58-26-70

Expected number of participants - 20

7. SELECTION OF PARTICIPANTS.

7.1. INCLUSION CRITERIA

1. Age between 18 and 80 years
2. Sleep disorder matching CI criteria (International Classification of Sleep Disorders-3) — assessed by clinical judgement
3. Ability to follow the procedures of the study, fluent Russian language, good access to internet — assessed by self-report

7.2. NON-INCLUSION CRITERIA

1. Presence of dementia (identified by history or a score < 25 on the Folstein Mini Mental Status Exam) — assessed by clinical judgement.
2. Severe depression or severe anxiety as measured with the Beck Depression Inventory (BDI-II; score > 28) and the Beck Anxiety Inventory (BAI; score > 25)—assessed by the questionnaires.
3. History of severe psychiatric comorbidities other than anxiety and depression (bipolar disorders, psychotic disorders) or substance use disorder—assessed by self-report and clinical history.
4. Untreated severe obstructive sleep apnea syndrome (apnea-hypopnea index [AHI] > 15), restless legs syndrome (movement index with arousal > 15 per hour) or other sleep disorders affecting night sleep—assessed by clinical judgement and clinical history.
5. Pregnancy, lactation—assessed by self-report.
6. Having a serious somatic condition or brain disorders (stroke, Parkinson's disease, etc.) preventing further participation— assessed by self-report.
7. Having high suicidality risk—assessed by clinical judgement, high total BDI-II score (>28) or score >1 on a BDI-II of suicidality subscale.

7.3. EXCLUSION CRITERIA

1. Refusal of the further participation;
2. Pregnancy
3. Exacerbation of Anxiety or depressive disorder as measured with the Beck Depression Inventory (BDI-II; score > 28) and the Beck Anxiety Inventory (BAI; score > 25)—assessed by the questionnaires at any timepoint
4. Increase of suicidality risk — as measured with BDI-II suicidality subscale score >1 at any timepoint

8.SAFETY ASSESSMENT

8.1. SAFETY ASSESSMENT MEASURES

The referring specialists will explain to each 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, voluntary participation, withdrawal from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment. After eligibility assessment, potential participants will receive a participant information sheet and a consent form. The informed consent (IC) is compiled in accordance with the National Standard of the Russian Federation for Clinical investigations and good clinical practice (GOST R ISO 14155- 2014) for the creation of an IC for information transfer. Each participant will have seven days to decide whether to

participate or not. After returning the signed IC, each participant will receive a copy of the IC signed by the authorized investigator.

The investigated method is not associated with serious adverse events. In order to avoid severe tiredness we have chosen more lenient minimal time in bed of 6 h. In the program, the caution to avoid severe sleep deprivation is made for elderly patients and for those who have duties in which drowsiness may be a danger to the patients themselves or others. These patients are recommended to flexibly extend sleep window.

8.2. RISKS FOR WOMEN OF CHILDBEARING POTENTIAL.

None

8.3. RISKS FOR MEN OF REPRODUCTIVE ABILITY

None

8.4. UNDESIRABLE EVENTS AND UNDESIRABLE EFFECTS OF THE METHOD UNDER INVESTIGATION

We will assess depressive and anxiety symptoms with the BDI and BAI as a safety outcome at all times of data collection, i.e., as part of the initial screening, during and after the intervention, as well as at the follow-up measures. Severe depression and anxiety are defined as BDI-II scores > 28 and BAI scores > 25, accordingly. If scores are higher than these cutoffs at the time of the screening, the person concerned will not be admitted to participate in the study and will be referred to a suitable authority such as a psychotherapist, a psychiatric clinic, or a hospital. Should this occur during another time throughout the study, participants will also be given information on suitable institutions to turn to and asked to inform the contact person for emergencies named by them at the beginning of the study. Furthermore, participants receive a weekly individualized automated e-mail during the intervention, acknowledging their progress and offering help if they encountered difficulties with the program. Persons who had to be directed to psychiatric/psychotherapeutic services will be contacted by the study team as soon as possible to assure that they are in professional care.

8.4.1. Procedure of documentation and report of adverse events

All adverse events arised during the study will be documented and reported to the local ethics commitee. All adverse events will be additionally analyzed

8.5. SUBSEQUENT MONITORING AFTER SERIOUS ADVERSE EVENTS

In the case of serious adverse events causing drop-out of a participant. This participant will be directed to psychiatric/psychotherapeutic services will be contacted by the study team as soon as possible to assure that they are in professional care. Subsequent monitoring of participants completed the study or dropped out is not provided.

9. STATISTICAL ANALYSIS

9.1. SAMPLE SIZE CALCULATION

We aim to detect a small to medium between-group effect size (Cohen's d) of 0.35 at post-treatment. The chosen effect size is reasonable since CAU being an active alternative treatment may decrease between-group outcome differences and a smaller effect size was considered to be irrelevant from a clinical point of view. Based on a-level of.05 and a power of.95 using a single-level repeated measures ANOVA power analysis with G*Power, the sample size needed is approximately 55 participants per group and 110 for the total sample. Our secondary aim is to find outcome predictors within participants who complete iCBT-I. In order to enlarge this sample, participants from the CAU group will get access to the iCBT-I program after the follow-up period

9.2. STATISTICAL ANALYSIS OF EFFECTIVENESS

The main analyses will be conducted on the intention-to-treat sample. Clinical effects of treatment will be evaluated using mixed-model repeated-measures analyses where the pre-post comparisons of all outcome measures will include time as a within-group variable and the condition as a between-group variable. An incremental cost-effectiveness ratio (ICER) will be calculated to obtain the additional costs of iCBT-I in comparison with control condition. Cohen's d will be reported for all within-between comparisons based on estimated means and the pooled standard deviation from the observed means at pre- and posttreatment. To test significance of the difference between the number of responders in each treatment condition, we will use X2-test. Regression analyses will be used to identify predictors of treatment outcome. We will test models using Akaike/Bayesian Information Criteria to select an optimal model with predictors of treatment outcome.

9.3. SAFETY DATA ANALYSIS

All adverse events arised during the study will be documented and reported to the local ethics commitee. All adverse events will be additionally analyzed. There are no statistical criteria for the study termination. The study has been approved by the local ethics committee of the I.M. Sechenov Moscow Medical University (No. 03-20/19.02.2020) and has been prospectively registered in ClinicalTrials.gov Protocol Registration and Results System (Identifier: NCT04300218 21.04.2020).

10.RESEARCH PLAN

10.1. RESPONSIBILITIES OF RESEARCH CENTRE

- Selection of participants in accordance with inclusion and non-inclusion criteria
- Carrying out the procedure of informed consent form signing
- Timely transferring participants data to the primary investigator (PI) and sub-investigators (SI).
- Providing assistance to participants during baseline online assessment and completion sleep diaries.

- Documentation of enrollment of participants, procedure of informed consent form signing, adverse events if any.
- Timely notice PI of adverse events.

10.2. DEVIATIONS FROM THE RESEARCH PLAN

All deviations from the research plan will be registered and justified. PI is responsible for notifications local ethical committee and the relevant authorities and will be notified about these deviations.

10.2.1. Corrections of the research plan

All corrections of research plan will be agreed with PI, registered and justified. Inclusion of additional clinical centres, SIs and research methods will be agreed with the PI and the local ethical committee. The deviations from the research plan will be analyzed in order to make a decision about possible corrections of the research plan or termination of the research.

10.3. ADVERSE EVENTS AND UNDESIRABLE EFFECTS OF THE INVESTIGATED METHOD

The local ethical committee will be timely notified about serious adverse events and serious undesirable effects of the investigated iCBT-I course.

10.4. EARLY STUDY TERMINATION OR SUSPENSION

The PI, local ethical committee or relevant authority is authorized to preliminarly terminate the study or suspend it in a particular clinical centre or in all clinical centres for significant and documented reasons. If an unacceptable risk for participants is suspected during the clinical study or serious and/or multiple deviations are revealed or if it is mandated by the local ethical committee the PI should suspend the study until its risks will be reevaluated. In case of an early study termination or suspension the PI should timely notify all participating entities and SIs. In case of an early study termination further monitoring of participants is not provided.

11. POSSIBILITY OF PUBLISHING THE RESULTS OF STUDY

Coded personal data of the participants (without specifying the last name, first name and other personal data) derived from Qualtrics and Sleepsy can be used for further statistical analysis and publication of results. The study has been registered in ClinicalTrials.gov Protocol Registration and Results System (Identifier: NCT04300218 21.04.2020). and the protocol of the study was published in a peer-reviewed journal. Results of this trial will be disseminated via peer-reviewed journal publications. Primary and secondary aims will be reported in a single publication. Other findings will be published separately. The results of this study will also be available on the ClinicalTrials.gov website when they become available.

12. INFORMED CONSENT FORM (ICF)

Informed consent is obtained during the procedure of the informed consent form signing with the personal signature and date. The informed consent form prepared in conformity with requirements Rules of Good Clinical Practice of the Eurasian Economic Union approved by Decision of the Eurasian Economic Commission No. 79 dated 3 November 2016. Participants of the study also sign the consent to process personal data, prepared in conformity with Federal Law dated 27 July 2006 N 152-FL (ed. dated 31 December 2017) "On Personal Data".

13. WORK WITH DATA AND DOCUMENTATION.

Personal data of participants of the study obtained at online platform Qualtrics are coded. Participants enter their name and surname solely during the procedure of informed consent form signing. Further communication with them is carried out through the emails. Access to the identification codes of participants will be password secured. Signed informed consent forms will be stored in the PI office. The data retention period is 10 years after completion of the study.

14. FUNDING AND INSURANCE

Work on the protocol is supported by ESKAS Swiss Government Excellence scholarship 2019-2020

15. PRIVACY

Personal data of participants of the study obtained at online platform Qualtrics are stored in depersonalized form. When a new participant is registered in the system only their email and identification code are entered. Identification of a participant is possible when matching individual code with email in Qualtrics and email with name and surname in the ICF. Access to the identification codes of participants in Qualtrics will be password secured; signed informed consent forms will be stored in the PI office. Data collected within iCBT-I program (Sleepsy) will be stored храниться on the password secured server. Privacy of the participants of the study will be protected by existing laws and regulations of Russian Federation. All the data of study participants obtained from medical records will be treated as confidential information. Participants have a right to have access to information on their state of health. Name, surname and other uncoded personal data will not be published in the study reports and publications.

16. TIMEFRAMES OF THE STUDY

- Study approval at a Chair of neurology of Sechenov University meeting 26.11.2019
- Study approval by local ethical committee – February 2020
- Experimental part of the study – February 2020 – December 2021:

- Start of data collection – February 2020;
- Inclusion of two additional clinical centres - February 2021;
- Completion of data collection - December 2021;
- Statistical analysis, publication of results – January-February 2022

17. COMPLIANCE WITH THE REQUIREMENTS OF CURRENT LEGISLATION

Study protocol is elaborated in accordance:

- GOST R ISO 14155-2014 Clinical investigation of medical devices for human subjects – Good clinical practice (ISO 14155:2011, IDT) dated - 2015-06-01
- Essential Principles - Global Harmonization Task Force, 1999
- Federal Law «on personal data» dated 27 July 2006 № 152-FL;
- Order of Ministry of Public Health of RF dated 1 April 2016 № 200н « On Establishing the Rules for Good Clinical Practice »;
- Rules of Good Clinical Practice of the Eurasian Economic Union approved by Decision of the Eurasian Economic Commission No. 79 dated 3 November 2016
- GOST R 52379-2005 «Good clinical practice», approved with the order Federal Agency for Technical Regulation and Metrology dated 27 September 2005 № 232-ст;
- Resolution of the State Commission for Academic Degrees and Titles Высшей аттестационной комиссии « On the biomedical research in humans», published in the State commission newsletter (2002, № 3);

18. REFERENCES

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The study corresponds to the passport of scientific specialty

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