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The effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: Protocol for a multicentric, real-world randomized controlled trial in China

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ABSTRACT

Introduction: Benzodiazepine (BZDs) and Z-drugs are the most prescribed drugs worldwide and their inappropriate use imposes a great burden on public health. As the main prescribers, psychiatrists' inappropriate prescriptions may be responsible for this situation. The research team developed an electronic intervention system for appropriate prescription of BZDs and Z-drugs for prescribing psychiatrists. The objective of the study is to explore the effectiveness and utility of the electronic intervention for decreasing the inappropriate prescribers on benzodiazepine and Z-drugs in out-patient settings in real-world circumstances.

Methods and analysis: A real-world multi-center randomized controlled study will be carried out among licensed psychiatrists with prescription qualifications from 5 of the most influential regional hospitals with high-quality mental services over China. Participants will be 1:1 randomized to either receive 3-month electronic intervention (11 related information pushing and 3 online lectures) or to a waiting list. The primary outcome is the change in proportion of inappropriate prescriptions on BZDs and Z-drugs within the baseline period (3 months before the intervention) and 3 months later after intervention. Secondary outcomes comprising psychiatrists' knowledge and attitudes towards appropriate BZDs and Z-drugs prescription, the related adverse effects with BZDs and Z-drugs among the patients and self-efficacy will be assessed at baseline, in the 3rd month and 6th month. To assess the utility, evaluation of the intervention and utilization data of the system in the intervention group will also be collected.

Ethics and dissemination: The study received ethics approval from the institutional review board and the ethics committee of Shanghai Mental Health Center, the Second Xiangya Hospital, the West China Hospital, Guangji Hospital and Wuhan Mental Health Center. Results of the study will be published in peer-reviewed journals or presented at conferences after study completion. If effective, the educational materials will be released to the public.

Clinical trial registration number: ClinicalTrials.gov NCT03724669, https://clinicaltrials.gov/ct2/show/NCT03724669.

Strengths and limitations of this study

- This will be the first study to assess the effectiveness of psychiatrist-targeted electronic intervention on inappropriate BZDs and Z-drugs prescriptions in Chinese psychiatric outpatient clinics.
- This is a multicenter study, and we selected five most influential hospitals with largest amount of outpatient visits for mental services in the east, middle, and west of China, which may have good representative of the country real situations.
- The study is an open-label and real-world study; therefore, it is impossible to blind the participants and investigators to group allocation.

INTRODUCTION

Benzodiazepines (BZDs) and Z-drugs (non-BZDs, e.g., zopiclone, zaleplon and zolpidem) belong to the class of hypnotic sedatives and are one of the most commonly prescribed drugs in clinical practice [1-3]. BZDs and Z-drugs bind to specific sites of the γ-aminobutyric acid (GABA) type A ($GABA_A$) receptors to exert sedating effects and facilitate sleep by potentiating the inhibitory effect of GABA [4]. Although the receptor affinities toward the $GABA_A$ subunits are different between BZDs and Z-drugs, their pharmacologic profiles, effectiveness and side-effect are similar [5]. Adverse drug reactions of BZDs and Z-drugs are associated with the risks of cognitive failures [6], psychomotor abnormalities [7] and hip fractures or car accidents due to falls [1 3], imposing a significant burden on patients and society. Moreover, long-term use of BZDs and Z-drugs may lead to tolerance which requires dose increment to achieve the same effect, otherwise the withdrawal symptoms such as anxiety, insomnia and restlessness may occur [8 9]. It is therefore recommended by the clinical guidelines that BZDs and Z-drugs are relatively safe for short-term use

(generally no more than 4 weeks) [10].

However, the problem of inappropriate prescription of BZDs and Z-drugs is prominent worldwide despite the fact that more people are increasingly aware of the associated risks [11 12]. For example, a retrospective observational study reported that roughly 5.2% of US adults (aged 18 to 80) used BZDs in 2008 and one-quarter of them receive BZDs for a long-term duration [13]. In a British study, only a third of patients with BZDs utilization considered appropriate prescription without exceeded guidelines in terms of indication or contraindications [14]. In a recent multi-center, retrospective patient-link prescription database study in Chinese psychiatric clinics by our research team, we found appropriately 3.03% outpatients were in hazardous use of BZDs and Z-drugs, and hazardous use here is defined as overdose [>40mg Diazepam Milligram Equivalence (DME)], long-term use (>consecutive 90 days), or both (unpublished).

Nowadays, the interventions for BZDs and Z-drugs abuse are mainly patient-oriented, including self-managed or supervised gradual dose reduction, educational books, minimal interventions, cognitive behavioral therapy and so on, to raise patients' awareness of potential risks of BZDs and Z-drugs [15 16]. Current research about the related interventions targeted at clinicians is rather little, and primarily by legislation restriction, education or providing resources for medication substitution among general practitioners [15]. Though partial clinicians realize the possible adverse consequences of long-term use of BZDs and Z-drugs, they claim that it is difficult to persuade patients to discontinue using the drugs and themselves also lack corresponding non-pharmacological therapy techniques and knowledge to reduce the inappropriate use of BZDs and Z-drugs [17]. Moore et al. [18]

recommended that BZDs should be strictly controlled and only prescribed by medical experts, such as psychiatrists, however, this is not the case. A recent cohort study indicated that prescription by psychiatrists is one of the clinical correlates of long-term BZDs use [19].

To our knowledge, there is no available intervention in China to reduce the inappropriate prescription of BZDs and Z-drugs. It is difficult for psychiatrists to spare a complete period of time for systematic learning on the latest knowledge about the appropriate use of BZDs and Z-drugs. New technologies such as web-based and mobile-based health services show potential effects and flexibility in health care services [20 21], making it possible for psychiatrists to receive electronic intervention to update related knowledge.

An electronic intervention system for appropriate use of BZDs and Z-drugs for prescribing psychiatrists based on the latest evidence-based guidelines and expert consensus was designed, and it was generated after fully discussion and confirmed by Chinese addiction experts. The intervention content 4 modules, including the basis of rational use of BZDs and Z-drugs, their rational use in common mental disorders, the quick identification and brief intervention for the BZDs and Z-drugs use disorders, and their use for the special groups, which are delivered by the forms of 11 related information pushing and 3 online lectures through the electronic intervention system.

The intervention system is based on WeChat, the most popular social media application in China, to realize multi-functions including intervention, assessment, feedback, notification and data management. Then, a real-world multi-center randomized controlled study design will be carried out to verify the effectiveness and utility of the

intervention system. The primary objective of this study is to explore whether the electronic intervention will be effective in decreasing the psychiatrists' inappropriate prescription behaviors of BZDs and Z-drugs use. The secondary objective is to assess the impact of intervention on their knowledge and attitudes towards appropriate BZDs and Z-drugs prescription, self-efficacy, common adverse effects in prescribing patients, and whether the electronic intervention is with good clinical utility in the real world.

METHODS AND ANALYSIS

Trial design

This is a real-world, multi-center, open-label, randomized controlled clinical trial with two parallel groups to investigate the effectiveness and utility of the electronic intervention system on appropriate BZDs and Z-drugs prescription in psychiatric outpatient clinics in China. In this study, psychiatrists with prescription qualifications will be randomly assigned to the standardized electronic intervention group, or to a waiting list (control group) in a ratio of 1:1.

Study setting

The study will recruit participants from 5 of the most influential regional tertiary hospitals with the highest-quality mental services in the east, middle, and west areas of China (three psychiatric hospitals and two general hospitals). All the hospitals (Shanghai Mental Health Center, the Second Xiangya Hospital of Central South University, the West China Hospital of Sichuan University, the Affiliated Guangji Hospital of Soochow University and Wuhan Mental Health Center) have the largest amount of outpatient visits

for mental services within their own areas.

Eligibility criteria

Licensed psychiatrists with prescription qualifications will be recruited for the study. The inclusion criteria are: (1) at least 3-year working experience as a psychiatrist; (2) provide outpatient services for at least 1 year with the frequency of more than once a week; and (3) willingness to receive the electronic interventions for the appropriate BZDs and Z-drugs prescription. The exclusion criteria are: (1) will retire within 6 months; and (2) refuse to extract their prescription information from the outpatient database.

Intervention

Intervention group

Psychiatrists in the intervention group will receive a three-month electronic educational intervention covering information on standardized use of BZDs and Z-drugs with two main components: (1) educational articles delivered through the WeChat Official Account Platform once a week (11 times in total); and (2) three additional online lectures from addiction specialists on Ding Talk platform. The detailed information about the online lectures will be sent twice to the WeChat individual messaging platform one day and one hour beforehand. Participants can watch the live lectures, or review the videos at any time on Ding Talk platform.

The initial educational contents were primarily based on the latest evidence-based guidelines and experts' consensus [9 22-26] for the appropriate use of BZDs and Z-drugs. Then a focus group was conducted among 8 mental health or addiction experts to discuss and confirm the final version of educational contents. The intervention content 4 modules,

including the basis for rational use of BZDs and Z-drugs, their rational use in common mental disorders, the quick identification and brief intervention for the BZDs and Z-drugs use disorders, and their use for the special groups (See details in Table 1).

Control group

Participants allocated to the control group will only have to finish the assessment modules and they will not receive any educational information about the online lectures. After the study ends, they will have access to receive the educational texts and view the online lectures.

Table 1 The educational contents for the standardized use of BZDs and Z-drugs.

No.	Content
Module 1: The basis for rational use of BZDs and Z-drugs	
1	Pharmacological effects and rational use of BZDs
2	Pharmacological effects and rational use of Z-drugs
3	The current situation of BZDs and Z-drugs abuse*
Module 2: Rational use of BZDs and Z-drugs in mental disorders	
4	Sleep physiology and rational use of BZDs and Z-drugs in insomnia
5	Non-pharmacological interventions for insomnia
6	Clinical practice of diagnosis and treatment for insomnia*
7	Rational use of BZDs and Z-drugs in other mental disorders
Module 3: Abuse, dependence and brief intervention of BZDs and Z-drugs	
8	Quick identification for BZDs and Z-drugs use disorders
9	Management for long-term use of BZDs and Z-drugs
10	Management and regulations of BZDs and Z-drugs prescription
11	The brief intervention for BZDs and Z-drugs use disorder*
Module 4: Other	
12	Physician-patient communication skills among hazardous use population
13	Situations that BZDs and Z-drugs should be banned or used with caution (case reports)
14	Rational use of BZDs and Z-drugs in special populations (including the elderly, drug abusers, pregnant and lactating women, patients with physical diseases, children and adolescents)

Note: * The educational contents are delivered by online lectures.

The electronic Intervention system

The electronic intervention system will be primarily delivered via the WeChat Official Account Platform (name in English: Intelligent Addiction Intervention System) which consists of three parts: the users' WeChat page in the mobile devices, the administrator web page for investigators, and a backend server to store information and data. The platform contains a range of modules, including the intervention, assessment, feedback and notification.

Upon following the WeChat Official Account Platform of the research team, participants have access to two primary menu buttons on the individual messaging platform: User center and Intervention & Assessment (Figure 1 A-B). The User center presents the participant with tabs of Accumulate points, Previous message and Feedback. Participants could see the points that they have earned from the Intervention in the Accumulate points tab and review the intervention content on a repeated basis in the Previous message tab. If the users have any technical problems, they can leave a message through the Feedback tab. In terms of the Intervention & Assessment menu, the users could see a list of tasks (intervention or assessment content) that are waiting to be finished or have been done. Each intervention content contains an article that can support image, video or audio elements and 2 to 4 corresponding exercises (Figure 1 C-D). For motivation purposes, users can earn 6 points by viewing the texts and 4 points by finishing the exercises. The assessment module will support online questionnaires completed by the participants. Further, if the users do not finish the intervention or assessment on time, they will receive a reminder sent automatically by the system. The investigator in each center will contact the participants directly by phone when the task is still not completed after three

notifications.

On the administrator web page (Figure 2), the investigators can manage the group allocation, set up the intervention and assessment content, track the implementation progress and send necessary notifications to promote participants' adherence. In addition, they can also receive feedback about any technical or other problems on use from the users. Each center has its own account to log into the administrator web page and a primary investigator to manage the participants in their own hospital.

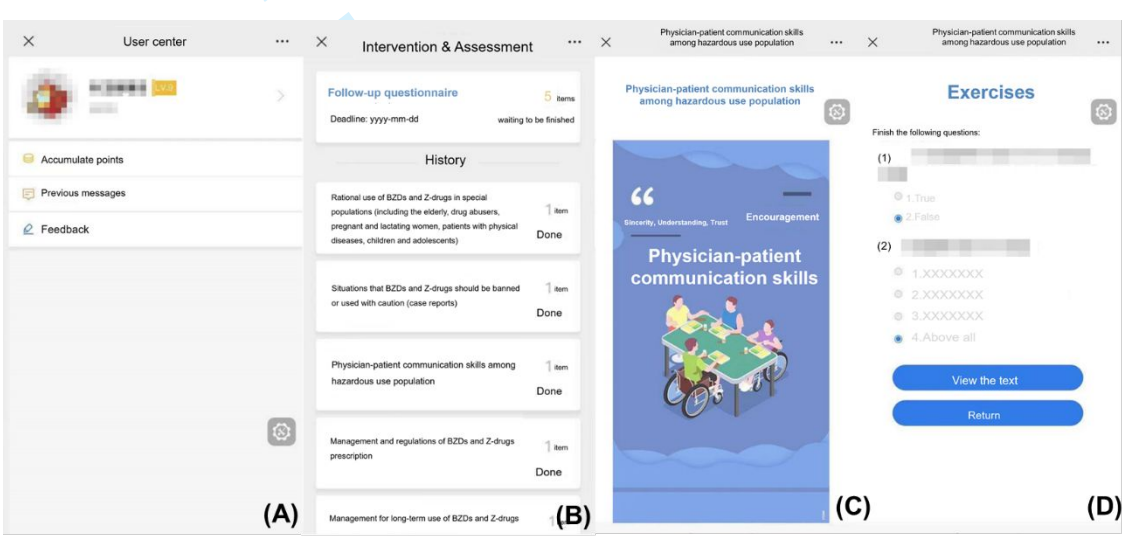

Figure 1 The screenshot of the WeChat Official Account Platform for users in the mobile devices: (A) User center interface, (B) Intervention & Assessment interface, (C) educational article of the Intervention module, (D) corresponding exercise after text reading. Note: The page which is actually in Chinese is translated into English.

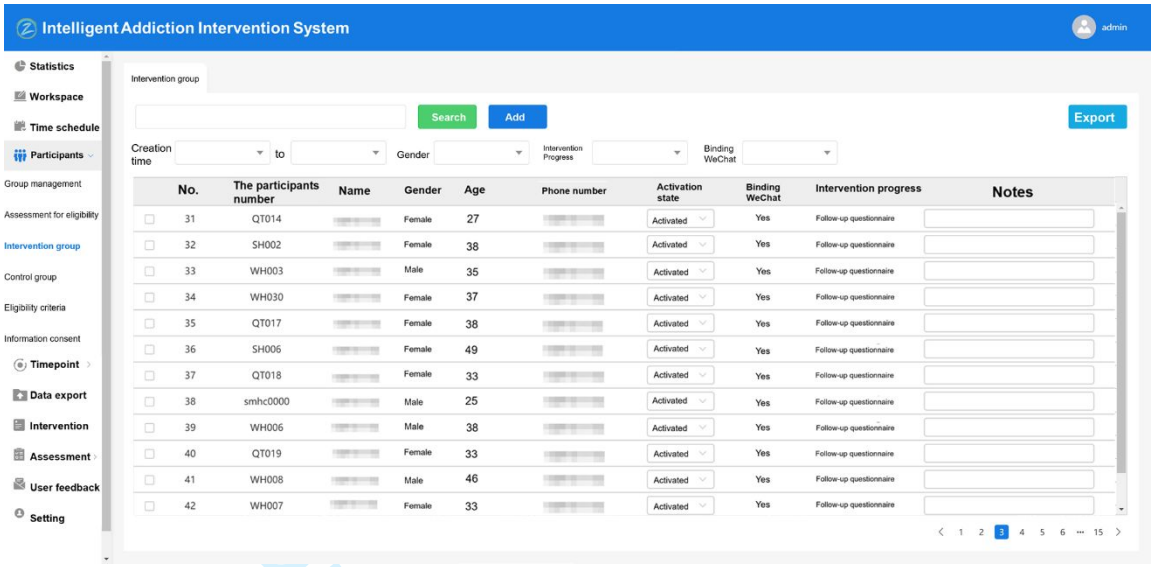

Figure 2 The screenshot of the administrator web page for investigators. Note: The web page which is actually in Chinese is translated into English.

Outcomes

The primary outcome of the study is proportion of inappropriate BZDs and Z-drugs prescriptions, which is identified by 9 consecutive monthly prescription data (3 months before, intervention period and 3 months after the intervention). The secondary outcomes include: (1) BZDs and Z-drugs related knowledge of the participants; (2) attitude towards BZDs and Z-drugs prescription of the participants; (3) common adverse effects in prescribing patients; (4) self-efficacy; and (5) utility and utilization of the electronic intervention. All the assessments required to be completed at each time points are shown in the Table 2.

Proportion of inappropriate BZDs and Z-drugs prescription

The BZDs and Z-drugs prescription information of each psychiatrist within the baseline period (3 months before the intervention) and intervention period (0-3 month) and follow-up period (3-6 month) will be extracted from the outpatient prescription database in each hospital. The quantities of different kinds of BZDs and Z-drugs will be firstly converted into

the DME and accumulated daily DME usage for a patient with each prescription will be calculated [27]. Then, the average daily dosage and continuous days of use per prescription will also be calculated based on the accumulated daily DME usage. The inappropriate prescription is defined as overdose use (>40mg DME according to the maximum dose of drug instruction), long-term use (>90 days) or over-indications use.

BZDs and Z-drugs related knowledge

BZDs and Z-drugs related knowledge is assessed using 22 true or false self-made questions concerning the pharmacological effects, indication of use, identification of addiction, adverse effects and so on.

Attitude towards BZDs and Z-drugs prescription

A 14-item self-made questionnaire which adopts a 4-point Likert format is used to measure participants' attitude towards various aspects of BZDs and Z-drugs prescription, including indication of use, adverse effects, related guidelines, drug regulations, identification for BZDs and Z-drugs use disorders, etc.

Common adverse effects in prescribing patients

The psychiatrists are asked to select how often the common adverse effects of BZDs and Z-drugs occur in their prescribing patients ranging from "Never" to "Always". The questionnaire has 8 questions and uses a 4-point Likert format, with a score of 1 indicating the lowest frequency.

Self-efficacy

An adapted 10-item version of General Self-Efficacy Scale (GSES) will be used to measure participants' self-efficacy, which refers to one's global confidence in dealing with

a variety of demanding situations [28]. Each question is scored on a 4-point Likert scale. The Chinese version of the GSES has been proven with good reliability and validity [29].

Utility and utilization of the electronic intervention

Participants in the intervention group will be asked to complete an online 17-item questionnaire to evaluate the forms, contents, effectiveness and clinical generalization of the intervention. In addition, utilization data will be automatically collected through the WeChat or Ding Talk platform, including accumulated scores, mean number and length of time of reading or watching.

Table 2 Time point for the schedule of assessments.

	Assessment Period			
Time point	**-3 month**	**Baseline**	**3 month**	**6 month**
Primary outcome				
Proportion of inappropriate BZDs and Z-drugs prescription	●	●●	●●	●
Secondary outcomes				
BZDs and Z-drugs related knowledge		×	×	×
Attitude towards BZDs and Z-drugs prescription		×	×	×
Common adverse effects in prescribing patients		×	×	×
Self-efficacy		×	×	×
Utility of the electronic intervention			×	
Utilization of the electronic intervention		●	●	

Participant timeline

Psychiatrists who meet the eligibility will be enrolled in the study by getting access to follow the WeChat Official Account Platform on their smartphones after signing electronic informed consent. The demographic information and baseline measurements of secondary outcomes (Table 2) will be collected before group allocation. Participants then will be

randomly assigned to receive either electronic interventions or to a waiting list for a period of 3 months. At the end of the 3rd and 6th month, participants will have to finish the online questionnaires comprising knowledge and attitudes towards BZDs and Z-drugs prescription, common adverse effects in prescribing patients and self-efficacy. The utility of the electronic intervention will be assessed online at the end of the 3rd month. Meanwhile, their consecutive monthly prescription information of BZDs and Z-drugs (between 3-month before and after the intervention period) will be extracted from the prescription database of the outpatient clinics. Figure 3 displays the flow chart of the study.

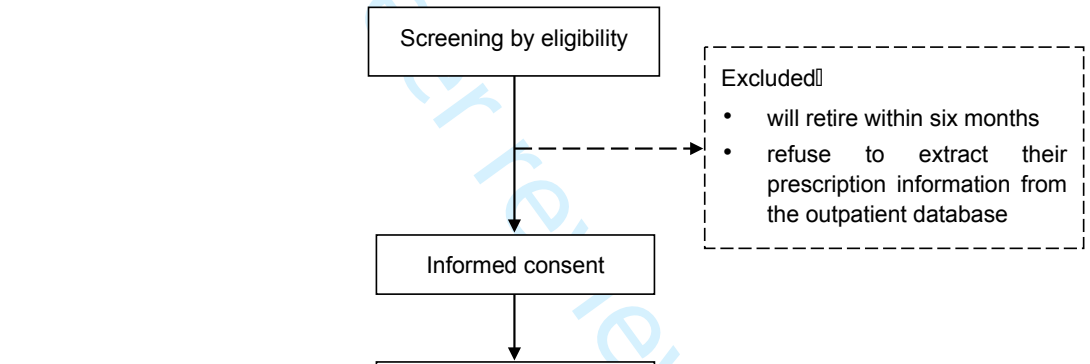

Figure 3 Flow chart of participants.

Discontinuation

The end point of the study is at the end of 6th month and participants could withdraw at any time for any reason during the study period. If possible, the reasons for withdrawal from the study will be recorded.

Sample size

Previous studies reported that intervention could result in a 19% reduction in BZDs prescriptions [30]. Assuming 95% confidence level, 90% statistical power and conservatively estimating a dropout rate of 20%, we will require a sample size of N=54 participants per group.

Recruitment

Five hospitals whose psychiatric outpatient clinics are the most frequently visited by patients within their own areas will be invited to take part in the study. Advertisement for the study is distributed to these five selected hospitals and presented to potential participants. In each of these hospitals, interested psychiatrists who meet the eligibility criteria will be recruited.

Allocation and Blinding

Participants who sign electronic informed consent will be randomized in a 1:1 ratio using block randomization tables generated by computer and assigned to receive either 3-month electronic interventions or to a waiting list. This is an open-label real world study and it is clearly hard to blind the participants and investigators to group allocation. However, participants in the intervention group will be informed not to discuss the educational content

or lecture videos with those in the control group.

Data Collection

Primary outcome data, the consecutively monthly prescription of each participant within 3-month before and after the intervention, will be extracted from the outpatient prescription database in each hospital. The database contained anonymous prescription information including: (1) patients unique code and demographic data; (2) doctor unique code; and (3) diagnosis and prescription information of drug type, dose, duration, usage, etc. In terms of the secondary outcome data, questionnaires will be collected through online assessments completed by participants on the WeChat official account platform and automatically uploaded to the administrator end. The utilization data of electronic intervention (including accumulated scores, mean number and length of time of reading or watching) will also be stored automatically in the WeChat and Ding Talk backend system of administrator.

Statistical methods

All analyses based on intention-to-treat principle will be conducted with IBM SPSS Statistics version 24.0 with significance level set at $p<0.05$ (two-sided). Student *t test* for continuous variables or *chi-square test* for the proportion of categorical variables will be used to test the baseline comparability of the two groups. The proportion of inappropriate BZDs and Z-drugs prescriptions 3-month before baseline, intervention period and 3-month after the intervention between the two groups will be calculated and reduction of the variable will be compared using the Wilcoxson signed rank test. In terms of the secondary outcomes, Fisher exact test will be used for dichotomous variables, and mixed-effects models for rating scales with group (intervention group vs control group) and time (0, 3, 6

month) as fixed factors. Descriptive data will be used to describe the utility and utilization of the electronic intervention.

ETHICS AND DISSEMINATION

Research ethics approval

The study was registered at ClinicalTrials.gov (NCT03724669) and designed in accordance with the principles of the Declaration of Helsinki. Ethics approval for the study was obtained from the institutional review boards and the ethics committees of Shanghai Mental Health Center, the Second Xiangya Hospital of Central South University, the West China Hospital of Sichuan University, the Affiliated Guangji Hospital of Soochow University and Wuhan Mental Health Center.

Consent or assent

Electronic files of informed consent including purpose, procedures, potential risks and benefits of the study will be sent to the participants through WeChat platform before recruitment. After fully understanding the content of the study, all participants need to sign an electronic informed consent to participate in the study.

Confidentiality

After obtaining informed consent from all participants, the investigators will generate a unique user identifier for each participant in the administrator end. All participant-specific data will be collected and stored in the server with password limiting the access at Shanghai Mental Health Center for privacy protection and data security and be released to the designated researchers who conduct the data analysis with permission.

Ancillary and Post-trial Care

Participants in the intervention group and control group will receive a gift (about 300 Chinese Yuan) at the end of the study. Meanwhile, participants in the control group will get access to the educational materials.

Dissemination policy

The results of the study will be published in peer-reviewed journals or presented at conferences. If the electronic intervention is effective in reducing doctors' inappropriate prescribing behaviors in psychiatric institutions, the educational materials will be released to the public.

RESULTS

The research started October 2020. The intervention has been completed and the follow-up assessment is expected to be completed at the end of 2021.

DISCUSSION

The study will verify the effectiveness and utility of the electronic intervention on the appropriate BZDs and Z-drugs prescription for psychiatrists. To the best of our knowledge, no psychiatrist-centered intervention to reduce inappropriate BZDs and Z-drugs prescriptions has been conducted in Chinese psychiatric clinics.

There are a variety of reasons for psychiatrists prescribing BZDs and Z-drugs inappropriately, including nonspecific BZDs and Z-drugs related knowledge, limited knowledge of evidence-based alternative treatment, and difficulties applying medication as per guidelines in clinical practice.[16] Therefore, it is essential to educate psychiatrists, who

play a key role in prescribing BZDs and Z-drugs and educating the patients in outpatient psychiatric settings [31 32], thereby promoting the appropriate prescription of BZDs and Z-drugs. Smartphones and social media may provide a more powerful and convenient platform for distant education. The multifunctional platform of our research team will not only deliver the core components of guidelines recommended BZDs and Z-drugs prescription, but also test the effectiveness and utility of the electronic form of intervention among psychiatrists. If this WeChat-based intervention is validated to be effective and with good utility, this will be of great significance for improving the current situations of inappropriate BZDs and Z-drugs prescription and relevant drug management policies.

Authors' contributions

XX and YY are co-first authors and contributed equally to this work. NZ and HJ supervise to conceive the original concept of the study. The other authors made a lot of contributions to the trial design and implementation. All authors critically reviewed the content and approved the final version for publication.

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Competing interests

The authors declare that they have no competing interests.

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The effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: Protocol for a multicentric, real-world randomized controlled trial in China

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The effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: Protocol for a multicentric, real-world randomized controlled trial in China

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ABSTRACT

Introduction: Benzodiazepine receptor agonists (BZRAs), including benzodiazepines (BZDs) and Z-drugs, are the most prescribed psychotropic drugs worldwide and their inappropriate use imposes a great burden on public health. As BZRAs are commonly used in psychiatric settings, psychiatrists' inappropriate prescriptions may be responsible for this situation. The research team developed an electronic intervention system for appropriate prescription of BZRAs for prescribing psychiatrists. The objective of the study is to explore the effectiveness and utility of electronic intervention for decreasing the inappropriate prescriptions of BZRAs in psychiatric outpatient settings in real-world circumstances.

Methods and analysis: A real-world multi-center randomized controlled study will be carried out among licensed psychiatrists with prescription qualifications from 5 of the most influential regional hospitals with high-quality mental services over China. Participants will be 1:1 randomized to either receive 3-month electronic intervention (11 related information pushing and 3 online lectures) or to a waiting list. The primary outcome is the change in proportion of inappropriate prescriptions on BZRAs within the baseline period (3 months before the intervention) and 3 months later after intervention. Secondary outcomes comprising psychiatrists' knowledge and attitudes towards appropriate BZRAs prescription, the related adverse effects with BZRAs among the patients and self-efficacy will be assessed at baseline, in the 3rd month and 6th month. To assess the utility, evaluation of the intervention and utilization data of the system in the intervention group will also be collected.

Ethics and dissemination: The study received ethics approval from the institutional review board and the ethics committee of Shanghai Mental Health Center, the Second Xiangya Hospital, the West China Hospital, Guangji Hospital and Wuhan Mental Health Center. Results of the study will be published in peer-reviewed journals or presented at conferences after study completion. If effective, the educational materials will be released to the public.

Clinical trial registration number: ClinicalTrials.gov NCT03724669, https://clinicaltrials.gov/ct2/show/NCT03724669.

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Strengths and limitations of this study

- This will be the first study to assess the effectiveness of psychiatrist-targeted electronic intervention on inappropriate BZRAs prescriptions in Chinese psychiatric outpatient clinics.
- This is a multicenter study, and we selected five most influential hospitals with the largest amount of outpatient visits for mental services in the east, central, and west of China, which may have good representative of the country's real situations.
- The study is an open-label and real-world study; therefore, it is impossible to blind the participants and investigators to group allocation.

INTRODUCTION

Benzodiazepine receptor agonists (BZRAs), including benzodiazepines (BZDs) and Z-drugs (e.g., zopiclone, zaleplon and zolpidem), are one of the most commonly prescribed psychotropic drugs worldwide in clinical practice.[1] BZRAs bind to specific sites of the γ-aminobutyric acid (GABA) type A ($GABA_A$) receptors to exert sedating effects and facilitate sleep by potentiating the inhibitory effect of GABA.[2] Therefore, they are mainly used for treatment of insomnia, anxiety, and panic disorder in psychiatric settings.[3-6] Although the receptor affinities toward the $GABA_A$ subunits are different between BZDs and Z-drugs, their pharmacologic profiles, effectiveness and side-effect are similar.[7] Adverse drug reactions of BZRAs are associated with the risks of cognitive impairment, psychomotor abnormalities, falls, hip fractures and car accidents,[7-10] imposing a significant burden on patients and society. Moreover, long-term use of BZRAs may lead to tolerance which requires dose increment to achieve the same effect, otherwise the withdrawal symptoms such as anxiety, insomnia and restlessness may occur.[11 12] It is therefore recommended by the clinical guidelines that BZRAs are relatively safe for short-term use (generally no more than 4 weeks).[13]

However, the problem of inappropriate prescription (long-term, overdose, or over-indications) of BZRAs is prominent worldwide despite the fact that more people are increasingly aware of the associated risks.[14 15] For example, a retrospective observational study reported that roughly 5.2% of US adults (aged 18 to 80) used BZDs in 2008 and one-quarter of them receive BZDs for a long-term duration (≥120 days).[1] In a British study, only a third of patients were considered to use BZRAs within indication.[16] In a recent study by our research team, we found approximately 3.0% outpatients were in hazardous use of BZRAs (co-occurrence of overdose and long-term use) and 55.9% patients were prescribed with over-indication via analysis of prescriptions in Chinese

psychiatric outpatient settings (unpublished).

Nowadays, the interventions for BZRAs use are mainly patient-oriented, including self-managed or supervised gradual dose reduction, educational books, minimal interventions, or cognitive behavioral therapy provided by physicians, to raise patients' awareness of potential risks of BZRAs.[17-20] Though some clinicians realize the possible adverse consequences of long-term use of BZRAs, they claim that it is difficult to persuade patients to discontinue using the drugs and themselves also lack corresponding non-pharmacological therapy techniques and knowledge to reduce the inappropriate use of BZRAs.[21] Interventions for service providers, the prescribing doctors, primarily include legislation restriction to limit prescriptions, education or providing resources for medication substitution among general practitioners.[17] Moore et al. [22] recommended that BZDs should be strictly controlled and only prescribed by medical experts, such as psychiatrists, however, this is not the case. A recent cohort study indicated that prescription by psychiatrists is one of the clinical correlates of long-term BZDs use.[23]

To our knowledge, related evidence about intervention for psychiatrists is not available to reduce the inappropriate prescription of BZRAs. It is difficult for psychiatrists in China to spare a complete period of time for systematic learning on the latest BZRAs-related knowledge due to the enormous population in China [24] and the nature of their professions in dealing with trouble people which require plenty of time.[25] Moreover, nonspecific BZRAs related knowledge, limited knowledge of evidence-based alternative treatment, and difficulties applying medication as per guidelines in clinical practice also contributed to this situation.[18]

New technologies such as web-based and mobile-based health services show potential effects and flexibility in health care services, [26 27] providing a powerful and convenient platform for distant

education. Our research team designed an intervention system which is based on WeChat, the most popular social media application in China, to realize multi-functions including educational intervention, assessment, feedback, notification, and data management. According to social cognitive theory, [28] self-monitoring such as assessment and education could increase self-efficacy beliefs to facilitate one's motivation and behaviors.

The electronic intervention system for appropriate BZRAs use for prescribing psychiatrists was based on the latest evidence-based guidelines and expert consensus, and it was generated after fully discussion and confirmed by Chinese addiction experts. The intervention content 4 modules, including the basis of rational use of BZRAs, their rational use in common mental disorders, the quick identification and brief intervention for the BZRAs use disorders, and their use for the special groups, which are delivered by the forms of 11 related information pushing and 3 online lectures through the electronic intervention system.

The primary objective of this study is to explore whether the electronic intervention will be effective in decreasing the psychiatrists' inappropriate prescription behaviors of BZRAs use. The secondary objective is to assess the impact of the intervention on their knowledge and attitudes towards appropriate BZRAs prescription, self-efficacy, common adverse effects in prescribing patients, and whether the electronic intervention is with good clinical utility in the real world.

METHODS AND ANALYSIS

Trial design

This is a real-world, multi-center, open-label, randomized controlled clinical trial with two parallel groups.

Study setting

The study will recruit participants from 5 of the most influential regional tertiary hospitals with the highest-quality mental services in the east, central, and west areas of China (three psychiatric hospitals and two general hospitals). All the hospitals (Shanghai Mental Health Center, the Second Xiangya Hospital of Central South University, the West China Hospital of Sichuan University, the Affiliated Guangji Hospital of Soochow University and Wuhan Mental Health Center) have the largest amount of outpatient visits for mental services within their own areas.

Eligibility criteria

Licensed psychiatrists with prescription qualifications will be recruited for the study. The inclusion criteria are: (1) at least 3-year working experience as a psychiatrist; (2) provide outpatient services for at least 1 year with the frequency of more than once a week; and (3) willingness to receive the electronic interventions for the appropriate BZRAs prescription. The exclusion criteria are: (1) will retire within 6 months; and (2) refuse to extract their prescription information from the outpatient database.

Patient and Public Involvement

No patients are involved in this study. For the patients whose prescribing data being included in the study, the requirement for informed consent was exempted from patients due to anonymity.

Interventions

Intervention group

Psychiatrists in the intervention group will receive a three-month electronic educational intervention covering information on standardized use of BZRAs with two main components: (1) educational articles delivered through the WeChat Official Account Platform once a week (11 times in total); and (2) three additional online lectures from addiction specialists on Ding Talk platform. The detailed information about the online lectures will be sent twice to the WeChat individual messaging platform one day and one hour beforehand. Participants can watch the live lectures or review the videos at any time on Ding Talk platform.

We first surveyed 595 doctors about their attitudes and knowledge of BZRAs. The initial educational contents were primarily based on the above surveys, latest evidence-based guidelines, and experts' consensus [5 12 29-32] for the appropriate use of BZRAs. Then a focus group was conducted among 8 mental health or addiction experts with more than 10-year working experience to fully discuss around the 4 topics, including the basis for rational use of BZRAs, their rational use in common mental disorders, the quick identification and brief intervention for the BZRAs use disorders, and their use for the special groups. The recordings were converted into transcripts and thematic analysis was used to confirm the key components. The intervention content was further summitted to 2 Chinese addiction experts to review and reach a consensus for the final version of educational contents (See details in Table 1).

Control group

Participants allocated to the control group will only have to finish the assessment modules and they will not receive any educational information about the online lectures. After the study ends, they will have access to receive educational texts and view the online lectures.

The electronic Intervention system

The electronic intervention system will be primarily delivered via the WeChat Official Account Platform (name in English: Intelligent Addiction Intervention System) which consists of three parts: the users' WeChat page in the mobile devices, the administrator web page for investigators, and a backend server to store information and data. The platform contains a range of modules, including intervention, assessment, feedback and notification.

Upon following the WeChat Official Account Platform of the research team, participants have access to two primary menu buttons on the individual messaging platform: User center and Intervention & Assessment (Figure 1 A-B). The User center presents the participant with tabs of Accumulate points, Previous message and Feedback. Participants could see the points that they have earned from the Intervention in the Accumulate points tab and review the intervention content on a repeated basis in the Previous message tab. If the users have any technical problems, they can leave a message through the Feedback tab. In terms of the Intervention & Assessment menu, the users could see a list of tasks (intervention or assessment content) that are waiting to be finished or have been done. Each intervention content contains an article that can support image, video or audio elements and 2 to 4 corresponding exercises (Figure 1 C-D). For motivation purposes, users can earn 6 points by viewing the texts and 4 points by finishing the exercises. The assessment module will support online questionnaires completed by the participants. Further, if the users do not finish the intervention or assessment on time, they will receive a reminder sent automatically by the system. The investigator in each center will contact the participants directly by phone when the task is still not completed after three notifications.

On the administrator web page (Figure 2), the investigators can manage the group allocation, set up the intervention and assessment content, track the implementation progress and send necessary notifications to promote participants' adherence. In addition, they can also receive feedback about any technical or other problems on use from the users. Each center has its own account to log into the administrator's web page and a primary investigator to manage the participants in their own hospital.

Outcomes

The primary outcome of the study is the proportion of inappropriate BZRAs prescriptions, which is identified by 9 consecutive monthly prescription data (3 months before, intervention period and 3 months after the intervention). The secondary outcomes include: (1) BZRAs related knowledge of the participants; (2) attitude towards BZRAs prescription of the participants; (3) common adverse effects in prescribing patients; (4) self-efficacy; and (5) utility and utilization of electronic intervention. All the assessments required to be completed at each time points are shown in the Table 2.

Proportion of inappropriate BZRAs prescription

The BZRAs prescription information of each psychiatrist within the baseline period (3 months before the intervention) and intervention period (0-3 month) and follow-up period (3-6 month) will be extracted from the outpatient prescription database in each hospital. The quantities of different kinds of BZRAs will be firstly converted into the DME and accumulated daily DME usage for a patient with each prescription will be calculated [33]. Then, the average daily dosage and continuous days of use per prescription will also be calculated based on the accumulated daily DME usage. The prescription in accordance with any of the following conditions is considered to be inappropriate:

overdose use, long-term use or over-indications use. If the average daily DME usage is more than 40mg/day according to the maximum dose of drug instruction, the prescription is defined as overdose. For the prescription length restrictions of no more than 30 days in China, we conservatively chose a 90-day cut-off as long-term use. Over-indication use is defined as use not in accordance with any of the indications approved by the Chinese FDA.

BZRAs related knowledge

BZRAs related knowledge is assessed using 22 true or false self-made questions concerning the pharmacological effects, indication of use, identification and treatment of addiction, and adverse effects.

Attitude towards BZRAs prescription

A 14-item self-made questionnaire which adopts a 4-point Likert format is used to measure participants' attitude towards various aspects of BZRAs prescription, including indication of use, adverse effects, related guidelines, drug regulations, identification and treatment for BZRAs use disorders, use among special populations and training about BZRAs.

Common adverse effects in prescribing patients

The psychiatrists are asked to select how often the common adverse effects of BZRAs occur in their prescribing patients ranging from "Never" to "Always". The questionnaire has 8 questions and uses a 4-point Likert format, with a score of 1 indicating the lowest frequency.

Self-efficacy

An adapted 10-item version of General Self-Efficacy Scale (GSES) will be used to measure participants' self-efficacy, which refers to one's global confidence in dealing with a variety of demanding situations [34]. Each question is scored on a 4-point Likert scale. The Chinese version of

the GSES has been proven with good reliability and validity [35].

Utility and utilization of electronic intervention

Participants in the intervention group will be asked to complete an online 17-item questionnaire to evaluate the forms, contents, effectiveness and clinical generalization of the intervention. In addition, utilization data will be automatically collected through the WeChat or Ding Talk platform, including accumulated scores, mean number and length of time of reading or watching.

Participant timeline

Psychiatrists who meet the eligibility will be enrolled in the study by getting access to follow the WeChat Official Account Platform on their smartphones after signing electronic informed consent. The demographic information and baseline measurements of secondary outcomes (Table 2) will be collected before group allocation. Participants then will be randomly assigned to receive either electronic interventions or to a waiting list for a period of 3 months. At the end of the 3rd and 6th month, participants will have to finish the online questionnaires comprising knowledge and attitudes towards BZRAs prescription, common adverse effects in prescribing patients and self-efficacy. The utility of electronic intervention will be assessed online at the end of the 3rd month. Meanwhile, their consecutive monthly prescription information of BZRAs (between 3-month before and after the intervention period) will be extracted from the prescription database of the outpatient clinics. Figure 3 displays the flow chart of the study.

Discontinuation

The end point of the study is at the end of 6th month and participants could withdraw at any time for any reason during the study period. If possible, the reasons for withdrawal from the study will

be recorded.

Sample size

Previous study reported that intervention could result in a 19% reduction in BZDs prescriptions after multi-strategic intervention, including local media involvement, provision of treatment guidelines and consumer information, and education and training from medical professionals.[36] Assuming 95% confidence level, 90% statistical power and conservatively estimating a dropout rate of 20%, we will require a sample size of N=54 participants per group.

Recruitment

Five hospitals whose psychiatric outpatient clinics are the most frequently visited by patients within their own areas will be invited to take part in the study. Advertisement for the study is distributed to these five selected hospitals and presented to potential participants. In each of these hospitals, interested psychiatrists who meet the eligibility criteria will be recruited.

Allocation and Blinding

Participants who sign electronic informed consent will be randomized in a 1:1 ratio using block randomization tables (according to different hospitals) generated by SPSS Statistics version 24 (IBM Corp) and assigned to receive either 3-month electronic interventions or to a waiting list. This is an open-label real world study, and it is clearly hard to blind the participants and investigators to group allocation. However, the intervention is an online intervention and conducted in personal private time. Participants in the intervention group will be informed not to

discuss the educational content or lecture videos with those in the control group.

Data Collection

Primary outcome data, the consecutively monthly prescription of each participant within 3-month before and after the intervention, will be extracted from the outpatient prescription database in each hospital. The database contained anonymous prescription information including: (1) patients unique code and demographic data; (2) doctor unique code; and (3) diagnosis and prescription information of drug type, dose, duration, usage, etc. In terms of the secondary outcome data, questionnaires will be collected through online assessments completed by participants on the WeChat official account platform and automatically uploaded to the administrator end. The utilization data of electronic intervention (including accumulated scores, mean number and length of time of reading or watching) will also be stored automatically in the WeChat and Ding Talk backend system of administrator.

Statistical methods

All analyses based on intention-to-treat principle will be conducted with IBM SPSS Statistics version 24.0 with significance level set at $p<0.05$ (two-sided). Student *t test* for continuous variables or *chi-square test* for the proportion of categorical variables will be used to test the baseline comparability of the two groups. The proportion of inappropriate BZRAs prescriptions 3-month before baseline, intervention period and 3-month after the intervention between the two groups will be calculated and reduction of the variable will be compared using the Wilcoxson signed rank test. In terms of the secondary outcomes, Fisher exact test will be used for dichotomous variables, and mixed-effects models for rating scales with group (intervention group vs control group) and time

(0, 3, 6 month) as fixed factors. Descriptive data will be used to describe the utility and utilization of the electronic intervention.

ETHICS AND DISSEMINATION

Research ethics approval

The study was registered at ClinicalTrials.gov (NCT03724669) and designed in accordance with the principles of the Declaration of Helsinki. Because the study collects data from five cities and the whole study would be monitored and approved by five institutional review boards and the ethics committees of Shanghai Mental Health Center (2019-22), the Second Xiangya Hospital of Central South University (2019-190), the West China Hospital of Sichuan University (2019-686), the Affiliated Guangji Hospital of Soochow University (2019-033) and Wuhan Mental Health Center (ky2019.03.01).

Consent or assent

Electronic files of informed consent including purpose, procedures, potential risks and benefits of the study will be sent to the participants through WeChat platform before recruitment. After fully understanding the content of the study, all participants need to sign an electronic informed consent to participate in the study.

Confidentiality

After obtaining informed consent from all participants, the investigators will generate a unique user identifier for each participant in the administrator end. All participant-specific data will be collected and stored in the server with password limiting the access at Shanghai Mental Health Center for privacy protection and data security and be released to the designated researchers who

conduct the data analysis with permission.

Ancillary and Post-trial Care

Participants in the intervention group and control group will receive a gift (about 300 Chinese Yuan) at the end of the study. Meanwhile, participants in the control group will get access to educational materials.

Dissemination policy

The results of the study will be published in peer-reviewed journals or presented at conferences. If the electronic intervention is effective in reducing doctors' inappropriate prescribing behaviors in psychiatric institutions, the educational materials will be released to the public.

RESULTS

The research started in October 2020. The intervention has been completed and the follow-up assessment is expected to be completed at the end of 2021.

DISCUSSION

To the best of our knowledge, no psychiatrist-centered intervention to reduce inappropriate BZRAs prescriptions has been conducted in Chinese psychiatric clinics. The study will verify the effectiveness and utility of the electronic intervention on the appropriate BZRAs prescription for psychiatrists. If this WeChat-based intervention is validated to be effective and with good utility, this will be of great significance for improving the current situations of inappropriate BZRAs prescription and relevant drug management policies. However, it should be noted that the findings could not be extended to psychiatrists in rural areas or other small-scale hospitals in China as the

selected psychiatrists come from tertiary hospitals in urban areas. Moreover, as the index of interest in this study is at psychiatrists' level, changes in BZRAs use at the patient level after intervention are unknown.

Authors' contributions

NZ and HJ conceived the original concept of the protocol for the study. XW, JX, CL, GW and YZ were responsible for the research implementation and data collection. XX, YY, NZ and HJ analyzed data and interpretated the results. XX and YY are co-first authors and drafted the manuscript. All authors critically reviewed the content and approved the final version for publication.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

The prescription data will not be shared with the public. However, if the intervention is effective, the educational materials will be released to the public.

PROTOCAL VERSION

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Protocol amendment number: 02

Table 1 The educational contents for the standardized use of BZRAs.

No.	Content
Module 1: The basis for rational use of BZRAs	
1	Pharmacological effects and rational use of BZDs
2	Pharmacological effects and rational use of Z-drugs
3	The current situation of BZRAs abuse*
Module 2: Rational use of BZRAs in mental disorders	
4	Sleep physiology and rational use of BZRAs in insomnia
5	Non-pharmacological interventions for insomnia
6	Clinical practice of diagnosis and treatment for insomnia*
7	Rational use of BZRAs in other mental disorders
Module 3: Abuse, dependence and brief intervention of BZRAs	
8	Quick identification for BZRAs use disorders
9	Management for long-term use of BZRAs
10	Management and regulations of BZRAs prescription
11	The brief intervention for BZRAs use disorder*
Module 4: Other	
12	Physician-patient communication skills among hazardous use population
13	Situations that BZRAs should be banned or used with caution (case reports)
14	Rational use of BZRAs in special populations (including the elderly, drug abusers, pregnant and lactating women, patients with physical diseases, children and adolescents)

Note: * The educational contents are delivered by online lectures.

Table 2 Time point for the schedule of assessments.

	Assessment Period			
Time point	**-3 month**	**Baseline**	**3 month**	**6 month**
Primary outcome				
Proportion of inappropriate BZRAs prescription		●——	——●——	——●
Secondary outcomes				
BZRAs related knowledge		×	×	×
Attitude towards BZRAs prescription		×	×	×
Common adverse effects in prescribing patients		×	×	×
Self-efficacy		×	×	×
Utility of the electronic intervention			×	
Utilization of the electronic intervention		●——	——●	

Figure 1 The screenshot of the WeChat Official Account Platform for users in the mobile devices: (A) User center interface, (B) Intervention & Assessment interface, (C) educational article of the Intervention module, (D) corresponding exercise after text reading. Note: The page which is actually in Chinese is translated into English.

Figure 2 The screenshot of the administrator web page for investigators. Note: The web page which is actually in Chinese is translated into English.

Figure 3 Flow chart of participants.

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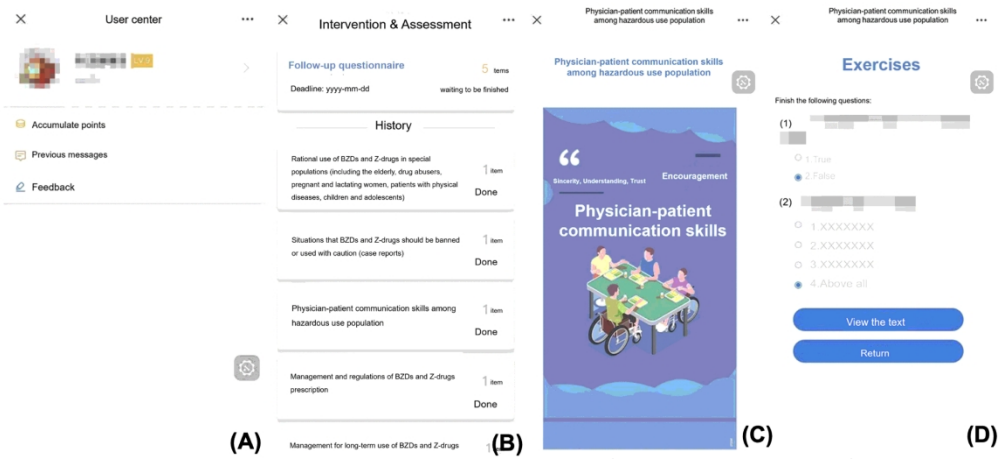

Figure 1 The screenshot of the WeChat Official Account Platform for users in the mobile devices: (A) User center interface, (B) Intervention & Assessment interface, (C) educational article of the Intervention module, (D) corresponding exercise after text reading. Note: The page which is actually in Chinese is translated into English.

419x191mm (300 x 300 DPI)

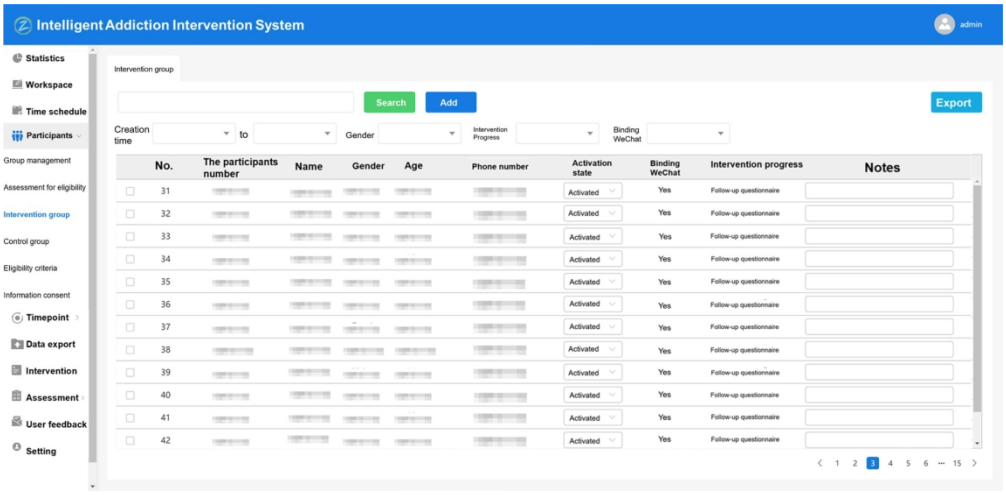

Figure 2 The screenshot of the administrator web page for investigators. Note: The web page which is actually in Chinese is translated into English.

338x165mm (300 x 300 DPI)

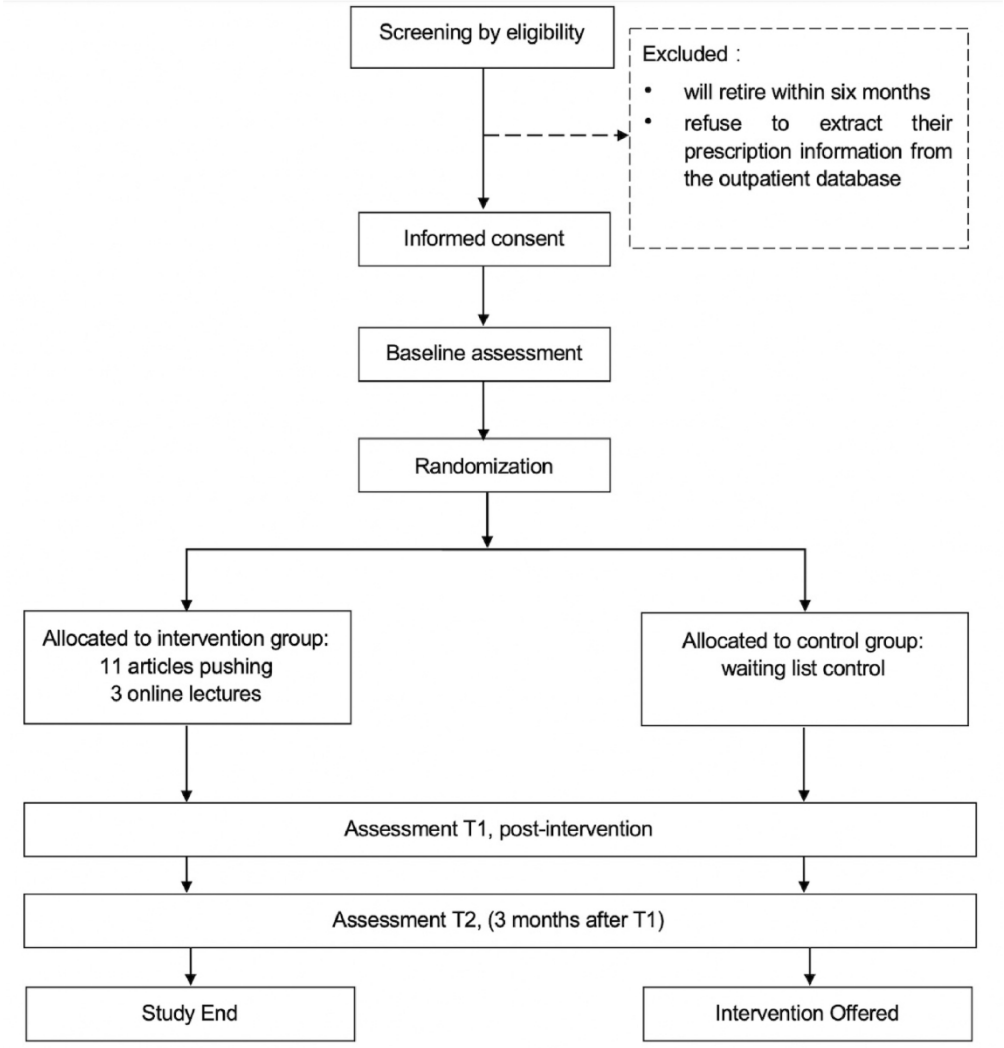

Figure 3 Flow chart of participants.

225x241mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	18
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	16

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: Protocol for a multicentric, real-world randomized controlled trial in China

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The effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: Protocol for a multicentric, real-world randomized controlled trial in China

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ABSTRACT

Introduction: Benzodiazepine receptor agonists (BZRAs), which include benzodiazepines (BZDs) and Z-drugs, are the most commonly prescribed psychotropic drugs worldwide, and their inappropriate use places a significant burden on public health. Given the widespread use of BZRAs in psychiatric settings, this condition may result from doctors' improper prescribing. Researchers have developed an electronic intervention system to assist psychiatrists in prescribing BZRAs appropriately. This study aims to determine the efficacy and utility of electronic intervention in reducing improper BZRAs prescriptions in real-world psychiatric outpatient settings.

Methods and analysis: A multi-center randomized controlled research study will be conducted in real-world settings with licensed psychiatrists with prescription qualifications from five of Chinese most significant regional hospitals that provide high-quality mental health care. Participants will be 1:1 randomly assigned to receive a three-month electronic intervention (11 related information pushing and three online lectures) or be placed on a waiting list. The primary outcome is the change in the proportion of inappropriate BZRAs prescriptions between the baseline period (three months before the intervention) and three months after the intervention. Secondary outcomes will be examined at baseline, the 3rd month and 6th month. The secondary outcomes include psychiatrists' knowledge and attitudes about appropriate BZRAs prescription, the associated side effects of BZRAs among patients, and self-efficacy. To measure the utility, intervention assessment and system utilization data from the intervention group were collected.

Ethics and dissemination: The institutional review board and ethics committees of Shanghai Mental Health Center, Second Xiangya Hospital, West China Hospital, Guangji Hospital, and Wuhan Mental Health Center approved the study. After the study is completed, the results will be published in peer-reviewed journals or presented at conferences. If the educational materials are effective, they are available to the general public.

Clinical trial registration number: ClinicalTrials.gov NCT03724669, https://clinicaltrials.gov/ct2/show/NCT03724669.

Word count: 285

Strengths and limitations of this study

- This will be the first study to evaluate the effectiveness of the psychiatrist-targeted electronic intervention on inappropriate BZRAs prescriptions in Chinese psychiatric outpatient clinics.
- This is a multicenter study, and five of the most influential hospitals in the east, central, and western parts of China were chosen because they have the highest number of outpatient visits for mental health services and thus may be indicative of the country's current situations.
- Because this is an open-label, real-world study, it is difficult to blind participants and investigators to group allocation.

INTRODUCTION

Benzodiazepine receptor agonists (BZRAs), which include benzodiazepines (BZDs) and Z-drugs (e.g., zopiclone, zaleplon, and zolpidem), are one of the most common prescribed psychotropic drugs given in clinical practice throughout the world.[1] BZRAs bind to specific sites on γ-aminobutyric acid (GABA) type A ($GABA_A$) receptors, exerting sedative effects and promoting sleep by amplifying GABA's inhibitory effect.[2] As a result, they are mostly utilized in psychiatric settings to treat insomnia, anxiety, and panic disorder.[3-6] Although BZDs and Z-drugs have distinct receptor affinities for $GABA_A$ subunits, their pharmacologic profiles, efficacy, and side effects are identical.[7] BZRAs adverse medication reactions are connected to an increased risk of cognitive impairment, psychomotor abnormalities, falls, hip fractures, and automobile accidents,[7-10] which greatly burden patients and society. Additionally, prolonged use of BZRAs may develop tolerance, requiring dose adjustment to obtain the desired effect; otherwise, withdrawal symptoms such as anxiety, sleeplessness, and restlessness arise.[11 12] As a result, clinical guidelines recommend that BZRAs are relatively safe for short-term use (generally no more than four weeks).[13]

However, despite growing awareness of the hazards associated with BZRAs, the problem of inappropriate prescription (long-term, overdose, or over-indications) persists globally.[14 15] For instance, a retrospective observational study found that approximately 5.2% of US individuals (aged 18 to 80) used BZDs in 2008, with one-quarter receiving them for an extended period (≥120 days).[1] In British research, only one-third of patients were assessed to be using BZRAs appropriately as per indication.[16] According to a recent study conducted by our research team, approximately 3.0% of outpatients were using BZRAs in a hazardous manner (co-occurrence of overdose and long-term use) and 55.9% of patients were prescribed with an over-indication via prescriptions analysis in

Chinese psychiatric outpatient settings (unpublished).

Nowadays, the interventions for BZRAs use are primarily patient-oriented, and may include self-managed or monitored gradual dose reduction, educational literature, minimal interventions, or physician-administered cognitive behavioral therapy, to increase patients' knowledge of the possible dangers of BZRAs.[17-20] While some physicians are aware of the potentially detrimental effects of long-term BZRA usage, they assert that it is difficult to convince patients to cease the medications. They lack suitable non-pharmacological therapeutic approaches and information to prevent improper BZRAs use.[21] Interventions for service providers, such as prescribing doctors, generally include legislation restriction to limit prescriptions, education, and providing resources for medication replacement among general practitioners.[17] Moore et al. [22] suggested that BZDs be rigorously regulated and prescribed only by medical experts such as psychiatrists. This, however, is not the case. According to a recent cohort study, prescription by psychiatrists is one of the clinical correlates of long-term BZDs use.[23]

To the best of our knowledge, there is no associated evidence about intervention for psychiatrists to reduce the inappropriate prescribing of BZRAs. Due to the vast population in China[24] and the nature of their professions in dealing with troubled people, [25] it is difficult for psychiatrists to devote a full length of time to systematic studies on the most recent BZRAs-related knowledge. Furthermore, nonspecific BZRAs knowledge, inadequate information of the evidence-based alternative treatment, and difficulties implementing medicine according to recommendations in clinical practice contributed to this situation.[18]

New technologies, such as web-based and mobile-based health services, demonstrate potential effects and flexibility in health care services, [26 27] also providing a powerful and easy platform for

distant education. Our research team created an intervention system based on WeChat, China's most popular social media application, to perform various functions such as educational intervention, assessment, feedback, notification, and data management.

The electronic intervention system for appropriate BZRAs use by prescribing psychiatrists was developed using the most recent evidence-based guidelines and expert consensus,. It was created after extensive debate and approval by Chinese addiction experts. The intervention content consists of four modules: the rational use of BZRAs, their rational use in common mental disorders, the quick identification and brief intervention for BZRAs use disorders, and their use for special groups, which are delivered in the form of eleven related information pushing and three online lectures through the electronic intervention system.

The major goal of this study is to determine whether the electronic intervention is beneficial in reducing psychiatrists' inappropriate prescription habits. The secondary goal is to evaluate the intervention's impact on their knowledge and attitudes about appropriate BZRAs prescription, self-efficacy, common side effects in prescribing patients, and whether the electronic intervention has good therapeutic utility in the real world.

METHODS AND ANALYSIS

Trial design

This is a real-world, multi-center, open-label, randomized, and controlled clinical trial involving two parallel groups.

Study setting and recruitment

Participants will be recruited from five of China's most significant regional tertiary hospitals that provide the highest-quality mental health treatments in the east, central, and western regions (three psychiatric hospitals and two general hospitals). All hospitals (Shanghai Mental Health Center, Second Xiangya Hospital of Central South University, West China Hospital of Sichuan University, Affiliated Guangji Hospital of Soochow University, and Wuhan Mental Health Center) have the highest number of outpatient visits for mental health services in their respective areas. The study's advertisement is sent to these five hospitals and given to potential volunteers. Interested psychiatrists who match the eligibility criteria will be recruited in these hospitals.

Eligibility criteria

The study will recruit licensed psychiatrists with prescription qualifications. The inclusion criteria are as follows: (1) at least three-year working experience as a psychiatrist; (2) providing outpatient services for at least one year with a frequency of more than once per week; and (3) willingness to accept electronic interventions for the appropriate BZRAs prescription. The exclusion criteria are as follows: (1) they will retire within 6 months; and (2) they refuse to retrieve their prescription information from the outpatient database.

Patient and Public Involvement

This study does not include any patients. Due to patient anonymity, the necessity for informed permission was waived for patients whose prescribing data were included in the study.

Description of the electronic Intervention system (TiDieR Checklist)

Brief Name

The Intelligent Addiction Intervention System is an electronic intervention system that utilizes WeChat to educate psychiatrists about BZRAs and to promote self-monitoring.

Why: intervention theory

Self-monitoring activities such as assessment and education according to social cognitive theory, [28] can boost self-efficacy beliefs, hence facilitating motivation and behavior.

Intervention Providers

The distant intervention is offered indirectly through text or video by mental health or addiction professionals. Five hundred ninety-five physicians were surveyed regarding their attitudes and knowledge of BZRAs. The initial teaching content was based on the surveys above, the most recent evidence-based guidelines, and experts' consensus [5 12 29-32] regarding the appropriate use of BZRAs. Then, a focus group of eight mental health or addiction experts with at least ten years of experience was convened to discuss in detail the four topics, which included the basis for BZRAs use, their rational use in common mental disorders, the rapid identification, and brief intervention for BZRAs use disorders, and their use in special groups. Transcripts of the recordings were created, and thematic analysis was performed to confirm the important components. Additionally, the intervention content was presented to two Chinese addiction experts for review and consensus on the final form of educational materials (Table 1).

Where: Intervention Location

The intervention is handled online and in personal private time via the WeChat Official Account Platform, which comprises three parts: the users' WeChat page on mobile devices, an administrator web page for investigators, and a backend server for data storage. The platform contains a range of modules, including intervention, assessment, feedback and notification.

Participants who follow the research team's WeChat Official Account Platform have access to two primary menu buttons on the individual chat platform: User center and Intervention & Assessment (Figure 1 A-B). The User center presents the participant with tabs of Accumulate points, Previous message and Feedback. The accumulate points page allows participants to check their points from the Intervention. The Previous message tab allows them to review the intervention content repeatedly. If users encounter any technical difficulties, they can submit a note via the Feedback tab. The Intervention & Assessment option allows users to view a list of tasks (intervention or assessment content) that are either pending completion or have been completed. Each intervention comprises an article that may include visual, video, or audio elements and two to four matching exercises (Figure 1 C-D). To encourage users, they can receive six points for reading the materials and four points for completing the tasks. The assessment module incorporated participant-completed online surveys. Additionally, if users do not complete the intervention or evaluation on time, the system immediately sends them a reminder. After three alerts, the center investigator contacted the participants personally by phone when the task is not completed.

The administrator web page (Figure 2) enables investigators to control group assignments, configure intervention and assessment content, track implementation progress, and send necessary alerts to participants to encourage adherence. Additionally, they can obtain feedback from users regarding any technical or other issues encountered during use. Each center has its name and

password to access the administrator's web page and a principal investigator to supervise the participants at their hospital.

Procedures and Materials

Psychiatrists who match the eligibility criteria will be enrolled in the study after signing electronic informed consent and gaining access to the WeChat Official Account Platform on their cellphones. Demographic data and baseline assessments of secondary outcomes (Table 2) will be obtained before group assignment. After that, participants will be randomized to receive electronic interventions or be placed on a waiting list for three months. Participants were required to complete online questionnaires after the 3rd and 6th month regarding their knowledge and attitudes towards BZRAs prescription, common side effects in prescribing patients, and self-efficacy. At the end of the third month, the utility of electronic intervention will be evaluated online. Meanwhile, the outpatient clinics' prescription database collected their consecutive monthly prescription data for BZRAs (three months before and after the intervention period). The study's flow chart is depicted in Figure 3. The following are the primary and secondary outcomes.

Primary outcome: proportion of inappropriate BZRAs prescription

The prescription data for BZRAs for each psychiatrist was retrieved from the outpatient prescription database at each institution during the baseline period (three months before the intervention) and the intervention period (0-3 months) and the follow-up period (3-6 months). The database includes anonymous prescription information such as (1) the patient's unique code and demographic information; (2) the doctors' unique code; and (3) diagnosis and prescription information on medicine kind, dose, duration, usage, etc. The amounts of various BZRAs will be

first converted to DME, and the cumulative daily DME usage for a patient with each prescription.[33] Then, based on the collected daily DME usage, the average daily dosage and continuous days of use per prescription were computed. Prescriptions written in compliance with any of the following conditions are deemed inappropriate: overdose, long-term usage, or use for contraindications. If the daily DME dose exceeds 40 mg/day, the prescription is an overdose. For the prescription length restrictions of no more than 30 days in China, we conservatively chose a 90-day cut-off as long-term use. Over-indication use is defined as the use, not by any indications approved by the Chinese FDA.

Secondary outcomes

BZRAs-related knowledge: BZRAs related knowledge is tested using 22 true or false self-created questions about the pharmacological effects, an indication of use, identification and treatment of addiction, and adverse effects.

Attitude towards BZRAs prescription: A 14-item self-created questionnaire with a 4-point Likert format is used to assess participants' attitudes toward various aspects of BZRAs prescription, such as an indication of use, adverse effects, related guidelines, drug regulations, identification, and treatment of BZRAs use disorders, use among special populations and BZRAs training.

Common adverse effects in prescribing patients: The psychiatrists are asked to rate how frequently the common side effects of BZRAs occur in their prescribing patients on a scale of "Never" to "Always." The questionnaire contains eight items and is scored on a 4-point Likert scale, with one signifying the lowest frequency.

Self-efficacy: To assess participants' self-efficacy, an adapted 10-item version of the General Self-

Efficacy Scale (GSES) was utilized. Self-efficacy, refers to one's overall confidence in dealing with various difficult situations [34]. Each question is graded on a 4-point Likert scale. The Chinese version of the GSES is reliable and valid. [35]

Electronic intervention utility and utilization: Participants in the intervention group will be asked to complete an online 17-item questionnaire to evaluate the intervention's forms, contents, efficacy, and clinical generalization. Furthermore, utilization data, such as accumulated scores, mean number and length of time reading or watching, were automatically stored in the administrator's WeChat and Ding Talk backend systems.

Randomization and Blinding

Participants will be randomized in a 1:1 ratio using block randomization tables prepared by SPSS Statistics version 24 (IBM Corp) and assigned to receive either three-month electronic interventions or be placed on a waiting list. This is an open-label real world study, and it is obvious that blinding participants and investigators to group allocation is difficult. The intervention group was instructed not to discuss the educational content or lecture videos with the control group.

Intervention

Intervention group. Psychiatrists in the intervention group will receive a three-month electronic educational intervention covering information on standardized use of BZRAs, consisting of two main components: (1) educational articles delivered once a week (11 times total) via the WeChat Official Account Platform, and (2) three additional online lectures from addiction specialists via the

Ding Talk platform, an intelligent working platform created by Alibaba Group. The comprehensive information about the online lectures will be given to the WeChat individual messaging platform twice, one a day and once an hour before the event. On the Ding Talk platform, participants can attend live lectures or examine the videos at any time with arbitrary intensity.

Control group: Participants in the control group will complete the assessment modules without any educational information regarding the online lectures. They acquired educational texts and view online lectures after completing their study.

Tailoring and Fidelity

Participants assigned to the intervention group receive the identical intervention material and the duration and intensity of the voluntary intervention. The participants will be observed and reminded by the lead investigator in each center to ensure that the intervention is carried out according to protocol. If users do not complete the intervention or evaluation on time, they send them an automatic reminder. After three notifications, the investigator contacts the participants directly via phone when the task has not been completed. The electronic intervention's utilization data is also used to assess adherence.

Discontinuation

The study's endpoint is after the sixth month, and participants may withdraw at any moment for any reason during the study term. If possible, the reasons for leaving the study will be documented.

Sample size

A previous study found that a multi-strategic intervention, involving local media involvement,

treatment guidelines, and consumer information, and education and training from medical professionals might result in a 19% reduction in BZDs prescriptions.[36] Assuming a 95% confidence level, 90% statistical power, and a dropout rate of 20%, a sample size of N=54 individuals per group was needed.

Statistical methods

All analyses based on the intention-to-treat principle will be carried out using IBM SPSS Statistics version 24.0 and a significant level of $p<0.05$ (two-sided). To compare the baselines of the two groups, the Student *t-test* for continuous variables and the *chi-square test* for categorical variables will be utilized. The proportion of inappropriate BZRAs prescriptions between the two groups is calculated three months before baseline, during the intervention period, and three months following the intervention, and the reduction of the variable will be compared using the Wilcoxson signed- rank test. In terms of secondary outcomes, the Fisher exact test will be utilized for dichotomous variables, and mixed-effects models will be used for rating scales with fixed factors (intervention group versus control group) and time (0, 3, and 6 months). Descriptive data will be employed to describe the utility and utilization of the electronic intervention.

ETHICS AND DISSEMINATION

Research ethics approval

The trial was filed at ClinicalTrials.gov (NCT03724669) and was designed in compliance with the Helsinki Declaration principles. Because the study collects data from five cities, the entire study would be monitored and approved by five institutional review boards and ethics committees:

Shanghai Mental Health Center (2019-22), Second Xiangya Hospital of Central South University (2019-190), West China Hospital of Sichuan University (2019-686), Affiliated Guangji Hospital of Soochow University (2019-033) and Wuhan Mental Health Center (ky2019.03.01).

Consent or assent

Before recruiting, participants received electronic consent files outlining the study's goal, methods, potential risks, and benefits via the WeChat platform. After thoroughly understanding the study's subject, all volunteers must sign an electronic informed consent form to participate.

Confidentiality

After receiving informed consent from all participants, the investigators will develop a unique user identifier for each participant in the administrator end. All participant-specific data will be gathered and stored on a server at the Shanghai Mental Health Center with password-protected access to protect participant privacy and data security and supplied to designated researchers who undertake data analysis with consent.

Ancillary and Post-trial Care

After the trial, each participant in the intervention and control groups will receive a gift (about 300 Chinese Yuan). Meanwhile, control group members have accessed educational resources.

Dissemination policy

The study's findings will be published in peer-reviewed publications or presented at professional meetings. If electronic intervention reduces physicians' inappropriate prescribing habits in mental facilities, teaching materials will be available to the general public.

RESULTS

The research is scheduled to begin in October 2020. The intervention has concluded, and a follow-up assessment is scheduled for the end of 2021.

DISCUSSION

To the best of our knowledge, no psychiatrist-centered intervention has been done in Chinese psychiatric clinics to reduce improper BZRA prescriptions. The study will confirm the effectiveness and value of the electronic intervention on psychiatrists' prescription of appropriate BZRAs. Suppose this WeChat-based intervention is shown to be effective and useful. In that case, it significantly impacted addressing the existing situation of inappropriate BZRAs prescription and associated drug control regulations.

There are various limitations of the study. It should be highlighted that the findings could not be applied to psychiatrists in rural areas or other small-scale hospitals in China because the selected psychiatrists are from tertiary institutions in urban areas. Furthermore, because the trial was conducted across five sites, it is unclear if psychiatrists at each site were randomly assigned to intervention and control groups, which raises concerns about contamination bias. We did not consider clustering in our analysis since we want to undertake a pilot study first to see how beneficial this intervention is in tertiary hospitals. The types are generally similar. Second, considering that steady dosage reduction can take many months, the time frame for evaluating this effect is relatively short. We believe that it is possible to notice improvements in doctors' prescribing patterns within 6 months. However, we will extend our follow-up period if adequate funds are available. Third, because the indicator of interest in this study is at the level of psychiatrists, changes in BZRAs use at the patient level after intervention are unknown.

Authors' contributions

NZ and HJ conceived the original concept of the protocol for the study. XW, JX, CL, GW and YZ were responsible for the research implementation and data collection. XX, YY, NZ and HJ analyzed data and interpreted the results. XX and YY are co-first authors and drafted the manuscript. All authors critically reviewed the content and approved the final version for publication.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

The prescription data will not be shared with the public. However, if the intervention is effective, the educational materials will be released to the public.

PROTOCOL VERSION

Issue date: 20 June 2018

Protocol amendment number: 02

Table 1 The educational contents for the standardized use of BZRAs.

No.	Content
Module 1: The basis for rational use of BZRAs	
1	Pharmacological effects and rational use of BZDs
2	Pharmacological effects and rational use of Z-drugs
3	The current situation of BZRAs abuse*
Module 2: Rational use of BZRAs in mental disorders	
4	Sleep physiology and rational use of BZRAs in insomnia
5	Non-pharmacological interventions for insomnia
6	Clinical practice of diagnosis and treatment for insomnia*
7	Rational use of BZRAs in other mental disorders
Module 3: Abuse, dependence and brief intervention of BZRAs	
8	Rapid identification for BZRAs use disorders
9	Management for long-term use of BZRAs
10	Management and regulations of BZRAs prescription
11	The brief intervention for BZRAs use disorder*
Module 4: Other	
12	Physician-patient communication skills among hazardous use population
13	Situations that BZRAs should be banned or used with caution (case reports)
14	Rational use of BZRAs in special populations (including the elderly, drug abusers, pregnant and lactating women, patients with physical diseases, children and adolescents)

Note: * The educational contents are delivered in the form of online lectures.

Table 2 Time point for the schedule of assessments.

	Assessment Period			
Time point	**-3 month**	**Baseline**	**3 month**	**6 month**
Primary outcome				
Proportion of inappropriate BZRAs prescription		●——	——●——	——●
Secondary outcomes				
BZRAs-related knowledge		×	×	×
Attitude towards BZRAs prescription		×	×	×
Common adverse effects in prescribing patients		×	×	×
Self-efficacy		×	×	×
Utility of the electronic intervention			×	
Utilization of the electronic intervention		●——	——●	

Figure 1 The screenshot of the WeChat Official Account Platform for users in the mobile devices: (A) User center interface, (B) Intervention & Assessment interface, (C) educational article of the Intervention module, (D) corresponding exercise after text reading. Note: The page which is actually in Chinese is translated into English.

Figure 2 The screenshot of the administrator web page for investigators. Note: The web page which is actually in Chinese is translated into English.

Figure 3 Flow chart of participants.

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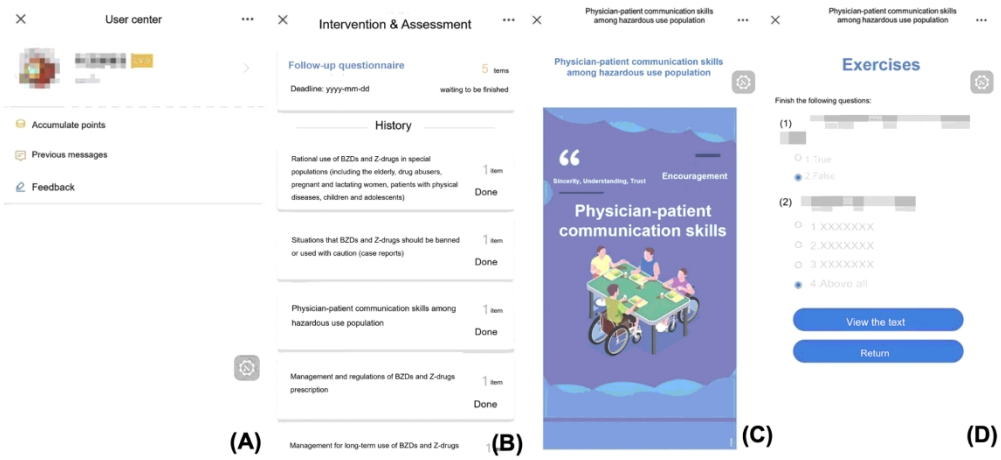

Figure 1 The screenshot of the WeChat Official Account Platform for users in the mobile devices: (A) User center interface, (B) Intervention & Assessment interface, (C) educational article of the Intervention module, (D) corresponding exercise after text reading. Note: The page which is actually in Chinese is translated into English.

419x191mm (400 x 400 DPI)

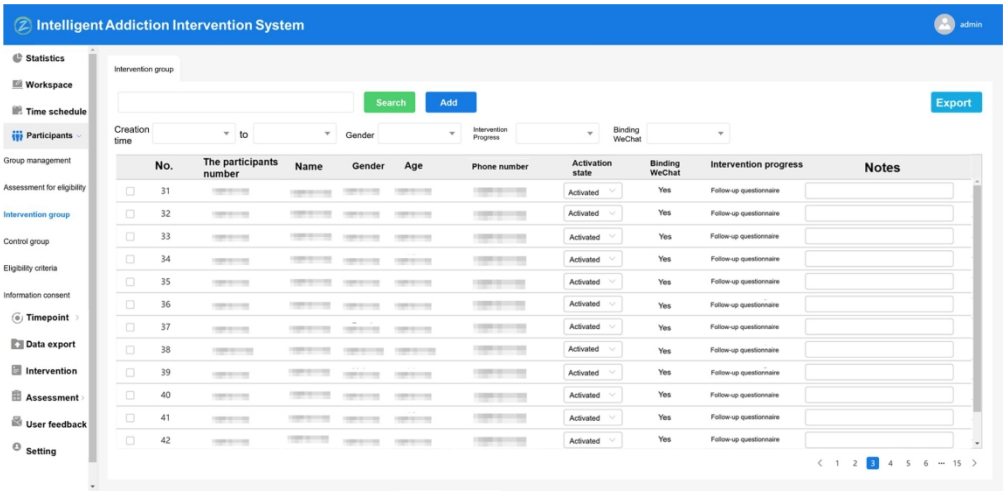

Figure 2 The screenshot of the administrator web page for investigators. Note: The web page which is actually in Chinese is translated into English.

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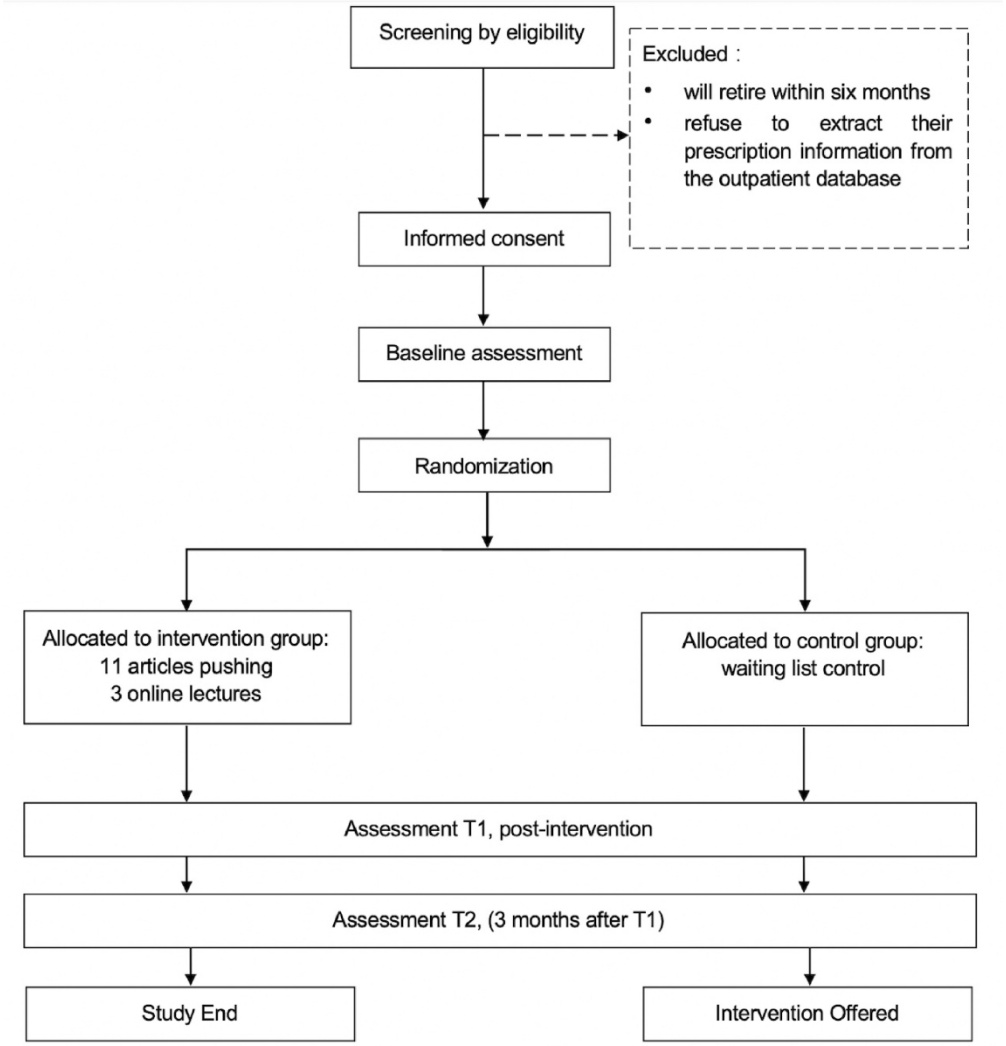

Figure 3 Flow chart of participants.

225x241mm (400 x 400 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	18
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13&15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10&20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8&15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14-15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15&17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: Protocol for a multicentric, real-world randomized controlled trial in China

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The effectiveness and utility of an electronic intervention for appropriate benzodiazepine and Z-drugs prescription in psychiatric clinics: Protocol for a multicentric, real-world randomized controlled trial in China

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ABSTRACT

Introduction: Benzodiazepine receptor agonists (BZRAs), which include benzodiazepines (BZDs) and Z-drugs, are the most commonly prescribed psychotropic drugs worldwide, and their inappropriate use places a significant burden on public health. Given the widespread use of BZRAs in psychiatric settings, this condition may result from doctors' improper prescribing. Researchers have developed an electronic intervention system to assist psychiatrists in prescribing BZRAs appropriately. This study aims to determine the efficacy and utility of electronic intervention in reducing improper BZRAs prescriptions in real-world psychiatric outpatient settings.

Methods and analysis: A multi-center randomized controlled research study will be conducted in real-world settings with licensed psychiatrists with prescription qualifications from five of Chinese most significant regional hospitals that provide high-quality mental health care. Participants will be 1:1 randomly assigned to receive a three-month electronic intervention (11 related information pushing and three online lectures) or be placed on a waiting list. The primary outcome is the change in the proportion of inappropriate BZRAs prescriptions between the baseline period (three months before the intervention) and three months after the intervention. Secondary outcomes will be examined at baseline, the 3rd month and 6th month. The secondary outcomes include psychiatrists' knowledge and attitudes about appropriate BZRAs prescription, the associated side effects of BZRAs among patients, and self-efficacy. To measure the utility, intervention assessment and system utilization data from the intervention group were collected.

Ethics and dissemination: The institutional review board and ethics committees of Shanghai Mental Health Center, Second Xiangya Hospital, West China Hospital, Guangji Hospital, and Wuhan Mental Health Center approved the study. After the study is completed, the results will be published in peer-reviewed journals or presented at conferences. If the educational materials are effective, they are available to the general public.

Clinical trial registration number: ClinicalTrials.gov NCT03724669, https://clinicaltrials.gov/ct2/show/NCT03724669.

Word count: 285

Strengths and limitations of this study

- This will be the first study to evaluate the effectiveness of the psychiatrist-targeted electronic intervention on inappropriate BZRAs prescriptions in Chinese psychiatric outpatient clinics.
- This is a multicenter study, and five of the most influential hospitals in the east, central, and western parts of China were chosen because they have the highest number of outpatient visits for mental health services and thus may be indicative of the country's current situations.
- Because this is an open-label, real-world study, it is difficult to blind participants and investigators to group allocation.

INTRODUCTION

Benzodiazepine receptor agonists (BZRAs), which include benzodiazepines (BZDs) and Z-drugs (e.g., zopiclone, zaleplon, and zolpidem), are one of the most common prescribed psychotropic drugs given in clinical practice throughout the world.[1] BZRAs bind to specific sites on γ-aminobutyric acid (GABA) type A ($GABA_A$) receptors, exerting sedative effects and promoting sleep by amplifying GABA's inhibitory effect.[2] As a result, they are mostly utilized in psychiatric settings to treat insomnia, anxiety, and panic disorder.[3-6] Although BZDs and Z-drugs have distinct receptor affinities for $GABA_A$ subunits, their pharmacologic profiles, efficacy, and side effects are identical.[7] BZRAs adverse medication reactions are connected to an increased risk of cognitive impairment, psychomotor abnormalities, falls, hip fractures, and automobile accidents,[7-10] which greatly burden patients and society. Additionally, prolonged use of BZRAs may develop tolerance, requiring dose adjustment to obtain the desired effect; otherwise, withdrawal symptoms such as anxiety, sleeplessness, and restlessness arise.[11 12] As a result, clinical guidelines recommend that BZRAs are relatively safe for short-term use (generally no more than four weeks).[13]

However, despite growing awareness of the hazards associated with BZRAs, the problem of inappropriate prescription (long-term, overdose, or over-indications) persists globally.[14 15] For instance, a retrospective observational study found that approximately 5.2% of US individuals (aged 18 to 80) used BZDs in 2008, with one-quarter receiving them for an extended period (≥120 days).[1] In British research, only one-third of patients were assessed to be using BZRAs appropriately as per indication.[16] According to a recent study conducted by our research team, approximately 3.0% of outpatients were using BZRAs in a hazardous manner (co-occurrence of overdose and long-term use) and 55.9% of patients were prescribed with an over-indication via prescriptions analysis in

Chinese psychiatric outpatient settings (unpublished).

Nowadays, the interventions for BZRAs use are primarily patient-oriented, and may include self-managed or monitored gradual dose reduction, educational literature, minimal interventions, or physician-administered cognitive behavioral therapy, to increase patients' knowledge of the possible dangers of BZRAs.[17-20] While some physicians are aware of the potentially detrimental effects of long-term BZRA usage, they assert that it is difficult to convince patients to cease the medications. They lack suitable non-pharmacological therapeutic approaches and information to prevent improper BZRAs use.[21] Interventions for service providers, such as prescribing doctors, generally include legislation restriction to limit prescriptions, education, and providing resources for medication replacement among general practitioners.[17] Moore et al. [22] suggested that BZDs be rigorously regulated and prescribed only by medical experts such as psychiatrists. This, however, is not the case. According to a recent cohort study, prescription by psychiatrists is one of the clinical correlates of long-term BZDs use.[23]

To the best of our knowledge, there is no associated evidence about intervention for psychiatrists to reduce the inappropriate prescribing of BZRAs. Due to the vast population in China[24] and the nature of their professions in dealing with troubled people, [25] it is difficult for psychiatrists to devote a full length of time to systematic studies on the most recent BZRAs-related knowledge. Furthermore, nonspecific BZRAs knowledge, inadequate information of the evidence-based alternative treatment, and difficulties implementing medicine according to recommendations in clinical practice contributed to this situation.[18]

New technologies, such as web-based and mobile-based health services, demonstrate potential effects and flexibility in health care services, [26 27] also providing a powerful and easy platform for

distant education. Our research team created an intervention system based on WeChat, China's most popular social media application, to perform various functions such as educational intervention, assessment, feedback, notification, and data management.

The electronic intervention system for appropriate BZRAs use by prescribing psychiatrists was developed using the most recent evidence-based guidelines and expert consensus,. It was created after extensive debate and approval by Chinese addiction experts. The intervention content consists of four modules: the rational use of BZRAs, their rational use in common mental disorders, the quick identification and brief intervention for BZRAs use disorders, and their use for special groups, which are delivered in the form of eleven related information pushing and three online lectures through the electronic intervention system.

The major goal of this study is to determine whether the electronic intervention is beneficial in reducing psychiatrists' inappropriate prescription habits. The secondary goal is to evaluate the intervention's impact on their knowledge and attitudes about appropriate BZRAs prescription, self-efficacy, common side effects in prescribing patients, and whether the electronic intervention has good therapeutic utility in the real world.

METHODS AND ANALYSIS

Trial design

This is a real-world, multi-center, open-label, randomized, and controlled clinical trial involving two parallel groups.

Study setting and recruitment

Participants will be recruited from five of China's most significant regional tertiary hospitals that provide the highest-quality mental health treatments in the east, central, and western regions (three psychiatric hospitals and two general hospitals). All hospitals (Shanghai Mental Health Center, Second Xiangya Hospital of Central South University, West China Hospital of Sichuan University, Affiliated Guangji Hospital of Soochow University, and Wuhan Mental Health Center) have the highest number of outpatient visits for mental health services in their respective areas. The study's advertisement is sent to these five hospitals and given to potential volunteers. Interested psychiatrists who match the eligibility criteria will be recruited in these hospitals.

Eligibility criteria

The study will recruit licensed psychiatrists with prescription qualifications. The inclusion criteria are as follows: (1) at least three-year working experience as a psychiatrist; (2) providing outpatient services for at least one year with a frequency of more than once per week; and (3) willingness to accept electronic interventions for the appropriate BZRAs prescription. The exclusion criteria are as follows: (1) they will retire within 6 months; and (2) they refuse to retrieve their prescription information from the outpatient database.

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Description of the electronic Intervention system (TiDieR Checklist)

Brief Name

The Intelligent Addiction Intervention System is an electronic intervention system that utilizes WeChat to educate psychiatrists about BZRAs and to promote self-monitoring.

Why: intervention theory

Self-monitoring activities such as assessment and education according to social cognitive theory, [28] can boost self-efficacy beliefs, hence facilitating motivation and behavior.

Intervention Providers

The distant intervention is offered indirectly through text or video by mental health or addiction professionals. Five hundred ninety-five physicians were surveyed regarding their attitudes and knowledge of BZRAs. The initial teaching content was based on the surveys above, the most recent evidence-based guidelines, and experts' consensus [5 12 29-32] regarding the appropriate use of BZRAs. Then, a focus group of eight mental health or addiction experts with at least ten years of experience was convened to discuss in detail the four topics, which included the basis for BZRAs use, their rational use in common mental disorders, the rapid identification, and brief intervention for BZRAs use disorders, and their use in special groups. Transcripts of the recordings were created, and thematic analysis was performed to confirm the important components. Additionally, the intervention content was presented to two Chinese addiction experts for review and consensus on the final form of educational materials (Table 1).

Where: Intervention Location

The intervention is handled online and in personal private time via the WeChat Official Account Platform, which comprises three parts: the users' WeChat page on mobile devices, an administrator web page for investigators, and a backend server for data storage. The platform contains a range of modules, including intervention, assessment, feedback and notification.

Participants who follow the research team's WeChat Official Account Platform have access to two primary menu buttons on the individual chat platform: User center and Intervention & Assessment (Figure 1 A-B). The User center presents the participant with tabs of Accumulate points, Previous message and Feedback. The accumulate points page allows participants to check their points from the Intervention. The Previous message tab allows them to review the intervention content repeatedly. If users encounter any technical difficulties, they can submit a note via the Feedback tab. The Intervention & Assessment option allows users to view a list of tasks (intervention or assessment content) that are either pending completion or have been completed. Each intervention comprises an article that may include visual, video, or audio elements and two to four matching exercises (Figure 1 C-D). To encourage users, they can receive six points for reading the materials and four points for completing the tasks. The assessment module incorporated participant-completed online surveys. Additionally, if users do not complete the intervention or evaluation on time, the system immediately sends them a reminder. After three alerts, the center investigator contacted the participants personally by phone when the task is not completed.

The administrator web page (Figure 2) enables investigators to control group assignments, configure intervention and assessment content, track implementation progress, and send necessary alerts to participants to encourage adherence. Additionally, they can obtain feedback from users regarding any technical or other issues encountered during use. Each center has its name and

password to access the administrator's web page and a principal investigator to supervise the participants at their hospital.

Procedures and Materials

Psychiatrists who match the eligibility criteria will be enrolled in the study after signing electronic informed consent and gaining access to the WeChat Official Account Platform on their cellphones. Demographic data and baseline assessments of secondary outcomes (Table 2) will be obtained before group assignment. After that, participants will be randomized to receive electronic interventions or be placed on a waiting list for three months. Participants were required to complete online questionnaires after the 3rd and 6th month regarding their knowledge and attitudes towards BZRAs prescription, common side effects in prescribing patients, and self-efficacy. At the end of the third month, the utility of electronic intervention will be evaluated online. Meanwhile, the outpatient clinics' prescription database collected their consecutive monthly prescription data for BZRAs (three months before and after the intervention period). The study's flow chart is depicted in Figure 3. The following are the primary and secondary outcomes.

Primary outcome: proportion of inappropriate BZRAs prescription

The prescription data for BZRAs for each psychiatrist was retrieved from the outpatient prescription database at each institution during the baseline period (three months before the intervention) and the intervention period (0-3 months) and the follow-up period (3-6 months). The database includes anonymous prescription information such as (1) the patient's unique code and demographic information; (2) the doctors' unique code; and (3) diagnosis and prescription information on medicine kind, dose, duration, usage, etc. The amounts of various BZRAs will be

first converted to DME, and the cumulative daily DME usage for a patient with each prescription.[33] Then, based on the collected daily DME usage, the average daily dosage and continuous days of use per prescription were computed. Prescriptions written in compliance with any of the following conditions are deemed inappropriate: overdose, long-term usage, or use for contraindications. If the daily DME dose exceeds 40 mg/day, the prescription is an overdose. For the prescription length restrictions of no more than 30 days in China, we conservatively chose a 90-day cut-off as long-term use. Over-indication use is defined as the use, not by any indications approved by the Chinese FDA.

Secondary outcomes

BZRAs-related knowledge: BZRAs related knowledge is tested using 22 true or false self-created questions about the pharmacological effects, an indication of use, identification and treatment of addiction, and adverse effects.

Attitude towards BZRAs prescription: A 14-item self-created questionnaire with a 4-point Likert format is used to assess participants' attitudes toward various aspects of BZRAs prescription, such as an indication of use, adverse effects, related guidelines, drug regulations, identification, and treatment of BZRAs use disorders, use among special populations and BZRAs training.

Common adverse effects in prescribing patients: The psychiatrists are asked to rate how frequently the common side effects of BZRAs occur in their prescribing patients on a scale of "Never" to "Always." The questionnaire contains eight items and is scored on a 4-point Likert scale, with one signifying the lowest frequency.

Self-efficacy: To assess participants' self-efficacy, an adapted 10-item version of the General Self-

Efficacy Scale (GSES) was utilized. Self-efficacy, refers to one's overall confidence in dealing with various difficult situations [34]. Each question is graded on a 4-point Likert scale. The Chinese version of the GSES is reliable and valid. [35]

Electronic intervention utility and utilization: Participants in the intervention group will be asked to complete an online 17-item questionnaire to evaluate the intervention's forms, contents, efficacy, and clinical generalization. Furthermore, utilization data, such as accumulated scores, mean number and length of time reading or watching, were automatically stored in the administrator's WeChat and Ding Talk backend systems.

Randomization and Blinding

Participants will be randomized in a 1:1 ratio using block randomization tables prepared by SPSS Statistics version 24 (IBM Corp) and assigned to receive either three-month electronic interventions or be placed on a waiting list. This is an open-label real world study, and it is obvious that blinding participants and investigators to group allocation is difficult. The intervention group was instructed not to discuss the educational content or lecture videos with the control group.

Intervention

Intervention group. Psychiatrists in the intervention group will receive a three-month electronic educational intervention covering information on standardized use of BZRAs, consisting of two main components: (1) educational articles delivered once a week (11 times total) via the WeChat Official Account Platform, and (2) three additional online lectures from addiction specialists via the

Ding Talk platform, an intelligent working platform created by Alibaba Group. The comprehensive information about the online lectures will be given to the WeChat individual messaging platform twice, one a day and once an hour before the event. On the Ding Talk platform, participants can attend live lectures or examine the videos at any time with arbitrary intensity.

Control group: Participants in the control group will complete the assessment modules without any educational information regarding the online lectures. They acquired educational texts and view online lectures after completing their study.

Tailoring and Fidelity

Participants assigned to the intervention group receive the identical intervention material and the duration and intensity of the voluntary intervention. The participants will be observed and reminded by the lead investigator in each center to ensure that the intervention is carried out according to protocol. If users do not complete the intervention or evaluation on time, they send them an automatic reminder. After three notifications, the investigator contacts the participants directly via phone when the task has not been completed. The electronic intervention's utilization data is also used to assess adherence.

Discontinuation

The study's endpoint is after the sixth month, and participants may withdraw at any moment for any reason during the study term. If possible, the reasons for leaving the study will be documented.

Sample size

A previous study found that a multi-strategic intervention, involving local media involvement,

treatment guidelines, and consumer information, and education and training from medical professionals might result in a 19% reduction in BZDs prescriptions.[36] Assuming a 95% confidence level, 90% statistical power, and a dropout rate of 20%, a sample size of N=54 individuals per group was needed.

Statistical methods

All analyses based on the intention-to-treat principle will be carried out using IBM SPSS Statistics version 24.0 and a significant level of $p<0.05$ (two-sided). To compare the baselines of the two groups, the Student *t-test* for continuous variables and the *chi-square test* for categorical variables will be utilized. The proportion of inappropriate BZRAs prescriptions between the two groups is calculated three months before baseline, during the intervention period, and three months following the intervention, and the reduction of the variable will be compared using the Wilcoxson signed- rank test. In terms of secondary outcomes, the Fisher exact test will be utilized for dichotomous variables, and mixed-effects models will be used for rating scales with fixed factors (intervention group versus control group) and time (0, 3, and 6 months). Descriptive data will be employed to describe the utility and utilization of the electronic intervention.

ETHICS AND DISSEMINATION

Research ethics approval

The trial was filed at ClinicalTrials.gov (NCT03724669) and was designed in compliance with the Helsinki Declaration principles. Because the study collects data from five cities, the entire study would be monitored and approved by five institutional review boards and ethics committees:

Shanghai Mental Health Center (2019-22), Second Xiangya Hospital of Central South University (2019-190), West China Hospital of Sichuan University (2019-686), Affiliated Guangji Hospital of Soochow University (2019-033) and Wuhan Mental Health Center (ky2019.03.01).

Consent or assent

Before recruiting, participants received electronic consent files outlining the study's goal, methods, potential risks, and benefits via the WeChat platform. After thoroughly understanding the study's subject, all volunteers must sign an electronic informed consent form to participate.

Confidentiality

After receiving informed consent from all participants, the investigators will develop a unique user identifier for each participant in the administrator end. All participant-specific data will be gathered and stored on a server at the Shanghai Mental Health Center with password-protected access to protect participant privacy and data security and supplied to designated researchers who undertake data analysis with consent.

Ancillary and Post-trial Care

After the trial, each participant in the intervention and control groups will receive a gift (about 300 Chinese Yuan). Meanwhile, control group members have accessed educational resources.

Dissemination policy

The study's findings will be published in peer-reviewed publications or presented at professional meetings. If electronic intervention reduces physicians' inappropriate prescribing habits in mental facilities, teaching materials will be available to the general public.

RESULTS

The research is scheduled to begin in October 2020. The intervention has concluded, and a follow-up assessment is scheduled for the end of 2021.

DISCUSSION

To the best of our knowledge, no psychiatrist-centered intervention has been done in Chinese psychiatric clinics to reduce improper BZRA prescriptions. The study will confirm the effectiveness and value of the electronic intervention on psychiatrists' prescription of appropriate BZRAs. Suppose this WeChat-based intervention is shown to be effective and useful. In that case, it significantly impacted addressing the existing situation of inappropriate BZRAs prescription and associated drug control regulations.

There are various limitations of the study. It should be highlighted that the findings could not be applied to psychiatrists in rural areas or other small-scale hospitals in China because the selected psychiatrists are from tertiary institutions in urban areas. Furthermore, because the trial was conducted across five sites, it is unclear if psychiatrists at each site were randomly assigned to intervention and control groups, which raises concerns about contamination bias. We did not consider clustering in our analysis since we want to undertake a pilot study first to see how beneficial this intervention is in tertiary hospitals. The types are generally similar. Second, considering that steady dosage reduction can take many months, the time frame for evaluating this effect is relatively short. We believe that it is possible to notice improvements in doctors' prescribing patterns within 6 months. However, we will extend our follow-up period if adequate funds are available. Third, because the indicator of interest in this study is at the level of psychiatrists, changes in BZRAs use at the patient level after intervention are unknown.

Authors' contributions

NZ and HJ conceived the original concept of the protocol for the study. XW, JX, CL, GW and YZ were responsible for the research implementation and data collection. XX, YY, NZ and HJ analyzed data and interpreted the results. XX and YY are co-first authors and drafted the manuscript. All authors critically reviewed the content and approved the final version for publication.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

The prescription data will not be shared with the public. However, if the intervention is effective, the educational materials will be released to the public.

PROTOCOL VERSION

Issue date: 20 June 2018

Protocol amendment number: 02

Table 1 The educational contents for the standardized use of BZRAs.

No.	Content
Module 1: The basis for rational use of BZRAs	
1	Pharmacological effects and rational use of BZDs
2	Pharmacological effects and rational use of Z-drugs
3	The current situation of BZRAs abuse*
Module 2: Rational use of BZRAs in mental disorders	
4	Sleep physiology and rational use of BZRAs in insomnia
5	Non-pharmacological interventions for insomnia
6	Clinical practice of diagnosis and treatment for insomnia*
7	Rational use of BZRAs in other mental disorders
Module 3: Abuse, dependence and brief intervention of BZRAs	
8	Rapid identification for BZRAs use disorders
9	Management for long-term use of BZRAs
10	Management and regulations of BZRAs prescription
11	The brief intervention for BZRAs use disorder*
Module 4: Other	
12	Physician-patient communication skills among hazardous use population
13	Situations that BZRAs should be banned or used with caution (case reports)
14	Rational use of BZRAs in special populations (including the elderly, drug abusers, pregnant and lactating women, patients with physical diseases, children and adolescents)

Note: * The educational contents are delivered in the form of online lectures.

Table 2 Time point for the schedule of assessments.

	Assessment Period			
Time point	**-3 month**	**Baseline**	**3 month**	**6 month**
Primary outcome				
Proportion of inappropriate BZRAs prescription		●———	●———	●
Secondary outcomes				
BZRAs-related knowledge		×	×	×
Attitude towards BZRAs prescription		×	×	×
Common adverse effects in prescribing patients		×	×	×
Self-efficacy		×	×	×
Utility of the electronic intervention			×	
Utilization of the electronic intervention		●———	●	

Figure 1 The screenshot of the WeChat Official Account Platform for users in the mobile devices: (A) User center interface, (B) Intervention & Assessment interface, (C) educational article of the Intervention module, (D) corresponding exercise after text reading. Note: The page which is actually in Chinese is translated into English.

Figure 2 The screenshot of the administrator web page for investigators. Note: The web page which is actually in Chinese is translated into English.

Figure 3 Flow chart of participants.

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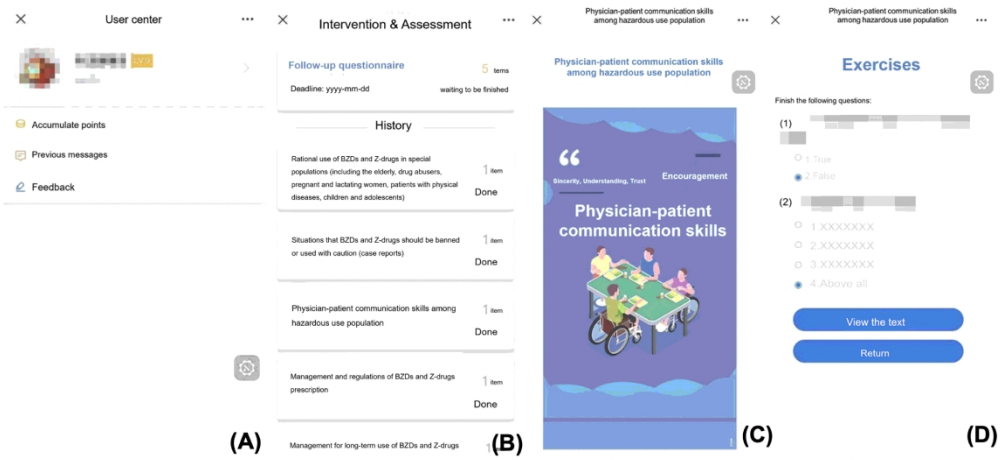

Figure 1 The screenshot of the WeChat Official Account Platform for users in the mobile devices: (A) User center interface, (B) Intervention & Assessment interface, (C) educational article of the Intervention module, (D) corresponding exercise after text reading. Note: The page which is actually in Chinese is translated into English.

419x191mm (400 x 400 DPI)

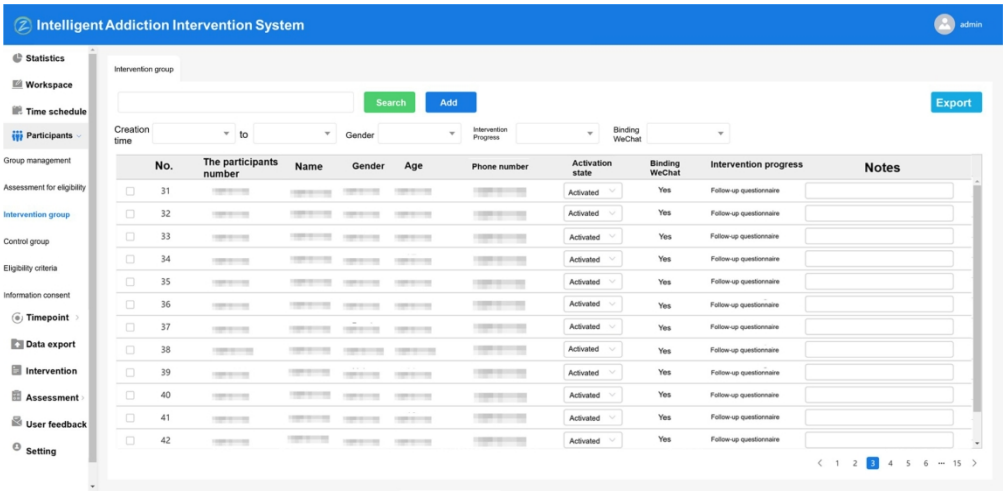

Figure 2 The screenshot of the administrator web page for investigators. Note: The web page which is actually in Chinese is translated into English.

338x165mm (400 x 400 DPI)

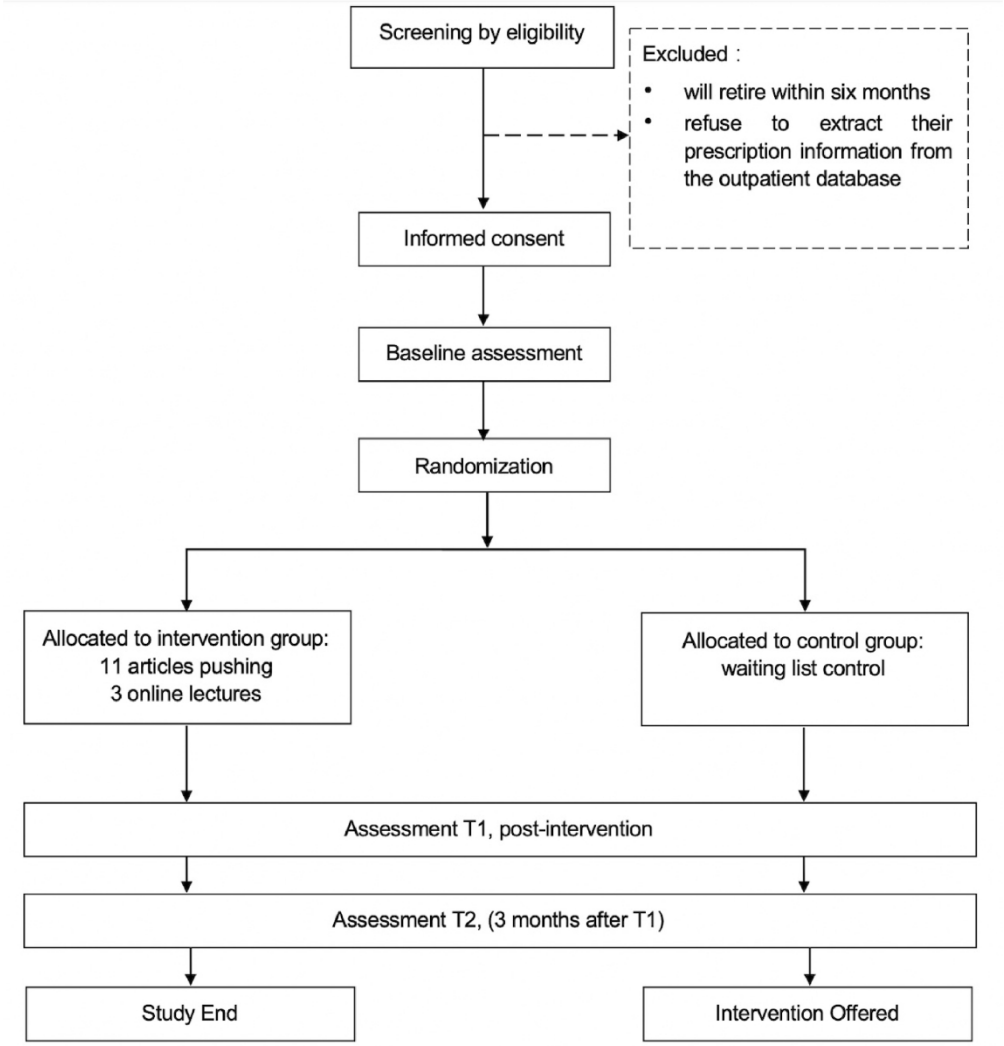

Figure 3 Flow chart of participants.

225x241mm (400 x 400 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	18
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1&17
	5b	Name and contact information for the trial sponsor	17
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13&15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10&20
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8&15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14-15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15&17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	15

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	8	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	8	_____
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	10-12	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	10	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	8	_____
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	8-10	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	8-10	_____

	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	12-13	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	13	_____
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	_____
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	13	_____
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	_____

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).