

# The effects of computer-assisted cognitive-behavior therapy as an adjunct to enhance postoperative recovery during perioperative period: study protocol for a randomized controlled trial

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## Study protocol

**Keywords:** Computer-assisted Cognitive Behavior Therapy(CCBT), surgery, anxiety, depression, insomnia , postoperative pain, psychosomatic symptom, functional Near Infrared Spectroscopy(fNIRS)

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# Abstract

Background: Some serious surgeries may pose likelihood of developing complications such as anxiety, depression, insomnia, chronic pain, which may aggravate discomfort, impair quality of life and even increase mortality after surgery. Non-pharmacological mind–body interventions for psychosomatic symptom is are an area of growing interest. CBT is the most recommended treatment for anxiety, depression, insomnia and pain. However, access to trained therapists is limited. A growing amount of research is producing effective evidence of CCBT. But , CCBT used for surgery patients have been not reported at present, and the effectiveness and feasibility have been not research ed and validated too. The primary aim of this trial is to explore targeted psychotherapy technique based on CCBT for surgical patients and assess the effectiveness and feasibility of the newly developed software of CCBT-Prs to improve anxiety, depression, insomnia and postoperative pain as an adjunct to UC by subjective and objective indexes.

Methods and analysis : It is a prospective, multi-centers, randomized controlled superiority trial which comprises two parallel groups (CCBT-Prs +UC and UC alone) . Participants who has been scheduled for surgery will be randomized to either of the two groups : (1) receiv ing CCBT- Prs software intervention based on UC as trial group (2) receiving UC intervention only as control group. All participants will undergo assessments using STAI-S, PHQ-9, AIS and VAS-Pain-10 at various time points in the perioperative period. Blood samples will be collected at baseline and pre - anesthesia to assess for Stress hormone markers(Cor and ACTH). Functional near infrared spectroscopy( fNIRS) will be applied to evaluate brain function before and after intervention.

Discussion: Some difficulty is inevitable and encountered in all clinical trials. The ultimate aim is that mental health services benefit more non-psychiatric inpatients. CCBT can have more wider dissemination and implementation in mental health. Ethics and dissemination : This study has been approved by Ethics Committee of First Hospital of Shanxi Medical University in China. Research findings will be disseminated in the form of at least one peer reviewed article and presentations at conferences. Trial registration: Chinese Clinical Trial Registry (ChiCTR)( [www.chictr.org.cn](http://www.chictr.org.cn) ) ChiCTR1900025994 . Registered on 17 September 2019. <http://www.chictr.org.cn/ChiCTR1900025994>.

## Introduction

With diagnosis and treat techniques developed and the spectrum of diseases changed, hospital surgeries volume has been large and growing fast in the whole world,<sup>1</sup> especially in China.<sup>2</sup> Surgery is a source of stress leading to easily anxiety and tension for patients scheduled for surgery. The source of stress may be future uncertainty, ignorance of surgery and anesthesia, overstating postoperative discomfort and pain, fear of death and so on.<sup>3</sup> Psychological factors and physical discomfort affect each other. Over anxiety may be cause violent fluctuations in vital signs,<sup>4</sup> sleep disorders,<sup>5</sup> aggravation of pain,<sup>6</sup> immune function decrease,<sup>7</sup> even cognitive impairment<sup>8</sup> and postoperative delirium.<sup>9</sup> It is found that perioperative anxiety and depression have been associated with increased mortality after cardiac

surgery.<sup>10</sup> It is generally known that pain has become a side effect for most surgery and someone may be suffered from chronic postoperative pain, especially incidence of orthopedic / trauma patients up to 57%.<sup>11</sup> Over anxiety as the most common negative emotional factor was a predictor to lead moderate and severe pain after operation(72%).<sup>12</sup> The pain and other physical discomfort by surgery can interfere with sleep during postoperative recovery, and prior insomnia in patients increases the risk of postoperative sleep problems.<sup>13</sup> It is found that general anesthesia can lead to sleep rhythm disorder and / or the change of biological clock gene, which can change the sleep structure and sleep quality of postoperative patients, so that it may increase the incidence of postoperative complications, such as postoperative delirium, postoperative cognitive dysfunction, immune suppression, cardiovascular adverse events and so on.<sup>14</sup> Moreover, patients with insomnia often complain that disturbances of mood and cognitive abilities is always accompanying by different levels of anxiousness, fatigue, pain and physical discomfort.<sup>15</sup>

As a result of these complications, not only the length of hospital stays and average hospitalization expenses were extended, but also patients have worse surgical experience and satisfaction.<sup>16</sup> Fatma Celik et al think that it is valuable for surgeons to gain a better understanding of how to identify and reduce surgical anxiety in their patients.<sup>17</sup> We hope to find some ways that *are easy, cheap, harmless and standardized* to identify and relieve psychosomatic symptom of patients during the perioperative period.

### **Non-pharmacological interventions for psychosomatic symptom- CBT**

The ways to reduce psychosomatic symptom for surgical patients are mostly medicine which is effective, but have the side effects. Relative to drug therapy, non-pharmacological interventions have obvious advantage and consist of Cognitive behavior therapy (CBT), Musical therapy<sup>18</sup>, Massage therapy, peri-operative education, Mind–body interventions <sup>19,20,21</sup>and even preoperative meeting of Multidisciplinary Diagnosis and Treatment (MDT)<sup>22,23,24</sup> A meta analysis found moderate quality evidence that cognitive behavioral therapy, relaxation therapy, or both are more effective reducing persistent post surgical pain and physical impairment than peri-operative education.<sup>6</sup> Cognitive behavior therapy (CBT) is the common psychotherapy to help change both negative emotions and body response by altering unsuitable thoughts.<sup>25</sup> Dao TK et al found that CBT is both feasible and acceptable to improve symptoms of depression/anxiety for patients undergoing artery bypass graft (CABG) surgery. Most important, it can improve quality of life and reduce in-hospital length of stay.<sup>26</sup> CBT for insomnia (CBT-I) has been shown many advantages and effects than long-term drugs treatment of primary insomnia, which was identified as the most commonly used treatment for insomnia by National Institutes of Health(NIH).<sup>27</sup> In a review of orthopedic surgery about non-pharmacological sleep aids reducing post-operative pain, CBT-I as a non-pharmacological sleep aid, has been shown to increase the quality of sleep and sleep time, decrease pain, and help patients maintain those gains<sup>28</sup>.

### **CCBT for psychosomatic symptom of physical illness**

Although CBT is effective and suitable for surgery patients, however, there are barriers to implementation of psychotherapy, such as time and travel burden for patients to attend face-to-face sessions, shortage of

adequately trained therapists, high costs, potential stigma associated with seeking professional help, and lack of accessibility in remote areas.<sup>29,30,31</sup> These limitations may be overcome by computerized interventions like computer-assisted cognitive-behavior therapy (CCBT), which is self-directed without a therapist and implemented by using a computer or smart-phone.<sup>32</sup> CCBT as a supplementary option is the most extensive research and application method for psychological problems. Relative to other psychotherapy, CCBT has the advantages of simple operation, structured format and problem-oriented.<sup>33</sup> Moreover, it is accepted easily by users, costed lowly and convenient for data collection, which promotes the application of computer in the field of psychotherapy.<sup>34</sup> There are many CCBT platforms widely used in the treatment of anxiety disorder, depression, insomnia and verified by large experimental data. For example MoodGYM, Beating the Blues, Good days Ahead. But, effectiveness of the results were inconsistent.<sup>33,34,35</sup> Another type of CCBT platform is developed to solve psychological problems for people with chronic physical health problems, for example MS Invigor8 for multiple sclerosis fatigue,<sup>36</sup> HARUToday for cancer patient anxiety and depression.<sup>37</sup> All the above studies suggest that the software developed to solve emotion problems aiming at physical health problems is more effective, the compliance is better and the dropout rate is lower than the CCBT platforms for depression or anxiety.<sup>36,37</sup> While, there is a lack of a CCBT software package targeted, practical and standardized measures for the intervention of negative emotion and associated insomnia and pain problems for surgery patients under the specific stress factor. Therefore, a set of CCBT software package named Psychosomatic Regulation System in peri-operative period (CCBT-Prs) has been designed by the research team of multidisciplinary professionals in the first stage of this study. The professional draft of software package was designed and finished in the team of Surgical Care Specialist and Mental Health Clinical Specialist. The computer program was programmed and improved with the help of some technical corporation. The second stage of this study is to test the effectiveness of the CCBT-Prs software package in improving psychosomatic symptom. This paper will mainly introduce a research protocol that evaluate effectiveness of the CCBT-Prs software package as an adjunct to enhance postoperative recovery for surgery patients. If results are positive, it would demonstrate the potential to become a routine and cost effective adjunct to enhance postoperative recovery. Research into mechanisms of treatment outcome in cognitive behavior therapy (CBT), as work evaluating potential mechanisms through mediator and moderator analyses, has been increasing. More refined analyses of functional components of treatment wish to be finished to provide important insights for clinicians in refining treatment programs.<sup>38</sup>

## **Objectives {7}**

The trial has two main objectives:

1. To test the clinical efficacy of the CCBT-Prs software package as an adjunct Usual Care(UC) compared to UC alone.
2. To explore targeted psychotherapy for surgical patients at higher risk for poor outcome and explanatory mechanisms of action for CCBT.

The trial hypotheses are:

1. a) CCBT-Prs software package will be more effective in reducing anxiety, depression, insomnia and postoperative pain for surgery patients in comparison to UC.
2. b) The mediators of treatment effects for CCBT on changes may be beliefs about disease, character trait, social support, attribution mode, the response to disease.

### **Trial design {8}**

This study is a prospective, randomized, controlled, assessor blinded, multicenters, superiority trial with two arms, including one experimental arm and one control arm. The study population will be independently randomized to receive either 5 sessions of CCBT-Pre +UC or alone UC (see Fig. 1).

Fig. 1 for a Consolidated Standards of Reporting Trials diagram of the study design.

## **Methods: Participants, Interventions And Outcomes**

### **Study setting {9}**

This study will be conducted at First Hospital of Shanxi Medical University, Shanxi Provincial Cancer Hospital and Shanxi Cardiovascular hospital in China. The research institutes are Grade 3A General Hospital and Grade 3A Specialized Hospital.

### **Eligibility criteria {10}**

**Inclusion criteria** for this study include aged 18-60 years, having been scheduled surgery within a week. The patients will be given general anesthesia. The median length of hospital stays was  $10 \pm 3$  days. Patients can read, understand and communicate in Chinese.

**Exclusion criteria** include psychosis, organic mental disorder, or current high risk of suicide, substance abuse or dependence within the 12 months prior to enrollment, antisocial personality disorder or unstable medical condition. Patients was postponed operation for more than a week or changed to emergent surgery will be excluded. Patients who are currently enrolled in another intervention study that could potentially impact the primary outcome will also be excluded from the study.

All participants will be evaluated by two researchers (a therapist and a nursing graduate students) who will also verify patient diagnosis and eligibility.

### **Who will take informed consent? {26a}**

Individuals will be identified and confirmed from surgical plan lists by the Electronic Medical Record System. All participants will be evaluated by two researchers (a therapist and a nursing graduate students) who will also verify patient diagnosis and eligibility. Once a candidate is eligible for enrollment, he or she will be approached by researcher to discuss the study in detail. Before initiation of any study

procedures, written informed consent will be obtained according to the ethical requirements. As all participants will continue to be treated by their doctor in charge, participants will be required to obtain permission from their doctor practitioners prior to study enrollment.

### **Additional consent provisions for collection and use of participant data and biological specimens {26b}**

At the same time blood bio-markers, fNIRS as objective markers could not involve and analyzed for each subject because of trauma and individual will. Additional consent provisions for collection has been written in informed consent. If participant would like to consent and will receive a small amount of cash compensation after the end of the test .

### **Interventions**

#### **Explanation for the choice of comparators {6b}**

#### **UC (Usual Care)**

Patients in the control group will undergo surgery and subsequent hospital stay according to the conventional treatment. Program schedule is the same as the routine of care. Participants will be permitted to continue using hypnotics or analgesic during the study period. There will be no restrictions on treatment options for participants who receive treatments from their doctors in charge. All changes in conventional treatment, along with the reasons for those changes, will be recorded throughout the study period. Perioperative diseases and psychological care routine will be carried out in accordance with Perioperative Care Manual and consensus on ERAS.<sup>39</sup> All surgery patients were assessed and screened using Psychological Experience Scale 1,2 like any other patients on admission. Once mild to moderate emotional problems are identified, regular psychological support will be provided by a therapist. Severe emotional problems are consulted further by psychiatrists.

#### **Intervention description {11a}**

##### **CCBT-Prs software package**

CCBT-Prs is a computer program that includes registration, evaluation, and therapy. The program was designed and developed five times treatments which are scheduled before and after surgery. This program is so simple and standardized that non-psychological personnel can be competent for this work that assist patients with treatment lasting about 20 minutes. Firstly participants are enrolled some information through the program and are informed the use of the software. As soon as registration, first assessment (A1) and treatment (T1) will be completed soon. The module of treatment in the program include cognitive therapy, cognitive consolidation and behavioral relaxing therapy. The primary components of cognitive therapy module include the following: (1) Preoperative psychological preparation. (2) Preoperative physical preparation and introduction of surgical environment. (3) Management of postoperative pain, insomnia and Anti-thrombus. (4) Postoperative exercise and diet. (5) Education of post-discharge. The behavioral therapy module includes relaxing training, such as Imaginative Relaxing Exercise, Progressive Muscle Relaxation, Breathing Exercises, Relaxing Sleep

Exercise, Mindfulness Meditation Body Scan. Homework is shown to answer questions in the form of a game, and the questions are a review of the previous cognitive therapy module. The cognitive therapy module and behavioral therapy module are presented by video form. Surgery patients who were selected and randomized grouping to CCBT-Prs intervention group will access to assessment and intervention from the software package.

### **Criteria for discontinuing or modifying allocated interventions {11b}**

Patients was postponed operation for more than a week or changed to emergent surgery will be excluded or discontinue interventions.

The study intervention is non-invasive, so it carries minimal risk. But participants are undergoing high-risk surgery, it is expected that they may encounter several adverse events unrelated to the study intervention during. An adverse event may be consisting of any unfavorable and unexpected sign, symptom or discomfort temporally associated with this study. All adverse events will be reported, and serious adverse events will be immediately reported to the Institutional Research Ethics Committee of First Hospital of Shanxi Medical University. An adverse event includes changes in the patient's depression. PHQ-9 will be monitored and reported and once suicide idea were perceived, the participant will be dropped out of the study for further

clinical evaluation and management.

### **Strategies to improve adherence to interventions {11c}**

A researcher in the research group specifically intervened the subjects with specialized tools and comfortable room rooms to improve the comfort of interventions. Making an appointment in advance and keeping track of the treatment progress of the subjects greatly increase the adherence and completion rate of the intervention.

### **Relevant concomitant care permitted or prohibited during the trial {11d}**

Patients in the control group will undergo surgery and subsequent hospital stay according to the conventional treatment. Program schedule is the same as the routine of care. Participants will be permitted to continue using hypnotics or analgesic during the study period. There will be no restrictions on treatment options for participants who receive treatments from their doctors in charge. All changes in conventional treatment, along with the reasons for those changes, will be recorded throughout the study period. Perioperative diseases and psychological care routine will be carried out in accordance with Perioperative Care Manual and consensus on ERAS.<sup>39</sup> All surgery patients were assessed and screened using Psychological Experience Scale 1,2 like any other patients on admission. Once mild to moderate emotional problems are identified, regular psychological support will be provided by a therapist. Severe emotional problems are consulted further by psychiatrists.

## Provisions for post-trial care {30}

The study intervention is non-invasive, so it carries minimal risk.

## Outcomes {12}

### Outcomes

#### Baseline and clinical characteristics

Baseline characteristics will include gender, age, education, marital status, employment status, main diagnosis, operation method, anesthesia. Moreover, treatment history will include past medical history, other prior treatments, current treatment (medication and others) at baseline and all changes in conventional treatment throughout the study period. At the same time, the factors that personality characteristics, social support, disease coping that may affect therapeutic outcome are assessed and collected at baseline. The most important of all, the baseline of anxiety, depression, pain, insomnia for participant are assessed and collected.

#### Primary outcome

The primary outcome of the study is exploratory to assess effects of the intervention on anxiety, depression, pain and sleep. The outcomes include both psychological and physiological. A trained research team member who remains blinded to treatment allocation will perform baseline anxiety, depression, pain, and insomnia assessments. **The Chinese version of State-Trait Anxiety Inventory (STAI)** which attempt respectively to measure transient and enduring levels of anxiety.<sup>40</sup> It is noteworthy that we used a state scale (STAI-S) in State Trait Anxiety Inventory (STAI) for the assessed instruments. Its Cronbach-a (estimated reliability) values are 0.89 and responses to the 20 statements on the STAI-S form are used to determine the current anxiety level of the patient.<sup>40</sup> The STAI-S forms require respondents to rate their agreement with each statement using a scale from 1 to 4 representing not at all, somewhat, moderately and very much, respectively. The total score on the scale ranges from 20 to 80 points wherein higher scores reflect higher anxiety.<sup>41</sup> Past studies display that a score of 37 for state anxiety was set as the cutoff and considered to be a clinically significant state of anxiety.<sup>42-43</sup>

**Patients Health Questionnaire Depression Scale-9 item (PHQ-9)** is a self-report questionnaire. The questionnaire is used to diagnose major depressive disorder (MDD) by nine diagnostic criteria and is based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).<sup>44</sup> Several studies validated the performance of PHQ-9 to screen for depression in primary care, including of its brevity and easy.<sup>45-46</sup> In a study at home, the Chinese version of PHQ-9 was shown to have good reliability and validity in general hospital inpatients. The internal consistency values and test-retest reliability values of PHQ-9 was 0.839 and 0.846.<sup>46</sup> 5, 10, 15 points were respectively recommended as cut points different levels by the scale developers.<sup>47</sup>

**Athens Insomnia Scale (AIS)** was developed by Soldatos and colleagues to assess the severity of insomnia based on the ICD-10 diagnostic criteria and it is an 8-item self-report questionnaire that estimates sleep difficulty in the past month.<sup>48</sup> Each item of AIS can be rated 0~3, with 0 corresponding to no problem at all and 3 to very serious problem. The sum of each item adds up to is the final sleep assessment score. Higher scores indicate greater severity of Insomnia symptom-ology. It has become a standard scale for evaluating insomnia recognized by the international medical community because of its accuracy and easy.<sup>49</sup> Soldatos in the study suggests that a cutoff score of 6 correctly distinguishes between insomnia patients and controls in 90% of cases.<sup>49</sup>

**Visual analogue Scale-pain-10(VAS-pain-10)** is a line to describe pain from 'no pain' to 'worst imaginable pain'. Subjects are asked to place a mark along the 10cm long line to indicate the intensity of their pain. The distance between the 'no pain' anchor to this mark is then measured and denotes the pain intensity Score, the higher the score, the more severe the pain.<sup>50</sup> Pain medication intake in the first 48 h postoperative will be ascertained and recorded from the medical record.

## **Secondary outcomes**

To assess study feasibility, we will evaluate compliance to the study protocol. Adherence to the interventions schedule will be assessed by calculating drop-out rates. For example, the difference that total number of participants in the CCBT group less total number of people who have finalized the entire process of CCBT divide by the total number of participants in the CCBT group.

Another evaluation indicator is satisfaction survey about personal feelings of interventions program, and the brief satisfaction survey was designed by ourselves. At the day of discharge or if a participant withdraws from the study, the individuals will be asked to complete a brief satisfaction survey. This survey asks about the patients' satisfaction of their body health, mental health and taken care overall in the perioperative period. Participants randomized and grouped will be asked about their experience completing practices, as well as a future study design will consider their feedback related to the study intervention.

At present, the treatment effect of CBT is mainly assessed by the scale. However, the results of the scale are subjective and limits the understanding of the biological mechanism of CBT. Compared with the evaluation results of the scale, biological markers are more objective, which is helpful to further explain the biological mechanism of CBT.<sup>51</sup>

## **Vital signs**

The psychological state before and after operation often affects the stability of vital signs of patients.<sup>4</sup> The values of Blood Pressure(BP) including of Systolic Pressure(SP) and Diastolic Pressure (DP) and Heart Rate(HR) are collected and recorded at 7 A.m during the intervention period. The effectiveness of the intervention can also be demonstrated by connecting the data together to observe the stability of the curve.

## Brain function

Functional near infrared spectroscopy(fNIRS) will be applied to evaluate brain function before and after intervention. Cerebration in the cerebral cortex are observed and recorded by concentration changes local blood Oxygen (Oxy - Hb, Deoxy - Hb, total-Hb) including the prefrontal cortex and bilateral temporal lobes cortex. Near-infrared spectroscopy(NIRS) is a technology that can fire near-infrared light through the surface of an organism,using near-infrared light to be absorbed by hemoglobin in the cerebral cortex to detect of blood oxygen in the cerebral cortex. The technology can detect the changes of cerebral blood volume in the range of 2~3cm from the epidermis of the head and capture brain activation response easily.It is also known as“fNIRS”functional NIRS”,“Quantitative imaging of brain function”. Prefrontal cortex is key brain region affecting mood and cognition function.<sup>52</sup> The participants decide whether or not to conduct fNIRS before and after intervention according to their wishes. Finally, the content of Oxy - Hb, Deoxy - Hb, total-Hb will analyzed as brain function markers to find characteristic of function change before and after intervention.

## Stress bio-markers

Ableson et al found that Cognitive intervention can significantly reduce the concentration of Adrenocorticotrophic Hormone (ACTH) and Cortisol (Cor) in the patients by adjusting the function of Hypothalamic-Pituitary-Adrenal (HPA) axis.<sup>53</sup> Blood will be collected to investigate whether CCBT results in a favorable modulation of stress bio-markers such as ACTH and Cor. Blood sample collection for CCBT group will occur at baseline and before anesthesia. At each time, approximately 5 cc will be collected. Then ACTH and Cor will be tested and analyzed by Laboratory.

## Participant timeline {13}

Table 1 show that the schedule of study enrollment, assessment and intervention time points.

**Table 1 Study enrollment, assessment and intervention points**

Time point	≥3days prior to surgery	1day prior to surgery	≤3days post to surgery	≤6days post to surgery	Day of discharge
Eligibility Screen	x				
Informed Consent	x				
Group Allocation	x				
Assessment	T1		T2		T3
STAI-S	x		x		x
PHQ-9	x		x		x
AIS	x		x		x
VAS-pain-10	x		x		x
SP/DP, HR	x	x	x	x	x
fNIRS	x				x
Blood Collection	x	x			
Satisfaction survey					x
Interventions	Topic1	Topic2	Topic3	Topic4	Topic5
	x	x	x	x	x

STAI-S, State scale (STAI-S) in State Trait Anxiety Inventory (STAI); PHQ-9, Patients Health Questionnaire Depression Scale-9 item; AIS, Athens Insomnia Scale; VAS-Pain-10, Visual analogue Scale-Pain-10; SP, Systolic Pressure; DP, Diastolic Pressure; HR, Heart Rate; fNIRS, functional Near Infrared Spectroscopy

### Sample size {14}

In the sample size estimation, according to previous literature reports,<sup>43</sup> the average value of STAI-S in the control group was  $44.7 \pm 10.3$ . In order to have a value  $\delta \geq 5$  (difference between the average levels of state anxiety), with a power of 0.90 and a significance of 95%, a sample size of 91 patients per arm was estimated according to the value of the standard deviation  $\sigma = 10.3$  calculated by PASS 11.0 version. Thus, allowing for a 10% dropout rate, about 100 cases will be included in per group in the actual study.

### Recruitment {15}

Individuals will be identified and confirmed from surgical plan lists by the Electronic Medical Record System. All participants will be evaluated by two researchers (a therapist and a nursing graduate students) who will also verify patient diagnosis and eligibility. Once a candidate is eligible for enrollment, he or she will be approached by researcher to discuss the study in detail.

### **Assignment of interventions: allocation**

#### **Sequence generation {16a}**

After obtaining consent, enrolled participants will be randomly assigned to one of two groups using randomization in a 1:1 allocation by a random digital table. The random digital tables will be produced by SPSS22.0 and distributed to different centers. Then each participant will be grouped randomly and assigned to one of the two treatment groups by order of admission. The stratified sampling is used to achieve sample equalization. Outcome collectors and data administrators will be blinded to the group assignment.

#### **Concealment mechanism {16b}**

After obtaining consent, enrolled participants will be randomly assigned to one of two groups using randomization in a 1:1 allocation by a random digital table. The random digital tables will be produced by SPSS22.0 and distributed to different centers. The random digital tables were Concealed in opaque, sealed envelopes. Then each participant will be grouped randomly and assigned to one of the two treatment groups by order of admission.

#### **Implementation {16c}**

All participants will be evaluated by two researchers (a therapist and a nursing graduate students) who will also verify patient diagnosis and eligibility. The random digital tables will be produced by SPSS22.0 and distributed to different centers. Then each participant will be grouped randomly and assigned to one of the two treatment groups by order of admission. A researcher (Non-data collectors) in the research group specifically intervened the subjects with specialized tools and comfortable room rooms to improve the comfort of interventions

### **Assignment of interventions: Blinding**

#### **Who will be blinded {17a}**

Data collectors and data administrators will be blinded to the group assignment.

#### **Procedure for unblinding if needed {17b}**

(1)When all subjects have completed the trial, it can be uncovered.

(2) If serious adverse events occur, suspicious unintended serious adverse reactions, it can be uncovered after asking the leading researcher.

## **Data collection and management**

### **Plans for assessment and collection of outcomes {18a}**

## **Data collection and management**

Standardized data collection and management system will be used to collect and manage data, such as Case Record Form and Electronic Data Capture(EDC) system ResMan ([www.medresman.org](http://www.medresman.org)). To ensure in process quality control (in-process QC) and real-time online quality control (on-line QC) during the management of data. After the trial is completed, primary data and statistical results will be uploaded to the clinical trial public management platform ResMan. The results will be shared to ResMan after one year.

### **Plans to promote participant retention and complete follow-up {18b}**

A researcher (Non-data collectors) in the research group specifically intervened the subjects with specialized tools and comfortable room rooms to improve the comfort of interventions. Making an appointment in advance and keeping track of the treatment progress of the subjects can help to greatly increase the adherence and completion rate of the intervention. Case Record Forms and reasonable flow scheme were prepared for subjects. Follow-up management will be carried out by WeChat.

## **Data management {19}**

Standardized data collection and management system will be used to collect and manage data, such as Case Record Form and Electronic Data Capture(EDC) **system ResMan ([www.medresman.org](http://www.medresman.org))**. **To ensure in process quality control (in-process QC) and real-time online quality control (on-line QC) during the management of data. After the trial is completed, primary data and statistical results will be uploaded to the clinical trial public management platform ResMan. The results will be shared to ResMan after one year.**

## **Confidentiality {27}**

All subjects will be arranged by numbers and made to maintain the confidentiality of patient data.

### **Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}**

## **Stress bio-markers**

Ableson et al found that Cognitive intervention can significantly reduce the concentration of Adrenocorticotrophic Hormone (ACTH) and Cortisol (Cor) in the patients by adjusting the function of

Hypothalamic-Pituitary-Adrenal (HPA) axis.<sup>53</sup> Blood will be collected to investigate whether CCBT results in a favorable modulation of stress bio-markers such as ACTH and Cor. Blood sample collection for CCBT group will occur at baseline and before anesthesia. At each time, approximately 5 cc will be collected. Then ACTH and Cor will be tested and analyzed by Laboratory.

## **Statistical methods**

### **Statistical methods for primary and secondary outcomes {20a}**

Statistical analysis and reporting of this trial will be conducted in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines. Data will be analyzed by SPSS 22.0 version. For baseline variables, demographic and clinical characteristics will be analyzed by descriptive statistical method. The self-assessment questionnaires for primary outcomes provide numerical score assimilated to continuous variable. Continuous data will be reported as means  $\pm$  standard deviations or median (quartile 1 and quartile 3) depending on distribution and assessed using analysis of variance (ANOVA). Categorical data will be reported as proportions and assessed with the use of a Chi-square or Fisher's exact test. A trajectory analysis will be performed to assess changes in the presence or changes primary outcomes in over time by Hierarchical Linear Model (HLM). All tests will be two-sided, with p values  $<0.05$  considered statistically significant. The study will record the proportion of patients eligible who meet inclusion, decide to participate, complete the trial because the overall feasibility of conducting the trial will be accessed. Patients who not start, complete or continue with their prescribed treatment will be analyzed based on the intention-to-treat principle.<sup>54</sup>

### **Interim analyses {21b}**

Statistical analysis and reporting of this trial will be conducted in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines. Data will be analyzed by SPSS 22.0 version. For baseline variables, demographic and clinical characteristics will be analyzed by descriptive statistical method. The self-assessment questionnaires for primary outcomes provide numerical score assimilated to continuous variable. Continuous data will be reported as means  $\pm$  standard deviations or median (quartile 1 and quartile 3) depending on distribution and assessed using analysis of variance (ANOVA). Categorical data will be reported as proportions and assessed with the use of a Chi-square or Fisher's exact test. A trajectory analysis will be performed to assess changes in the presence or changes primary outcomes in over time by Hierarchical Linear Model (HLM). All tests will be two-sided, with p values  $<0.05$  considered statistically significant. The study will record the proportion of patients eligible who meet inclusion, decide to participate, complete the trial because the overall feasibility of conducting the trial will be accessed.

### **Methods for additional analyses (e.g. subgroup analyses) {20b}**

Statistical analysis and reporting of this trial will be conducted in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines. Data will be analyzed by SPSS 22.0 version. For

baseline variables, demographic and clinical characteristics will be analyzed by descriptive statistical method. The self-assessment questionnaires for primary outcomes provide numerical score assimilated to continuous variable. Continuous data will be reported as means  $\pm$  standard deviations or median (quartile 1 and quartile 3) depending on distribution and assessed using analysis of variance (ANOVA). Categorical data will be reported as proportions and assessed with the use of a Chi-square or Fisher's exact test. A trajectory analysis will be performed to assess changes in the presence or changes primary outcomes in over time by Hierarchical Linear Model (HLM). All tests will be two-sided, with p values  $<0.05$  considered statistically significant. The study will record the proportion of patients eligible who meet inclusion, decide to participate, complete the trial because the overall feasibility of conducting the trial will be assessed.

### **Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}**

Patients who not start, complete or continue with their prescribed treatment will be analyzed based on the intention-to-treat principle.<sup>54</sup>

### **Plans to give access to the full protocol, participant level-data and statistical code {31c}**

Standardized data collection and management system will be used to collect and manage data, such as Case Record Form and Electronic Data Capture(EDC) system ResMan ([www.medresman.org](http://www.medresman.org)). **After the trial is completed, primary data and statistical results will be uploaded to the clinical trial public management platform ResMan. The results will be shared to ResMan after one year.** The full protocol can be accessed by URL(<http://www.chictr.org.cn/listbycreator.aspx>).

### **Oversight and monitoring**

#### **Composition of the coordinating centre and trial steering committee {5d}**

The coordinating centre is composed of President Wang Binqun, President Xu Yong, Director Li Yuling and responsible for coordination and communication of different sub-centers overseeing the trial.

#### **Composition of the data monitoring committee, its role and reporting structure {21a}**

The data monitoring committee (DMC) is composed of President Wang Binqun, President Xu Yong, Director Li Yuling and responsible for interim data audit and final data audit. The DMC state that it is independent from the sponsor and competing interests.

#### **Adverse event reporting and harms {22}**

The study intervention is non-invasive, so it carries minimal risk. But participants are undergoing high-risk surgery, it is expected that they may encounter several adverse events unrelated to the study intervention during. An adverse event may be consisting of any unfavorable and unexpected sign, symptom or discomfort temporally associated with this study. All adverse events will be reported, and serious adverse

events will be immediately reported to the Institutional Research Ethics Committee of First Hospital of Shanxi Medical University. An adverse event includes changes in the patient's depression. PHQ-9 will be monitored and reported and once suicide idea were perceived, the participant will be dropped out of the study for further

clinical evaluation and management.

### **Frequency and plans for auditing trial conduct {23}**

The data monitoring committee (DMC) will audit trial conduct in the medium term and at the end term.

### **Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}**

The trial is currently ongoing and recruiting. This study will be conducted at the in-patient department at head and neck surgery, department of orthopedics, general surgery, cardiac surgery in the pilot hospital. The potential participants will be informed of the study objectives and asked their willing to participate, when they contact with the study researcher. All participation is voluntary and fully anonymity all the way. They will be required to provide written informed consent before starting and can drop out at any time. All participants will receive UC from their doctors in charge and that half of the recruited participants will be informed of receiving CCBT in addition to their UC. The above will be informed to each participant in detail by researchers.

### **Dissemination plans {31a}**

Regardless of the outcome, study outcomes will be published in international journals.

## **Discussion**

## **Significance**

Mind–body practices are more and more popular in Non-pharmacological interventions for psychosomatic disease. Few studies have investigated application of CCBT in the perioperative period during complex surgeries. Therefore, this study will use a comparative randomized controlled trial design, exploring clinical effects of CCBT software in mind–body practices in multiple diseases during the perioperative period. This study was planned to address the lack of trials examining the administration of CCBT relieving negative emotion, pain and insomnia in patients with surgery. If results are positive, the findings of this study will provide valuable evidence to facilitate the development of non-pharmacological interventions for treating psychosomatic symptom. Most important of all, it can meet the mental health needs of non-psychotic inpatients with physical health problems and relieve a conflict from shortage of psychotherapists and strong demand for psychological services .(55) If future direction of the study is to determine a large advantage in cost effectiveness of the CCBT-Prs than UC, CCBT will be used more widely in clinical.

# Limitations

The foreseen limitations of this study are the following. First, subjective and objective measures will be wished to evaluation treatment effect in the study protocol because patients with insomnia underestimate their actual sleep time, or some implicit character of some Chinese people. However, using polysomnography monitoring sleep brings significant burden on participants. At the same time blood biomarkers, fNIRS as objective markers could not involve and analyzed for each subject because of trauma and individual will. Additional consent provisions for collection has been written in informed consent. If participant would like to consent and will receive a small amount of cash compensation after the end of the test .The second limitation is that we will be unable to elucidate specific effects of the CCBT program because a psychological placebo group to control for non-specific factors will not be employed, such as psychological counseling or some health education software. The third limitation is the lack of follow-up to the subjects and the lack of knowledge of the long-term effects of CCBT intervention.

# Trial Status

The protocol version number is 2019.08V1.0 and developed on the 2019.08.

This trial is currently recruiting participants. Recruitment has been started on 2019.11.01 and anticipated to be completed by May 2020.

# Abbreviations

Cognitive behavior therapy (CBT)

Computer-assisted Cognitive-behavior therapy(CCBT)

Enhanced Recovery After Surgery (ERAS)

Usual Care(UC)

CCBT-Psychosomatic regulation in Perioperative periods software (CCBT-Prs)

The Chinese version of State-Trait Anxiety Inventory (STAI)

Patients Health Questionnaire Depression Scale-9 item (PHQ-9)

Athens Insomnia Scale (AIS)

Visual analogue Scale-pain-10(VAS-pain-10)

Functional near infrared spectroscopy(fNIRS)

Oxygenated hemoglobin (Oxy - Hb)

Deoxyhemoglobin (Deoxy - Hb)

total hemoglobin (total-Hb)

Adrenocorticotrophic Hormone (ACTH)

Cortisol (Cor)

## **Declarations**

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### **Authors' contributions {31b}**

YY and XY especially made contribution to the design of this study, development of the original study protocol and drafting the initial manuscript. L Zf, Z Hb and L Xr contributed to develop the statistical analysis plan and assisted in the preparation of the manuscript. W Bq, XY and L Yl contributed to the conceptualization and design of this study and the critical revision of the article for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately resolved.

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The role of the funding body can only provide funding and have no effect in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

### **Availability of data and materials {29}**

All data generated or analyzed during this study are included in this published article.

### **Ethics approval and consent to participate {24}**

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of First Hospital of Shanxi Medical University in

China on 31 July 2019 (document number [2019]K-SK028). Written informed consent was obtained from individual or guardian participants.

### **Consent for publication {32}**

Not applicable. Because there is no refers to consent for the publication of identifying images or other personal or clinical details of participants that compromise anonymity in this protocol.

### **Competing interests {28}**

The authors declare that they have no competing interests.

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## Figures

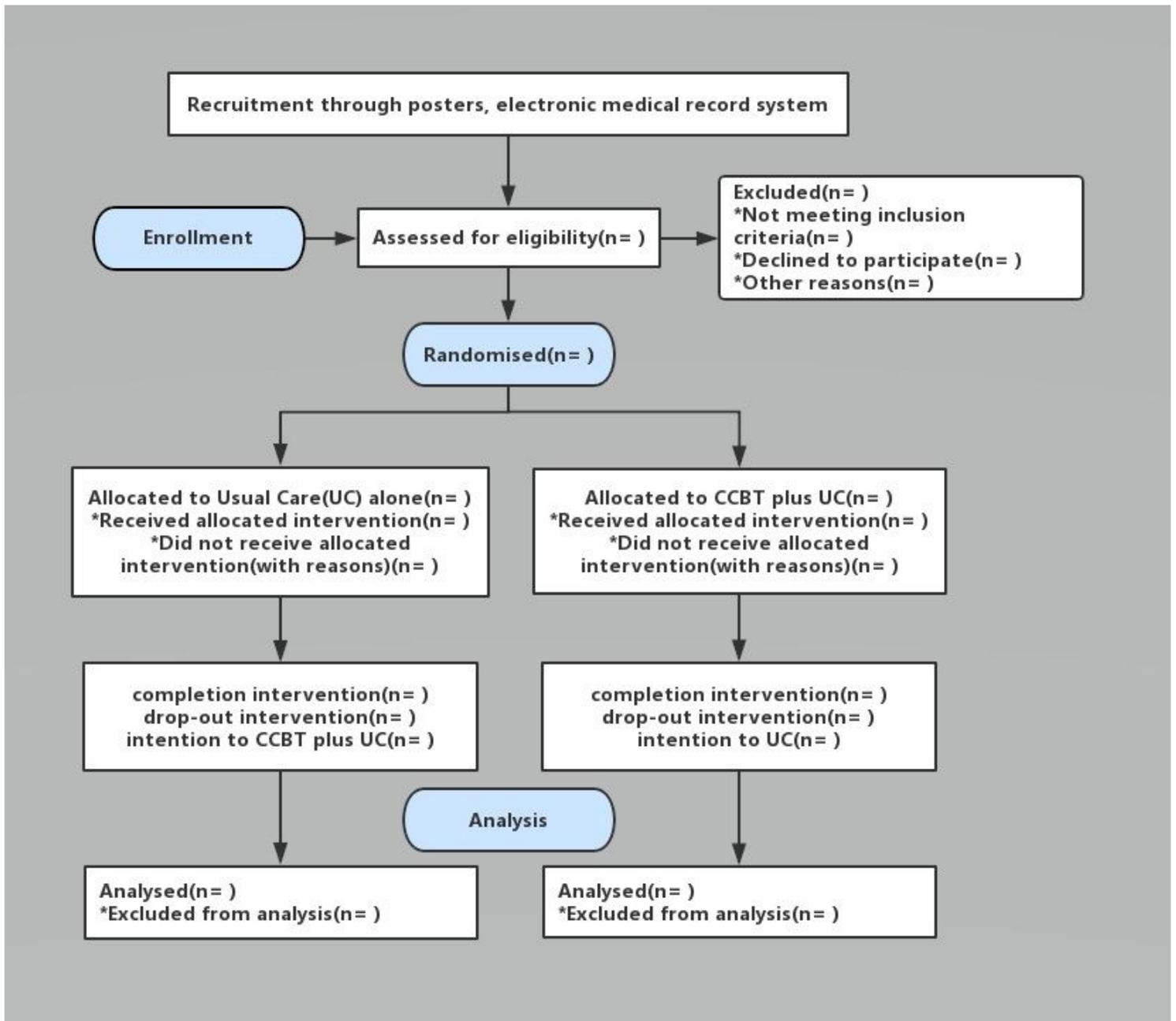


Figure 1

for a Consolidated Standards of Reporting Trials diagram of the study design.



Figure 2

Legend not provided in this version

## Supplementary Files

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