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Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial

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Abstract

Introduction: Schizophrenia is a severe, chronic, and disabling mental illness. Non-adherence to medication and relapse may lead to poorer patient function. This randomized controlled study, under the acronym LEAN, is designed to improve medication adherence and high relapse among people with schizophrenia in resource poor settings. **Methods/Analysis**: the community-based **LEAN** has four parts: 1) **L**ay health supporters (LHSs), mostly family members who will help supervise patient medication, monitor relapse and side effects, and facilitate access to care, 2) an **E**-platform to support two-way mobile text and voice messaging to remind patients to take medication; and alert LHSs when patients are non-adherent, 3) an **A**ward system to motivate patients and strengthen LHS support, and 4) iNtegration of the efforts of patients and LHSs with those of village doctors, township mental health administrators and psychiatrist via the e-platform. A random sample of 258 villagers with schizophrenia will be drawn from the schizophrenic "686" Program registry for the 9 Xiang-dialect towns of the Liuyang municipality in China. The sample will be further randomized into a control group and a treatment group of equal sizes, and each group will be followed for 6 months after launch of the intervention. The primary outcome will be medication adherence as measured by pill-counts and supplemented by pharmacy records. Other outcomes include symptoms and level of function. Outcomes will be assessed primarily when patients present for medication refill visits scheduled every two months over the 6-month follow-up period. Data from the study will

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be analyzed using ANCOVA for the program effect and an intent-to-treat approach. **Ethics and dissemination**: University of Washington: 49464 G; Central South University: CTXY-150002-6. Results will be published in peer-reviewed journals with deidentified data made available on FigShare. **Trial Registration**: ChiCTR-ICR-15006053

Keywords*:* schizophrenia, medication adherence, mHealth, lay health worker, implementation science, wait-list control, RCT, "686" program

Strengths and Limitations

Strengths:

- The application of mHealth is designed to synergize the patient support capacity of lay health supporters, village doctors, mental health administrators and psychiatrists in an integrated manner so that the technology actually strengthens the health system.
- The active engagement of family members augments case supervision.
- The study, evaluating the real world effectiveness of LEAN, emphasizes the implementation parts so as to increase the likelihood of adopting the potentially effective solution.
- The trial is intent to have global implications, especially insofar as the intervention is designed to exclude elements peculiar to China's socio-economic and/or political situation.

Limitations:

- The short duration may not allow sufficient assessment of functional changes and limit analysis of the long-term effect on adherence.
- The choice of relatively simple assessment tools (pill-counts vs. urinalysis) may create challenges of obtaining accurate adherence level.
- Assuming that improved medication adherence will lead to better patient life-functioning may be problematic.

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WHO Trial Registration Data Set

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	ChiCTR-ICR-15006053
Date of registration in primary registry	8 Mar, 2015
Secondary identifying numbers	N/A
Source(s) of monetary or material support	China Medical Board Fogarty International Center, NIH
Primary sponsor	Central South University, China
Secondary sponsor(s)	University of Washington, USA
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Public title	Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial
Scientific title	Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial
Countries of recruitment	China
Health condition(s) or problem(s) studied	Schizophrenia
Intervention(s)	Intervention: Lay Health Supporter plus SMS Messaging System Control: Case as ususal (ie. “686” Program)
Key inclusion and exclusion criteria	Inclusion: “686” program participant; diagnosed as schizophrenia; residing in Liuyang Xiang-dialect area Exclusion: Patients who missed past 3 drug refills; currently hospitalized; people physically not capable of using voice or text messaging
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: subject not blinded; caregiver, investigator,

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DATA CATEGORY	INFORMATION
	outcomes assessor blinded Primary purpose: improving health Effectiveness study
Date of first enrolment	July 2015
Target sample size	258
Recruitment status	Recruiting
Primary outcome(s)	Medication adherence as measured by pill-counts (medication taken over medication prescribed)
Key secondary outcomes	Symptoms as measured by Clinical Global Impression in Schizophrenia; and functions as measured by 12-item proxy-administered WHO Disability Assessment Schedule 2.0

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Introduction

Background and Rationale

Schizophrenia, characterized by hallucination, delusion, disorganized thinking and negative symptoms, is a chronic and disabling mental disorder which is commonly associated with impairment in social and occupational functioning[1]. Though schizophrenia cannot be cured, most people with schizophrenia can be effectively treated for symptoms with antipsychotic medicines[2]. However, of treated patients, 50% are non-adherent with medication[3]; moreover, even under conditions of compliance, 50% of patients suffer relapse within 1 year of their latest episode[4]. The "686" Program, a massive coutry-wide government effort in China, is a relatively inexpensive and practical model that provides community-based mental health care with limited human and financial resources[5 6]. But the program faces the challenges of poor medication adherence and high relapse - 26% of the program participants never, 39% intermittently, and only 35% regularly take prescribed medications[7]. This research aims to develop, and evaluate, a financially and operationally feasible and sustainable intervention (with the acronym LEAN) to address those "686" program challenges.

Hypothesis

We hypothesize that the LEAN plus "686" solution, as compared to the present "686" standard of care only, will improve medication adherence, reduce the incidence of schizophrenia symptoms, and ultimately result in improved social and occupational functioning for enrollees.

Study Setting

The intervention will be implemented and tested in "686" program particiants in the Xiang-dialect area (a total of 9 towns) of the rural townships of Liuyang Municipality in the Hunan province of China, with an intent to produce solutions that can be adapted and applied in other LMCs with limited mental health resources. Liuyang has developed a three-tier "686" model extending from Liuyang Mental Health Hospital (MHH) to township health centers (THCs) to village clinics that consists of five compnents: 1) patient screening by village doctors (VDs) and mental health administrators (MHAs); 2) registering confirmed cases into"686" with consent; 3) Psychiatrists

touring townships to provide free consultation and medication every two months ("bi-monthly visits"); 4) case management by MHA; and 5) regular monitoring by VDs[8 9 10] (Figure 1).

FIGURE 1 THE "686" PROGRAM SERVICE MODEL

Source: authors.

LEAN

LEAN as an acronym is somehow inspired by Toyota's principle in lean manufacturing[11] although our focus is to add value, minimize waste, and maintain simplicity throughout program implementation. The acronym LEAN summarizes the critical components of the proposed intervention (Figure 2). The LEAN participants can opt out of LEAN anytime by texting us or inform VDs, MHAs by phone or in person.

FIGURE 2 LEAN

LEAN
L: Lay health supporter (LHS)
E: E-platform with e-reminder, e-monitor, and e-educator via mobile text/voice messaging
A: Award system analogous to Taekwondo ranks
N: iNtegrating the L, E and A and "686" Program structure into a lean and coordinated approach

Source: authors.

Lay Health Supporter (LHS)

For each patient in the intervention, LEAN will identify a LHS — a member of the patient's family if possible or a community volunteer (such as a member of the village senior club) — who will perform simple but important roles in support of the patient: 1) facilitate patient medication adherence with prompts from the e-reminders, 2) monitor for early signs of relapse and for medication side effects using checklists from the e-monitor, and 3) team up with the village doctor and the township mental health administrator to facilitate treatment adjustments and, if needed, emergent hospital care.

E-platform

The e-platform employs three main modules: The e-reminder sends the patient up to two reminders either by text or voice messages at 15 minutes interval until the patient responds with confirmation that the scheduled

medication has been taken. Failure to send a confirmation will trigger up to two text alerts to the patient's LHS, prompting the LHS to check in with the patient and text back the result. The e-monitor assists LHSs and patients in detecting signs of relapse and monitoring medication side effects using relevant checklists texted to the patient and LHS at regular intervals (See relapse checklist in appendix. And findally, the e-educator will send periodic SMS messages to the patient, LHS, MHA, and VD educating them on schizophrenia symptoms, medication, adherence strategies, relapse, rehabilitation and social resources.

Award System

Patients and LHSs will accumulate points for responding to SMS messages. Each of their texted confirmation back to the LEAN system will accumulate one point, which will be recorded automatically by the computer system. The points, counted every two months, will advance their Taekwondo-like belt ranking and entitle them to a small gift when they come for the bi-monthly visit to be presented by a LEAN program staff.

iNtegration

The efforts of the patient and LHS to improve medication adherence and reduce relapses will be integrated, facilitated by the e-platform, with those of the VD, MHA and psychiatrist so that the innovations of LEAN strengthens the existing health system. With this integration, non-adherence and relapses detected can then be actually handled with LHS, VDs, MHAs and psychiatrist take concerted effort for promot treatment adjustments or referrals for emergent hospitalization.

Mechanism of LEAN

The mechanism of LEAN medication adherence is based on an adapted health belief model (HBM) (Figure 3)[12 13]. According to this theory, people with schizophrenia make their medication adherence decisions based on push (patients' self-motivation in improving health) and pull factors that include three elements: 1) Patients' perception of the threat posed by schizophrenia; 2) Patients' perceived net benefit of adhering to therapy, a calculation involving the benefits of therapy minus costs; and 3) Action cues such as the above-mentioned e-reminders or

mass media health promotion campaigns. Figure 3 illustrates the interface of various LEAN elements with the components of the health belief model.

FIGURE 3 MECHANISM FOR LEAN MEDICATION ADHERENCE

Note: The red dots indicate LEAN components.

Source: adapted from the health belief model[17].

The development of LEAN has been guided not only by the HBM as a theoretical framework, but was also informed by empirical evidence, particularly in the areas of human resources for health (HRH) and mobile health (mHealth). Much of the literature in HRH suggests that "task shifting" - cascading appropriate tasks from more skilled psychiatrists to less specialized MHAs/VDs and to LHS improves access and efficacy when HRH are lacking or deficient[14 15] (Liuyang has only 1.35 psychiatrists/1.42 specialist nurses versus 8.59 psychiatrists/29.15 nurses for high income countries per 100,000 population in 2011[12]). The e-platform facilitates efficient communication and integration of this network of human resources. Moreover, much evidence supports the use of reminders to improve medication adherence[16 17 18 19 20].

Study Population and the LEAN Sample

People in Liuyang speak three distinct dialects: Gan, Xiang and Hakka. The Xiang-dialect area, located in the west of Liuyang municipality, has 9 townships, 98 villages and a population of 356,900. The "686" Program maintains a roster of patients with schizophrenia in the Xiang-dialect area of Liuyang municipality (total: 631 in 2011) (Figure 4), which forms the study population. The characteristics of this population most relevant to our study are summarized in Table 1.

FIGURE 4 MAP OF THE XIANG-DIALECT AREA OF LIUYANG

Note: Yellow-shaded region on the map of China is Hunan Province.

TABLE 1 "686" PROGRAM ENROLLEES WITH SCHIZOPHRENIA IN THE XIANG-DIALECT AREA OF LIUYANG (YEAR 2011)

(1). "686" enrollees with schizophrenia only, accounting for approximately 80% of all "686" patients in Liuyang

(2). Cell phone ownership by family members of "686" Program enrollees

(3). Function assessed by MHAs using three sub-categories: daily living, social activities and work.

(4). A score of 0-1 calculated as the percentage of prescribed drugs taken by the patient in the month immediately before the survey

Source: author, Liuyang "686" Program Registry (Year 2011)

Inclusion and Exclusion Criteria

The following criteria more precisely define the study population by establishing eligibility requirements for subject recruitment. Rationales for inclusion and exclusion criteria are given in parentheses.

Inclusion:

1. "686" Program enrollees.
2. Diagnosed as having schizophrenia according to criteria established in the *Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-5®)[21]
3. Physically reside in the Xiang-dialect area of Liuyang Municipality

Exclusion:

1. Individuals registered in the Xiang-dialect area of Liuyang Municipality, but living elsewhere as migrant workers (as a community-based intervention, LEAN requires residence in the local community)
2. Patients who have missed three immediate past drug refills (in this case, they have *de facto* dropped out of the "686" Program)
3. People who are currently hospitalized (again, LEAN intervention requires sustained community residence)
4. People physically incapable of using voice or text messaging, e.g. individuals with hearing and/or vision impairment, or who are severely disabled (ability to utilize SMS is necessary for the LEAN intervention)

Sampling Frame, the LEAN Sample and Recruitment

The most recent "686" Program registry of patients with schizophrenia will be used as the sampling frame, from which we aim to draw 258 patients as the LEAN sample. To that end, a statistician otherwise not associated with the project will first create a recruitment list of 400 people drawn at random from the sampling frame. Assuming

that 15% of those selected will prove ineligible and that a further 20% will elect not to participate, an initial list of 400 should ensure a final recruitment of no less than 258 subjects. MHAs will provide an initial screening by cross-checking the recruitment list against their own records in order to verify eligibility. Recruitment by project staff will occur during patients' bi-monthly medication refill visits, when psychiatrists will re-confirm the diagnoses of those on the list. Project staff will conduct home visits within one month of their expected bi-monthly visit to recruit those not contacted at the refill visits. At the end of the recruitment, the LEAN sample will be randomly divided by the same statistician into a treatment group and a control group of equal sizes by a statistician not otherwise involved in the study (Figure 5).

FIGURE 5 THE LEAN POPULATION, SAMPLE AND ASSIGNMENT

Source: authors

Sample Size Calculation

Though the distribution of our primary outcome (adherence, scored as the percentage of drugs taken of those prescribed) is unlikely to be normally distributed, the sample calculation follows standard procedures for the hypothesis of equal population means based on t-test and the comparison of sample means. Since our sample size is large, the central limit theorem ensures that our sample means will be approximately normally distributed, regardless of the underlying distribution of the data.

Assuming a 5% type I error and a 10% dropout ratio for a total sample size of 258 (129 for each of the two comparison groups), the study of 232 participants (after 10% dropping out of 258) will have 85% power to detect an effect size of 0.13 (see appendices). This means that if the adherence score for the control group is 0.72 (SD=0.33), the study will have sufficient power to detect a program effect if adherence for the treatment group is equal to or greater than 0.85. The control adherence of 0.72 used in the sample calculation is based on the self-reported adherence of 0.75 in our study population from the "686" registry.

The proposed sample size of 258 will also satisfy the power requirement for a subgroup analysis of patients who are non-adherent at baseline. Given the ratio of non-adherence to full-adherence (0.55:0.45) of the population reported in the registry, the study will include at least 140 baseline non-adherent subjects available for the sub-

group analysis. Again, assuming 5% type I error and a 10% dropout rate, the study will have 85% power to detect an effect size of 0.18 among the sub-group: If the adherence rate for the control is 0.42 (SD=0.35), the study will be powered to detect a program effect if the adherence of the treatment group is equal to or greater than 0.6 (Table 2).

TABLE 2 SAMPLE SIZE CALCULATION SCENARIOS

(1). Standard deviation in parentheses

(2). Sample calculation assuming power of 0.85, significance level of 0.05, and a 10% dropout rate

(3). See the STATA codes for the sample calculation in appendix

(4). Sample size of the baseline non-adherent sub-group achieved with a LEAN total sample of 258.

Source: authors

Metrics & Measurement

Primary and Secondary Outcomes

The primary outcome will be a continuous medication adherence score from 0 (no adherence) to 1 (complete adherence), calculated as the percentage of drugs taken out of those prescribed over a designated time period (the preceding month). Medication adherence was chosen as the primary outcome on the grounds that 1) adherence correlates with symptom relief, and symptoms correlate with function[22 23]; 2) significant improvement in symptoms, and function, is likely to extend beyond the duration of the study; and 3) improving adherence is valuable in its own right. However, symptoms and functions will also be tracked as the secondary outcomes.

Methods of Assessment and Timeline

Figure 6 summaries how and when we assess outcomes, which piggyback on "686" Program activities, in particular, the bi-monthly meetings with patients. All data will be double-entered into and managed by Research electronic data capture (REDCap) system[24]. All outcome assessors, including psychiatrists and program staff, will be blinded to the control or treatment status of program participants; any inadvertent un-blinding will be noted in order to record the time of the incident and persons involved.

FIGURE 6 RECRUITMENT AND OUTCOME ASSESSMENT

Source: authors

Medication Adherence: Pill counts

Pill counts, to be conducted by project staff when patients bring their pill bottles to the bi-monthly refill, will be used as the primary, objective and inexpensive measurement of medication adherence, to be complemented by pharmacy dispensing records from the "686" registry system. Other objective measures, such serum/urine drug level[25], are clinically and financially impossible to implement. In addition, the Morisky Medication Adherence Scale[26], the Brief Adherence Rating Scale (BARS)[27], and the Drug Attitude Inventory-10 (DAI-10) [28] will supplement the objective assessment. At baseline and again at the end of the study, patients who were no-shows at the bi-monthly visit will be visited and assessed at their homes.

Symptoms – CGI-Sch

From among the "big three" instruments for schizophrenic symptoms[29] we chose the Clinical Global Impression in Schizophrenia (CGI-Sch) primarily due to its brevity and ease of use[30]. "686" Program psychiatrists will assess patients using the CGI-Sch during bi-monthly visits throughout the trial.

Functions – WHODAS 2.0

LEAN will use the 12-item proxy-administered WHO Disability Assessment Schedule 2.0 to assess patient functions, considering its brevity to administer, excellent psychometric properties, and availability of a validated Chinese version[31 32]. Public health students enlisted as program staff will administer the WHODAS to patients and their family members during bi-monthly visits.

A few other "public health" indicators such as suicide, drug abuse, attacking people, destroying things and wandering will be captured by the existing "686" registry. In addition many process, cost and service utilization indicators will be captured and recorded by the e-platform logs and "686" administrative registry. These process indicators will facilitate analysis of various links in the LEAN mechanism, and surveillance for breaks in the chain.

Trial Design

We adopt a wait-list design with subjects followed-up for six months after launch of the intervention. The wait-list control design is increasingly used in psychotherapy studies, primarily to address the ethical dilemma involved in

withholding a potentially beneficial treatment from the control group. Participants recruited into the study are randomized into a treatment group and a "wait-listed" control group. In stage one (the 6 month period following program initiation), the intervention will be applied to the intervention group only, while the wait-list group will receive usual care per the regular "686" protocol; in stage two (a subsequent 6 month period), the wait-list group will receive the intervention, having "waited" through stage one. Analysis of the intervention will be conducted based on baseline and end-point data collected on both groups during stage one only due to our budget constraint for data collection. Consequently, the only difference between a wait-list design and a traditional two-arm randomized control trial (RCT) is that the control group is also able to benefit from the treatment once the formal study is complete.

Model & Analysis

Unadjusted analysis, ANCOVA and DiD

We mainly considered the issue of efficiency (precision of the estimator) and bias in our choice of the analytical methods. The literature suggests that ANCOVA provides higher efficiency than difference-in-difference (DiD) and the unadjusted model in RCT and is the optimal model for RCT analysis [33](Figure 7). The LEAN analysis will include as covariates the strong baseline predictors of outcome that are empirically suggested by other studies, and will comprise adherence, WHODAS and CGI-Sch scores, as well as indices of negative symptoms, substance use, medication side effects, and family supervision[34]. It should be noted that while our response variable, expressed as an adherence score from 0-1, may yield values greater than one, those out-of-bound predictions do not invalidate the model since the study's purpose is to produce a "risk difference" (difference in mean adherence between intervention and control groups) rather than an individual prediction. Critically, the large sample size and the central limit theorem ensure that this approach will yield valid inferences of the risk difference despite non-normal adherence outcomes.

FIGURE 7 THREE APPROACHES TO RCT ANALYSIS

Source: adapted from Siyuan Zhang paper[35]

Intent-to-Treat

An intent-to-treat (IIT) analysis will be used to analyze all subjects regardless of treatment actually received. Estimating the IIT effect is more appropriate than the per-protocol or per-treat methods since the LEAN trial is a pragmatic trial, which is to say, it is meant to determine the effectiveness of LEAN as a real-world solution.

Subgroup Analysis

We plan to conduct two subgroup analyses, both with strong theory base and possible interaction effects. The first concerning the non-adherent group at baseline is sufficiently powered (Table 2) (our adherence-focused intervention is more likely to work better for the initially non-adherent group). The other subgroup analyses will be conducted to assess level of functions.

Missing Data

Reasons for missing data will be recorded. Multiple imputation methods will be used so that sensitivity analyses will be conducted to assess the robustness of trial results under different methods.

Monitoring

Considering the short duration of the intervention, we do not have a data monitoring committee. At the mid-point of the trial, outcomes and text messaging data will be analyzed to detect any abnormality. The text messaging system also provides a means for ongoing monitoring of any patient response.

Ethics and Dissemination

The study has obtained IRB approval from University of Washington (49464 G) and Central South University (CTXY-150002-6). Any substantive modification to the protocol will seek a formal approval from the IRBs. Program staff will train and obtain informed consent from both patients and LHSs. Patient data will be securely entered and stored in RedCap and only de-identified information will be used for analysis. Study results will seek peer-reviewed publications with de-identified data made available on Figshare[36].

Discussion

Several aspects of this study is worth noting. First, the application of mHealth is designed to synergize the patient support capacity of LHSs, VDs, MHAs and psychiatrists in an integrated manner so that the technology actually

strengthens the health system. Second, the active engagement of LHS augment case supervision. Third, the study, evaluating the real world effectiveness of LEAN, emphasizes the implementation parts so as to increase the likelihood of adopting the potentially effective solution. Fourth, the trial is intent to have global implications, especially insofar as the intervention is designed to exclude elements peculiar to China's socio-economic and/or political situation.

The study is faced with several limitations. First, its short duration may not allow sufficient assessment of functional changes and limit analysis of the long-term effect on adherence. Second, our choice of relatively simple assessment tools (pill-counts vs. urinalysis) may create challenges of obtaining accurate adherence level. Third, assuming that improved medication adherence will lead to better patient life-functioning may be problematic. There is concern that the psychiatrists with limited training from Liuyang MHH may deliver inappropriate treatments, adherence to which will be of insufficient benefit. Finally, despite efforts to ensure the generalizability of LEAN, the existing "686" infrastructure may make Liuyang a unique location, although spirit of LEAN should provide useful information for other LMCs.

List of abbreviations

BPRS: Brief Psychiatric Rating Scale

CGI-Sch: Clinical Global Impression in Schizophrenia

DiD: difference-in-difference model

DSM-5® : Diagnostic and Statistical Manual of Mental Disorders-5

HBM: health belief model

HRH: human resources for health

IIT: intent-to-treat

LHS: Lay health supporter

LMC: low and mid-income countries

MHA: mental health administrators

mHealth: mobile health

MHH: mental health hospital

PANSS, Positive and Negative Syndrome Scale

RCT: randomized control trial (RCT)

THC: township health centers

VD: village doctor

Competing interests

The authors declare that they have no competing interests

Authors' contributions

All authors contributed to the conceptualization and the design of the study. WG obtained majority of the funding. DX and WG conceived of the prototype of the intervention, the study design, analytical methods and creation of the team. DX drafted the first manuscript. SX and WG secured the study site. EC and SX contributed significantly to the intervention strategy and the methods of outcome assessment. JH, MN and HH provided critical review and revision to the design and analytical methods of the study. JS contributed to the theoretical framework of the study. KS edited and improved the manuscript. HB helped design and write the economic evaluation part of the protocol. SG steered the direction of the study and contributed significantly to the revision of the manuscript. All authors read and revised the initial manuscript and approved the final version.

Authors' information

A researcher at the Sun Yat-sen University School of Public Health, DX is leading an effort to develop the Sun Yat-sen Global Health Institute; concurrently as the PhD candidate in Global Health (implementation science tract) at the University of Washington (UW) and a Fogarty Global Health fellow, he is conducting LEAN as his dissertation project (DX's LinkedIn profile https://www.linkedin.com/in/romanxu). As a researcher and a clinical doctor of

the School of Public Health (SPH) of Central South University (CSU), WG is the principle investigator of this project awarded by the China Medical Board (CMB) through a highly competitive open completion in 2012. SG (health system researcher/professor at UW) chairs the dissertation committee of DX which consists of EC (psychiatrist/professor at University of Rochester), JS (psychologist/professor at UW), JH (bio-statistician/professor at UW), and MN (bio-statistician/assistant professor at UW). SX, a leading public health psychiatrist/professor in China, heads the Mental Health Policy Program of CSU. HH is an associate professor of bio-statistics at Tulane University. KS, a medical dcotor/professor, and HB, an economist specialized in cost-efffectivenss analysis, are both at the Univesity of Texas.

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Appendices

E-reminder example

"Xiao Wang (Little Wang in Chinese, a diminuitive often used in friendly conversation), we have the forecast for two beautiful sunny days and hope you will enjoy some sunshine (or: you may see more and more children in the village as the winter break starts today). We also hope you have taken your meds today. If yes, please text "yes" to let us know. Lao Zhang (Old Zhang)".

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Sample Calculation in STATA

sampsi .72 .85, sd1(.33) sd2(.33) alpha(0.05) power(.85)

Estimated sample size for two-sample comparison of means

Test Ho: m1 = m2, where m1 is the mean in population 1

and m2 is the mean in population 2

Assumptions:

alpha = 0.0500 (two-sided)

power = 0.8500

m1 = .72

m2 = .85

sd1 = .33

sd2 = .33

n2/n1 = 1.00

Estimated required sample sizes:

n1 = 116

n2 = 116

Early Signs Questionnaire, Short Form

The following form is reprinted with permission from Marvin Herz, MD. From The University of Rochester.

NAME_____ DATE_____

Compared to last week, has there been an increase in any of the following symptoms?

	YES	NO
1. Problems with sleep	_____	_____
2. Problems with appetite	_____	_____

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3. Depression . . . . . _____

_____

4. Problems with concentration . . . . . _____ _____

5. Restlessness . . . . . _____ _____

6. Tension or nervousness . . . . . _____ _____

7. Use of alcohol . . . . . _____

_____

8. Use of street drugs (includes marijuana) . . . . . _____ _____

9. Hearing voices or seeing things that others can't hear or see . . . . . _____ _____

10. Less pleasure gained from things you usually enjoy . . . . . _____ _____

11. Feeling people were watching you, were against you,

or were talking about you . . . . . _____ _____

12. Preference for being alone and/or been spending less time

with other people . . . . . _____ _____

13. Arguments with others . . . . . _____ _____

14. Inability to get your mind off of one or two things . . . . . _____ _____

Have any other symptoms appeared or increased? . . . . . _____ _____

If so, what were they?_____

_____

_____

Did anything specific happen last week which upset you? . . . . . _____

_____

If so, what was it?_____

_____

_____

Have you been taking your medication as it is prescribed for you? . . . . . _____ _____

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Reprinted with permission from Marvin Herz, MD. Clinicians may reproduce this scale for use in their clinical practice. Researchers who wish to use the Early Signs Questionnaire in multi-patient studies should contact Dr. Herz at University of Rochester Medical Center, Strong Ties Community Support Program, 1650 Elmwood Avenue, Rochester, NY 14620, (716)275-0300, x2337, marvin_herz@urmc.rochester.edu

E-educator Example

The example below illustrates a two way and adaptive "conversation" to be directed by the e-educator.

The example below illustrates a two-way adaptive "conversation" to be directed by the e-educator.

Sender: "Have you had challenges lately in persuading (patient name) to take medication? Text "yes" or "no"."

If the response is "no," the conversation terminates. The answer "yes" will prompt the following message:

Sender: "Please choose from among the following four items the reasons why (patient name) is not taking his medicine by texting back the number: 1. He feels good and does not want to; 2. … 3. ….

The chosen items will prompt more detailed information/instruction for the recipient.

Patient informed Consent form

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、枨冲和镇头九镇开展"中国浏阳乡村精神分裂症患者手机短信支持项目"（简称"林项目"）。现邀请您参加本项目，在参加项目之前，请仔细阅读以下内容，它可以帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

"林项目"的目的是提高资源匮乏地区精神分裂症患者用药依从性，从而提高他们的功能和生活质量；核心内容是为志愿参加国家重症精神病项目管理的精神分裂症患者提供额外的免费服务，服务内容包括：每日为患者提供手机短信用药提醒；选择一位家庭成员或其他患者能接受的人员作为"非专业照看人"（简称"照看人"），照看人将接受简单培训，

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在手机短信的帮助下，帮助发现患者疾病复发的征兆以及病人用药后的副作用情况，并通过手机短信进行报告；收到报告后，精防专干将协助照看人和患者提高用药依从性，或通过浏阳精神病院医生调整用药，或安排紧急门诊或住院治疗。为了验证试验的效果，参加“林项目”的人员将随机（计算机抽签）分成两组，在头六个月，一组接受“林项目”的手机短信等服务；另一组作为对照，仅接受原有日常服务；六个月后，原仅接受日常服务的对照组也开始接受短信服务（除非当时数据证明干预效果为负面），至少进行六个月。

在项目过程中，我们将收集若干数据用于验证项目的有效性。数据收集将主要在您每两月领药时进行，主要由您的主治医生根据您的诊断状况填写，或通过您自身填报相关表格。我们估计每次占用您 20 分钟左右的额外时间。收集的主要数据包括：您的基本人口学信息（如年龄，性别，民族等）；精神分裂症的症状和功能；服药情况。您的这些数据大部分已经在目前的国家重症精神病项目中采集。项目组将在法律的范围内，严格为您的数据保密，将遵守中国和美国两国给病人隐私安全的保密要求。您的数据将存储在严格加密的“红帽”电子平台；书面信息将保留在加锁的安全之地，保留五年后销毁。我们承诺您的数据将仅作为研究所用。我们所有的研究报告在分析和报告时，您所有的身份信息都将隐去（包括您的所有身份证号码，姓名，所在地，健康档案号等等）。

“林项目”的参与完全是志愿的。您可以在任何时候决定退出“林项目”的服务。退出“林项目”项目不会影响您目前参与的国家重症精神病项目中所享有的任何服务和福利。退出的方式可以是：短信回复退出项目；电话或信件通知村医或精防专干；电话或信件通知中南大学项目团队。

通过参与“林项目”，您可能福利包括：接收到与精神卫生有关的知识性短信；短信用药提醒；可能更快捷的药物调整；可能更快捷的门诊和住院安排。如果您没有手机或手机短信计划，项目组可能会为您提供一台免费的简易手机。与“林项目”有关的所有短信都是免费的（包括您回复我们的短信）。虽然如前我们将竭尽全力来保护您的隐私数据，参加项目的可能风险主要是您隐私的泄露。

如您对项目有任何疑问，请随时联系项目团队。我们的联系方式如下：龚雯洁（中南大学）13607445252 gongwenjie@csu.edu.cn 徐东（美国华盛顿大学）13910988979 roman.xu@gmail.com

如您在了解以上信息后，决定参加“林项目”，请在下页签字：

研究项目：“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）

Ver 14-7Oct15

课题协作单位：中南大学、美国华盛顿大学

同意申明：

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我知道参加本研究可能产生的风险和收益。我知晓参加研究是自愿的，我确认已有充足时间对此进行考虑，而且明白：

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我将获得一份注明日期的知情同意书副本。

最后，我决定同意参加本项研究，并保证尽量遵从医嘱。

参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

LHS informed consent form

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、枨冲和镇头九镇开展“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）。现邀请您作为患者的照看人参加本项目，在参加项目之前，请仔细阅读以下内容，它可以帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

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科医生发放病人相关的报告，以便与他们可以及时的作出反馈，调整用药，安排门诊和住院服务等。具体而言，这些任务包括

- 如果病人没有回复确认我们给他/她的反复的短信用药提醒，我们将给您发短信，请您去查看一下病人服药的情况并用短信告知我们查看的结果。
- 我们将偶尔用短信给您发送与病人疾病复发或药物副作用相关的核对单，以方便您及时发现和报告病人的疾病复发和副作用情况。
- 我们将偶尔给您用短信发送如何应对疾病的相关资源情况和知识。

为了验证试验的效果，参加“林项目”的人员将随机（计算机抽签）分成两组，在头六个月，一组接受“林项目”的手机短信等服务；另一组作为对照，仅接受原有日常服务；六个月后，原仅接受日常服务的对照组也开始接受短信服务（除非当时数据证明干预效果为负面），至少进行六个月。

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Ver 14-7Oct15

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我将获得一份注明日期的知情同意书副本。

最后，我决定同意作为_____的照看人参加本项研究，并保证尽量遵从医嘱。

参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

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

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 0
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	P3-4
Protocol version	3	Date and version identifier	All Pages
Funding	4	Sources and types of financial, material, and other support	P17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P16
	5b	Name and contact information for the trial sponsor	P0
	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	P17
	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)	N/A
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	P5-7
	6b	Explanation for choice of comparators	P5-8
Objectives	7	Specific objectives or hypotheses	P5
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)	P12-13

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	P5-6
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)	P9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P6-8
	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)	P6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P6-7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P5-6
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	P11-12
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)	P11-12
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	P10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P9-10

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	P9-10

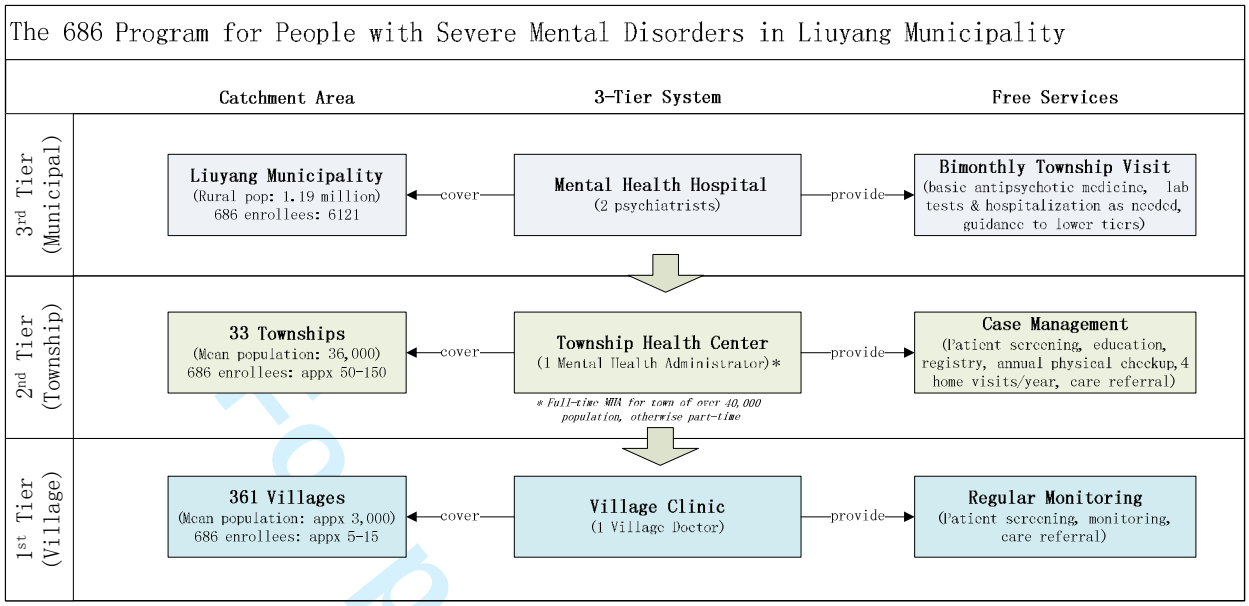
	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	P9-10
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9-10
Blinding (masking)		17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P11
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P11
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	P11-12
		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	P11-12
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	P11
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	P13
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P14
		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)	P14
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	P14

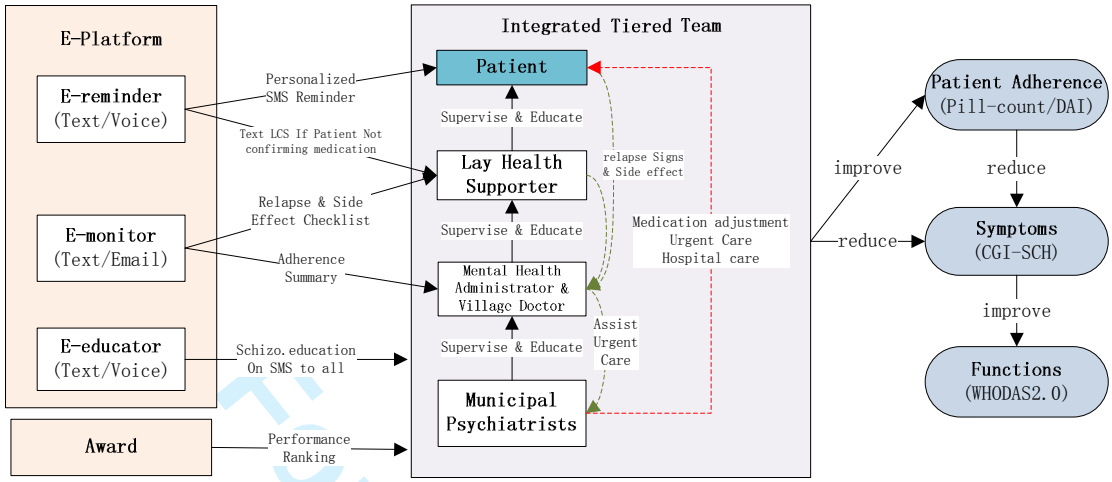
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	P14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	P14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14
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)	P14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	P14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P16
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	P14
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	P13
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	P14
	31b	Authorship eligibility guidelines and any intended use of professional writers	P16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P14

Appendices

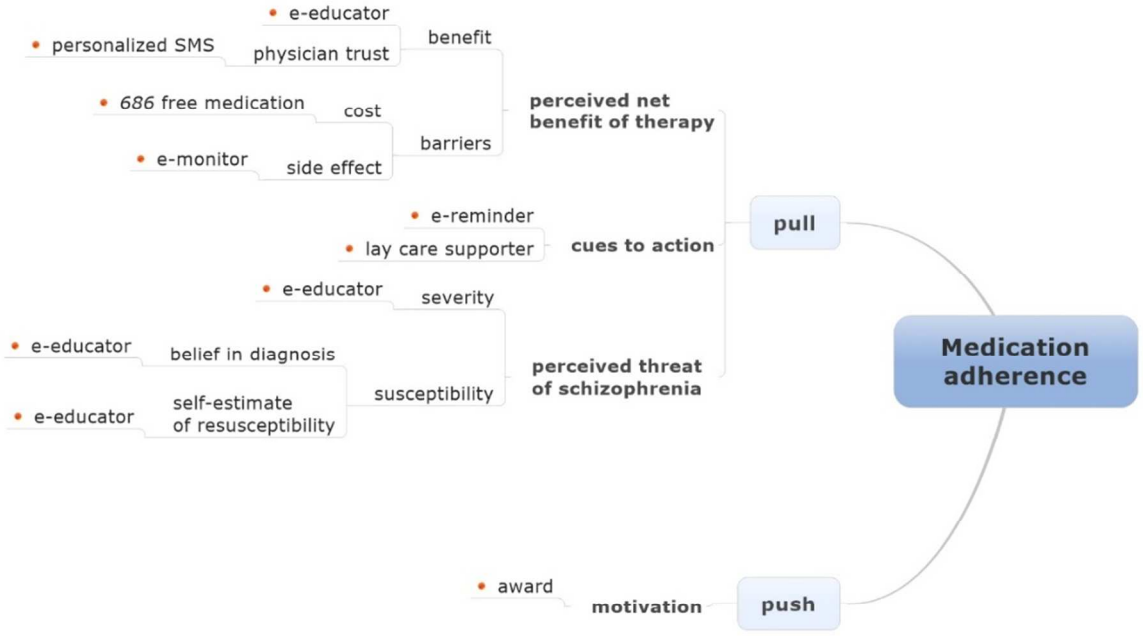
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	P20-24
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

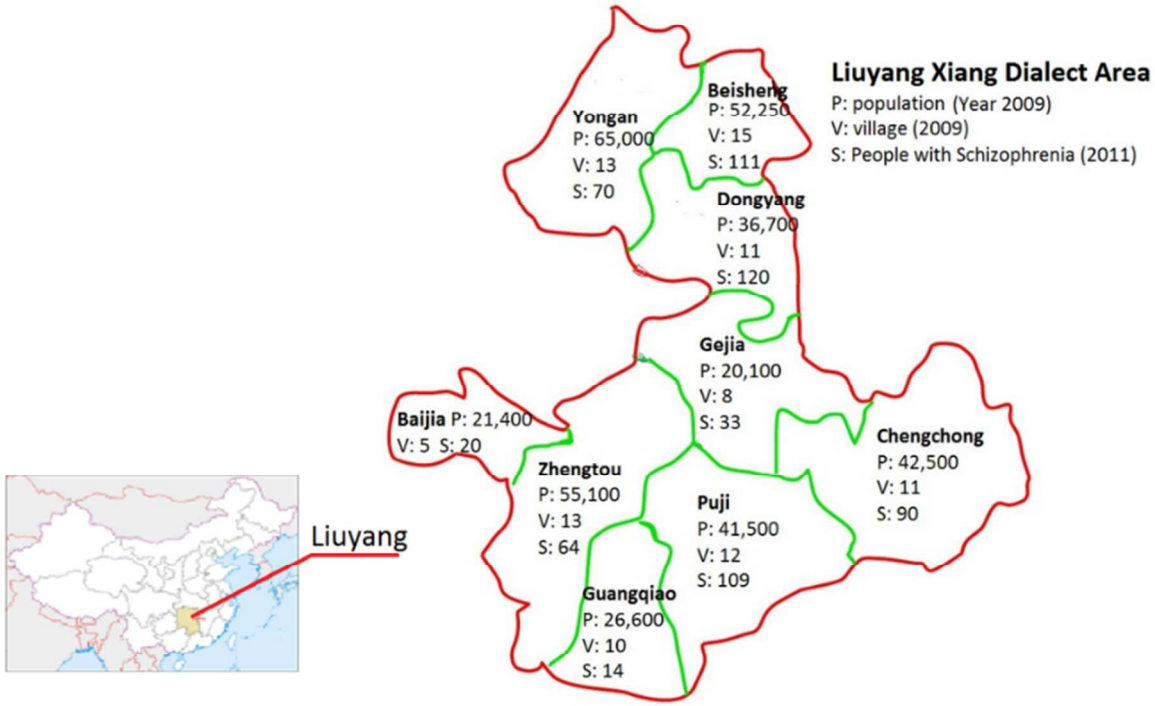
*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs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

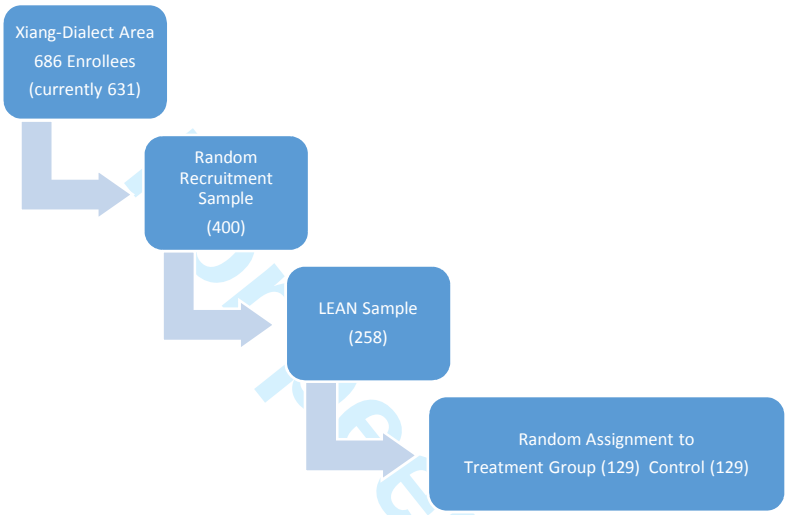


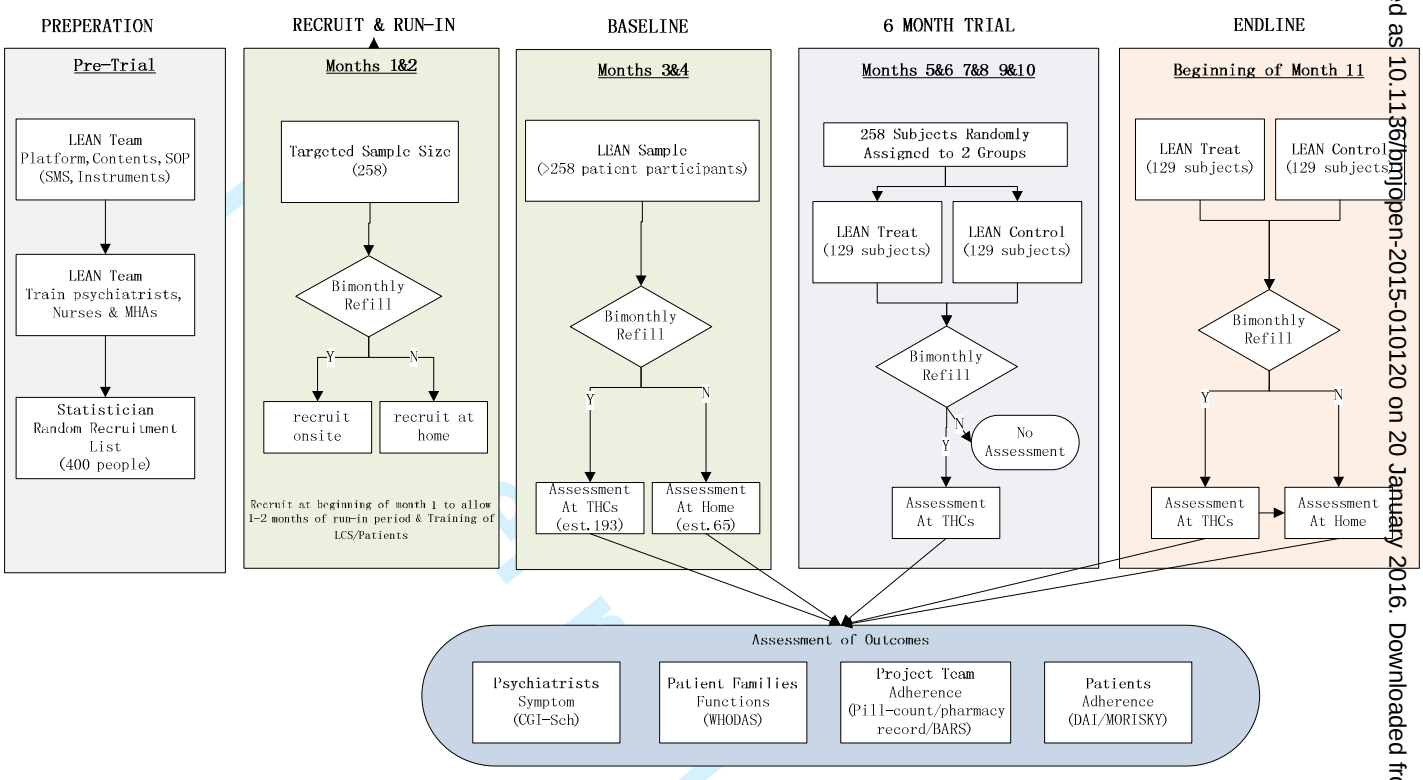


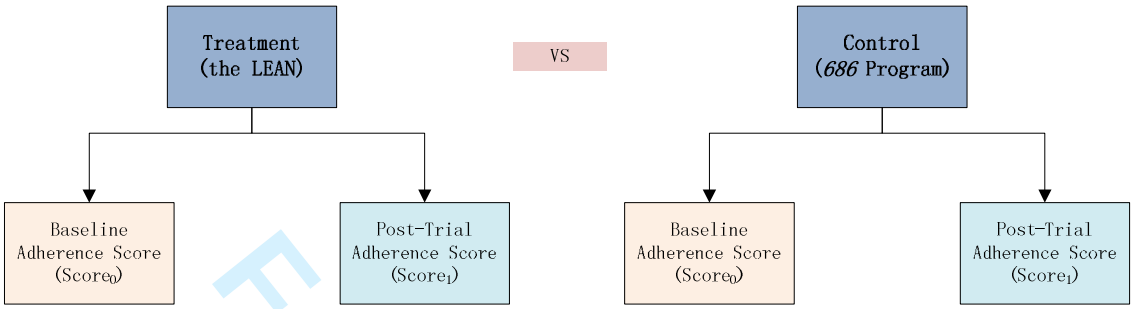
iNtegrated as the LEAN solution











1. Unadjusted: ($Score_1$) vs ($Score_1$)

2. ANCOVA: ($Score_1$ with $Score_0$ as covariate) vs ($Score_1$ with $Score_0$ as covariate)

3. DiD ($Score_1 - Score_0$) vs ($Scoree_1 - Score_0$)

Township	Popula-tion	No. of village	"686" Enrollees w/ schiz.[1]	Age (mean)	Men (%)	Married (%)	Education < Middle School (%)	Cell Phone[2] (%)	Under Family Care (%)	Fully Functioning[3] (No. / %)		Adhe-rence[4] (%)
1. Beijia	21,000	4	20	47.2	40.0%	55.0%	50.0%	80.0%	100.0%	4	20.0%	0.78
2. Beisheng	52,000	13	111	42.0	45.4%	56.7%	40.8%	55.9%	93.9%	16	14.4%	0.70
3. Dongyang	36,075	5	120	44.6	42.5%	62.6%	41.9%	69.2%	93.5%	45	37.5%	0.62
4. Gejia	20,004	8	33	46.3	51.5%	38.7%	93.9%	63.6%	100.0%	5	15.2%	0.70
5. Guangqiao	26,347	10	14	38.1	50.0%	61.5%	25.0%	78.6%	92.3%	3	21.4%	0.75
6. Puji	41,022	9	109	44.2	32.4%	63.6%	58.0%	56.0%	97.8%	18	16.5%	0.76
7. Yongan	58,883	13	70	43.8	55.4%	61.4%	51.5%	71.4%	98.5%	6	8.6%	0.78
8. Zhengtou	56,000	13	64	43.7	46.0%	69.0%	42.6%	75.0%	96.2%	6	9.4%	0.75
9. Chengchong	43,000	9	90	43.0	40.0%	52.3%	61.4%	68.9%	100.0%	16	17.8%	0.80
Total	**354,331**	**84**	**631**	**43.7**	**43.2%**	**59.1%**	**51.4%**	**65.6%**	**96.6%**	**119**	**18.9%**	**0.725**

	Adherence Score		Sample Size Needed[2]		
	Control	**Treat**	**Control**	**Treat**	Total
LEAN Sample	**0.72** (0.33) [1]	**0.85** (0.33)	**129**	**129**	**258**[3]
Non-adherent Subgroup[4]	0.42 (0.35)	0.60(0.35)	70	70	140

UNIVERSITY of WASHINGTON
HUMAN SUBJECTS DIVISION
Box 359470
Seattle, WA 98195-9470
Phone: 206-543-0098
Fax: 206-543-9218

RESPONSE: Cover Sheet, Conditional Approval

This document contains no hidden branching or guidance.

For HSD Office Use Only

- ☐ Master Copy
- ☐ IRB Working Copy
- ☒ Researcher Copy
- ☒ **YES**: Conditions of IRB approval have been met (verification)
- ☐ **NO**: Conditions of IRB approval are not met. These materials must be reviewed by the IRB.

Date Received:

RECEIVED
Human Subjects Division
APR 20 2015
UW

Printed name of verifier: Deborah Dickstein

Date of verification: 4/21/2015

In response to: Initial review

DORA MOD #: 1

Role/position of verifier:

☒ HSD staff person ☐ IRB member (not HSD staff) ☐ Other (specify):

Notes:

PURPOSE and INSTRUCTIONS

***Purpose**: Use this form to respond to an IRB review letter when your application has received **Conditional Approval**.*

***Instructions**:*

1. *Complete this form.*
2. ***Open the IRB review letter in an electronic format, and then write your answers to IRB questions directly under each question. Please change the date to the date of your response, make it clear that the new letter is from the PI to the IRB (or HSD), and clearly mark your responses with italics, widely separated paragraphs or a contrasting font of some kind.***
3. ***Print out the IRB review letter with your answers.***
4. ***Attach those pages to this form.***
6. *If you are submitting changes to the consent and/or recruitment materials at the IRB's request, please include copies in "tracked changes."*
7. *When preparing double-sided copies, each item (e.g. application, consent form, study instruments, etc.) should begin on the front of a new piece of paper.*
8. *Collate all attachments so that you have three complete "application packets."*
9. *Use clips, not staples, on at least one packet, so that the IRB staff may easily distribute your materials to additional IRB reviewers, as needed.*
10. *Submit the original and two copies.*
11. ***Do not include a revised application form or any part of an application form** unless requested.*

If the instructions above are not followed as stated, the Human Subjects Division will not review your form.

1. Research Study Information

IRB Application Number:	IRB Committee:	IRB Review Date:
49464	G	4/17/2015

IRB Application Title:

Lay Care Supporters Aided by a Mobile Phone Messaging System to Improve Care of Villagers with Schizophrenia in Liuyang China

Lead Researcher Name:	Box #:
Dong (Roman) Xu	

IRB Contact Name (if other than Lead Researcher):	Phone #:	Email:
		romanxu@uw.edu

END PART ONE

2. List of Attachments

- ☐ Assent form(s)

- [ ] Confidentiality Agreement (*1 copy ONLY*)
- [x] Consent form(s) (*Include 1 'clean' copy and 1 'tracked changes' copy per packet*)
- [ ] Consent materials translated into a language other than English
- [ ] Consent materials: addendum consent, information sheets, oral consent scripts
- [ ] Data collection instruments/forms
- [ ] Data safety and monitoring charter and/or report(s)
- [ ] Data Safety Monitoring Plan (DSMP)
- [ ] Data Use Agreement(s)
- [ ] Embryonic Stem Cell Research Oversight committee (ESCRO) approvals/letters/report
- [ ] Environmental Health and Safety (EHS) approvals/letters/report
- [ ] Federal Certificate of Confidentiality
- [ ] GIM 10 Review Letter/Conflict of Interest Management Plan Letter

- [ ] Grant application and title page of grant application (*1 copy ONLY*)
- [ ] HIPAA Authorization Form
- [ ] Implant and Investigational Device Committee (IIDC) approvals/letters/report
- [ ] Individual Investigator Agreements
- [ ] Institutional Biosafety Committee (IBC) approvals/letters/report
- [ ] Investigator brochure (*1 copy ONLY*)
- [ ] IRB Authorization Agreements
- [ ] Letters of cooperation
- [ ] Literature or abstracts supporting the purpose of your research
- [ ] Material Transfer Agreement(s) (MTA)
- [ ] Oral scripts
- [ ] Other funding documentation, only if you have funding that is not a grant application/proposal
- [ ] Other IRB approval letters/notifications
- [ ] Other IRB approvals
- [ ] Other, specify:
- [ ] Protocol (*1 copy ONLY*)
- [ ] Radiation Safety Applications or Radiation Safety Approval Letters (RS)
- [ ] Radioactive Drug Research Committee (RDRC) approvals/letters/report
- [ ] Recruitment-electronic materials: scripts for emails, and/or copies of web pages
- [ ] Recruitment-oral materials: scripts, radio ads
- [ ] Recruitment-written materials: flyers, brochures, newspaper ads, and/or letters
- [ ] Study instruments: surveys, questionnaires, assessment tools, tracking forms, web surveys
- [ ] SUPPLEMENT: Department of Defense (DOD) Involvement
- [ ] SUPPLEMENT: Department of Justice
- [ ] SUPPLEMENT: Devices
- [ ] SUPPLEMENT: Drugs, Biologics, Botanicals
- [ ] SUPPLEMENT: Genetic Research
- [ ] SUPPLEMENT: GWAS dbGaP
- [ ] SUPPLEMENT: Protected and/or Vulnerable Populations
- [ ] SUPPLEMENT: Waiver Request, Consent Requirements
- [ ] SUPPLEMENT: Waiver Request, HIPAA Authorization

END PART TWO

20 April 2015

Deborah Dickstein, MSPH
Administrator, Committee G

Application number: 49464
Application title: *Lay Care Supporters Aided by a Mobile Phone Messaging System to Improve Care of Villagers with Schizophrenia in Liuyang China*
IRB Review date: 4/17/2015
Application type: NEW
Approval type Conditional approval

cc: Stephen Gloyd, MD, MPH

Dear Ms. Dickstein,

I am writing this letter in response to the above-referenced application and CONDITIONAL APPROVAL.

My Response to the IRB Conditions of Approval

1. Please confirm that patients must have Lay Care Supporters (LCS) to be in the study. Also confirm that this is true for both the intervention arm and the control arm.

   Yes, we confirm this. All patients in the study will have LCSs. In majority of the cases, the LCS will be the family members who are already listed on the "686" program who normally accompany the patients to the bimonthly "686" physician visit. Should some patient have no LCS, we will search and identify one for them. This is true for both arms.

2. Please confirm that the LCS are subjects because you collect some data from or about them, and that this is true for both the intervention arm and the control arm.

   Yes, this is true for both control and intervention arms.

3. The application says that you want approval for 250 subjects: 125 in the intervention arm and 125 in the control arm. Please confirm that because the LCS are also subjects, you actually want approval for 250 dyads or a total of 500 individual subjects.

   Sorry for my mistake in the protocol. We confirm we will actually recruit 250 patient subjects and 250 LCS subjects.

4. The LCS consent form sometimes seems to address the patient subject, and it does not tell the LCS enough about their role as study subjects and what you are asking them to do. Please make the following revisions to the LCS consent form. Submit the revised combined form, and a new Chinese-only translation. Add to both a footer showing the revision date, to ensure that you use the correct version. In the second paragraph, delete the current second English sentence and replace it with the following:

   "The core of the LEAN is to provide additional free services for the "686" program enrollees with schizophrenia, including daily medication reminders by SMS (voice or text message). For each

patient, LEAN will also train a family member or other person—you--to help the patient with medication, side effects and relapses. Your role includes sending reports about the patient to the mental health administrator and psychiatrist so that they can respond quickly to adjust medication and/or arrange for outpatient or inpatient services. Specifically:

--If the patient does not respond to repeated medication reminders, we will send you text messages asking you to check on the patient and text back to us.

--We will occasionally send you a checklist for reporting on the patient's relapse signs and side effects.

--We will occasionally send messages with information and resources for dealing with schizophrenia."

We have revised the form. We have enclosed both the Chinese and English version (the clean and tracked-change copies)

After you have made the above revision, at the end of the final sentence of the same paragraph change "your outcome" to "the patient's outcome".

We have revised the form. We have enclosed both the Chinese and English version (the clean and tracked-change copies)

Throughout the rest of the LCS consent form, change "your patient" or "your patients" to "the patient". The LCS is not a care provider in the usual sense of having patients, and in any case is connected to only one patient subject.

We have revised the form. We have enclosed both the Chinese and English version (the clean and tracked-change copies)

LEAN Trial Informed Consent - LCS

We are the Central South University and the University of Washington School of Public Health research team. With the support of a charitable foundation the China Medical Board, we will carry out a project to improve the outcome of the people with schizophrenia with the help of mobile phone messaging (the LEAN Project) in nine townships of Liuyang including Baijia, Beisheng, Dongyang, Gejia, Guangqiao, Puji, Yongan, Chengchong and Zhentou. We cordially invite you as the lay care supporter to participate in the project. Before taking part in the project, please read the following carefully, which can help you understand the purpose, content, duration, and the benefits and risks of your participation in the project. If you like, you are welcome to consult with your relatives or friends to help your decision or to discuss this further with the project team for clarification on any points concerning your participation.

"The LEAN Project" aims to improve medication adherence in patients with schizophrenia in resource poor areas, thereby improving their function and quality of life. The core of the LEAN is to provide additional free services for the "686" program enrollees with schizophrenia, including daily medication reminders by SMS (voice or text message). For each patient, LEAN will also train a family member or other person—you--to help the patient with medication, side effects and relapses. Your role includes sending reports about the patient to the mental health administrator and psychiatrist so that they can respond quickly to adjust medication and/or arrange for outpatient or inpatient services. Specifically:

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- We will occasionally send you a checklist for reporting on the patient's relapse signs and side effects.
- We will occasionally send messages with information and resources for dealing with schizophrenia.

In order to test the effect of the project, patient participants of the LEAN will be randomly (drawing lots by a computer) divided into two groups, in the first six months, one group will receive the LEAN services and their regular "686" services; the other group will serve as controls, receiving only existing "686" program services; after six months, both the control group will also receive the LEAN services unless we find the project not useful or even detrimental to improve the patient's outcome at that time.

In the course of the project, we will collect some data to test the effect of the project. Most data related to you will be concerning your demographic information such as sex, age, education; and your interaction with us on the SMS platform. The project team will stick to the strict confidentiality requirement of your data according to both the US and China patient privacy requirement in the scope of the law. Your data will be stored in an encrypted electronic system called "RedCap"; written information will be kept in a locked safe place, to be retain for five years and then will be destroyed. We promise that your data will only be used for our research purposes. In all of our research in the analysis and reporting, all your identifiable information will be de-identified including your ID number, name, location, health record number, etc.).

Participation in the "LEAN Project" is completely voluntary. You can decide to quit the service at any time. Dropping out of the LEAN will not affect any of the services and the welfare you patients have been receiving through the “686” program or other programs. There are also multiple ways of quitting the program including: messaging with SMS to the project team to quit the project; telephone or mail notification of quitting to your village doctors or MHAs or the project team at the Central South University.

By participating in the LEAN project, you may benefit from the following: receiving mental health-related knowledge on SMS; more efficient medication adjustment to the patients; and easier access to urgent outpatient and inpatient care for the patients. All those may help you take better care of the patients. All texting related to the LEAN project is free as well, including your replies on SMS to our SMS. Possible risks involved in the project is mainly your privacy violation, although we will make every effort to protect your privacy and data.

If you have any questions about the project, please feel free to contact the project team. Our contact information is as follows: Gong Wenjie (Central South University) 13607445252 gongwenjie@csu.edu.cn Dong Xu (University of Washington) 13910988979 roman.xu@gmail.com.

If you understand the above information and decide to participate in the "LEAN Project", please sign this document.

Research project: "China Liuyang schizophrenic patients SMS Support Project" (the LEAN project)

Research cooperative units: Central South University, University of Washington

I agree:

I have read the above information about this study, and also have the opportunity to discuss the study with the project members for questions. All my questions have been satisfied with their answers.

I understand the possible risks and benefits of participating in this study. I know that participation in the study is voluntary, and I have adequate time to consider this and make my decision. I understand:

I can always ask for more information to the project team.

I can withdraw from this study at any time, without discrimination or retaliation, and my current benefits to medical treatment will not be affected.

I agree that the LEAN research team can use the data collected in the course of the project on the study while deidentify my personal information.

I will receive a copy of this informed consent.

Finally, I decided to agree to participate in this study as the LCS for _____, and will try to follow the protocols of the intervention.

照看人知情同意书 LCS Informed Consent

signature：_____

Name (print): _____

Date：_____

照看人知情同意书 LCS Informed Consent

LEAN Trial Informed Consent - LCS

We are the Central South University and the University of Washington School of Public Health research team. With the support of a charitable foundation the China Medical Board, we will carry out a project to improve the outcome of the people with schizophrenia with the help of mobile phone messaging (the LEAN Project) in nine townships of Liuyang including Baijia, Beisheng, Dongyang, Gejia, Guangqiao, Puji, Yongan, Chengchong and Zhentou. We cordially invite you as the lay care supporter to participate in the project. Before taking part in the project, please read the following carefully, which can help you understand the purpose, content, duration, and the benefits and risks of your participation in the project. If you like, you are welcome to consult with your relatives or friends to help your decision or to discuss this further with the project team for clarification on any points concerning your participation.

"The LEAN Project" aims to improve medication adherence in patients with schizophrenia in resource poor areas, thereby improving their function and quality of life. The core of the LEAN is to provide additional free services for the "686" program enrollees with schizophrenia, including daily medication reminders by SMS (voice or text message). For each patient, LEAN will also train a family member or other person—you--to help the patient with medication, side effects and relapses. Your role includes sending reports about the patient to the mental health administrator and psychiatrist so that they can respond quickly to adjust medication and/or arrange for outpatient or inpatient services. Specifically:

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- We will occasionally send you a checklist for reporting on the patient's relapse signs and side effects.
- We will occasionally send messages with information and resources for dealing with schizophrenia.

~~The core of the LEAN is to provide additional free services for the "686" program enrollees with schizophrenia, including daily SMS to provide you with medication reminders; and training a family member or other person acceptable to you as "Lay Care Supporter" (LCS, ie, "you"), who will help the patient with medication, side effects and relapses by reporting early signs of relapse and side effects to the mental health administrator and psychiatrists so that they can respond quickly to adjust your medication and/or arrange for urgent outpatient or inpatient services.~~

In order to test the effect of the project, patient participants of the LEAN will be randomly (drawing lots by a computer) divided into two groups, in the first six months, one group will receive the LEAN services and their regular "686" services; the other group will serve as controls, receiving only existing "686" program services; after six months, both the control group will also receive the LEAN services unless we find the project not useful or even detrimental to improve the patient's outcome at that time.

In the course of the project, we will collect some data to test the effect of the project. Most data related to you will be concerning your demographic information such as sex, age, education; and your interaction with us on the SMS platform. The project team will stick to the strict confidentiality requirement of your data according to both the US and China patient privacy requirement in the scope of the law. Your data will be stored in an encrypted electronic system called "RedCap"; written

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information will be kept in a locked safe place, to be retain for five years and then will be destroyed. We promise that your data will only be used for our research purposes. In all of our research in the analysis and reporting, all your identifiable information will be de-identified including your ID number, name, location, health record number, etc.).

Participation in the "LEAN Project" is completely voluntary. You can decide to quit the service at any time. Dropping out of the LEAN will not affect any of the services and the welfare you patients have been receiving through the "686" program or other programs. There are also multiple ways of quitting the program including: messaging with SMS to the project team to quit the project; telephone or mail notification of quitting to your village doctors or MHAs or the project team at the Central South University.

By participating in the LEAN project, you may benefit from the following: receiving mental health-related knowledge on SMS; more efficient medication adjustment to ~~your~~ the patients; and easier access to urgent outpatient and inpatient care for ~~your~~ the patients. All those may help you take better care of ~~your~~ the patients. All texting related to the LEAN project is free as well, including your replies on SMS to our SMS. Possible risks involved in the project is mainly your privacy violation, although we will make every effort to protect your privacy and data.

If you have any questions about the project, please feel free to contact the project team. Our contact information is as follows: Gong Wenjie (Central South University) 13607445252 gongwenjie@csu.edu.cn Dong Xu (University of Washington) 13910988979 roman.xu@gmail.com.

If you understand the above information and decide to participate in the "LEAN Project", please sign this document.

Research project: "China Liuyang schizophrenic patients SMS Support Project" (the LEAN project)

Research cooperative units: Central South University, University of Washington

I agree:

I have read the above information about this study, and also have the opportunity to discuss the study with the project members for questions. All my questions have been satisfied with their answers.

I understand the possible risks and benefits of participating in this study. I know that participation in the study is voluntary, and I have adequate time to consider this and make my decision. I understand:

I can always ask for more information to the project team.

I can withdraw from this study at any time, without discrimination or retaliation, and my current benefits to medical treatment will not be affected.

I agree that the LEAN research team can use the data collected in the course of the project on the study while deidentify my personal information.

I will receive a copy of this informed consent.

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Finally, I decided to agree to participate in this study as the LCS for _____, and will try to follow the protocols of the intervention.

~~signigure~~signature: _____

Name (print): _____

Date: _____

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[表 004.1]

“林项目”照看人知情同意书

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、枨冲和镇头九镇开展“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）。现邀请您作为患者的照看人参加本项目，在参加项目之前，请仔细阅读以下内容，它可以帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

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研究项目：“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）

课题协作单位：中南大学、美国华盛顿大学

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参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

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[表 004.1]

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签名日期：_____

Revised 04.20.15

中南大学临床药理研究所医学伦理委员会

编号:CTXY-150002-6号

中南大学临床药理研究所伦理委员会临床试验审核表

项目名称: 中国浏阳农村精神分裂症患者服药手机短信支持项目			
研究机构	中南大学湘雅医学院、美国华盛顿大学全球卫生系	主要研究者	姜雯洁
会议地点	中南大学临床药理研究所会议室	日 期	2015.02.27
委员名单	刘昭前、王连生、陈碧莲、田晓山、王 丹、朱继明、阳国平		
主要研究者资格	姓名: 姜雯洁	职称: 讲师	

伦理委员会委员投票结果

应到委员	实到委员	同意	不同意	弃权
7 名	7 名	7票	0票	0票

委员签名	陈碧莲 王连生 朱继明 阳国平		
结论	同意	主任委员	

地址: 湖南省长沙市湘雅路 110 号 电话: 0731-84805380 E-mail: liuzhaoqian63@126.com

中南大学临床药理研究所医学伦理委员会

单位：中南大学公共卫生学院

经中南大学临床药理研究所医学伦理委员会审议，同意你们按照研究计划和申请报告进行基于中国浏阳农村精神分裂症患者的手机短信支持项目 临床研究。

请在临床实验过程中严格遵循医学伦理道德原则，确定保障受试对象的权益，并及时向本伦理委员会报告研究中发生的意外事件和处理情况。

中南大学临床药理研究所医学伦理委员会

2015年02月04日

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BMJ Open

Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-010120.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Oct-2015
Complete List of Authors:	Xu, Dong; Sun Yat-sen University, Sun Yat-sen Global Health Institute; University of Washington, Dept. of Global Health Gong, Wenjie; Central South University, School of Public Health; University of Rochester Medical Center, Department of Psychi Caine, Eric; University of Rochester Medical Center, Department of Psychiatry Xiao, Shuiyuan; Central South University, School of Public Health Hughes, James; University of Washington, Department of Biostatistics Ng, Marie; Institute of Health Metrics and Evaluation, University of Washington, Seattle Simoni, Jane; University of Washington, Department of Phycology He, Hua; Tulane University, Department of Epidemiology, School of Public Health and Tropical Medicine Smith, Kirk ; University of Texas Health Science Center School of Public Health at Houston Brown, Henry ; UTHealth School of Public Health, Austin Regional Campus Michael & Susan Dell Center for Healthy Living Gloyd, Stephen; University of Washington, Dept. of Global Health
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Health services research
Keywords:	schizophrenia, medication adherence, mHealth, lay health worker, implementation science, "686" program

Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial

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Corresponding author: Wenjie Gong, PhD, School of Public Health, Central South University, 110 Xiangya Road, Changsha, 410078, Hunan, China (gongwenjie@csu.edu.cn)

Abstract

Introduction: Schizophrenia is a severe, chronic, and disabling mental illness. Non-adherence to medication and relapse may lead to poorer patient function. This randomized controlled study, under the acronym LEAN, is designed to improve medication adherence and high relapse among people with schizophrenia in resource poor settings. **Methods/Analysis**: the community-based **LEAN** has four parts: 1) **L**ay health supporters (LHSs), mostly family members who will help supervise patient medication, monitor relapse and side effects, and facilitate access to care, 2) an **E**-platform to support two-way mobile text and voice messaging to remind patients to take medication; and alert LHSs when patients are non-adherent, 3) an **A**ward system to motivate patients and strengthen LHS support, and 4) iNtegration of the efforts of patients and LHSs with those of village doctors, township mental health administrators and psychiatrist via the e-platform. A random sample of 258 villagers with schizophrenia will be drawn from the schizophrenic "686" Program registry for the 9 Xiang-dialect towns of the Liuyang municipality in China. The sample will be further randomized into a control group and a treatment group of equal sizes, and each group will be followed for 6 months after launch of the intervention. The primary outcome will be medication adherence as measured by pill-counts and supplemented by pharmacy records. Other outcomes include symptoms and level of function. Outcomes will be assessed primarily when patients present for medication refill visits scheduled every two months over the 6-month follow-up period. Data from the study will

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be analyzed using ANCOVA for the program effect and an intent-to-treat approach. **Ethics and dissemination**: University of Washington: 49464 G; Central South University: CTXY-150002-6. Results will be published in peer-reviewed journals with deidentified data made available on FigShare. **Trial Registration**: ChiCTR-ICR-15006053

Keywords*:* schizophrenia, medication adherence, mHealth, lay health worker, implementation science, wait-list control, RCT, "686" program

Strengths and Limitations

Strengths:

- The application of mHealth is designed not as a standalone technological solution but a health system strengthening tool that serves to integrate the patient care provided by lay health supporters, village doctors, mental health administrators and psychiatrists.
- The active engagement of family members augments case supervision.
- The study, evaluating the real world effectiveness of LEAN, emphasizes the implementation parts so as to increase the likelihood of scaling up the potentially effective solution.
- The trial is intent to have global implications, especially insofar as the intervention is designed to exclude elements peculiar to China's socio-economic and/or political situation.

Limitations:

- The short duration may not allow sufficient assessment of functional changes and limit analysis of the long-term effect on adherence.
- The choice of relatively simple assessment tools (pill-counts vs. urinalysis) may create challenges of obtaining accurate adherence level.
- Assuming that improved medication adherence will lead to better patient life-functioning may be problematic.

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WHO Trial Registration Data Set

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	ChiCTR-ICR-15006053
Date of registration in primary registry	8 Mar, 2015
Secondary identifying numbers	N/A
Source(s) of monetary or material support	China Medical Board Fogarty International Center, NIH
Primary sponsor	Central South University, China
Secondary sponsor(s)	University of Washington, USA
Contact for public queries	Dong Xu, MPP [+86 20 5969 5071] [romanxu@uw.edu]
Contact for scientific queries	Dong Xu, MPP [+86 20 5969 5071] [romanxu@uw.edu] Sun Yat-sen University
Public title	Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial
Scientific title	Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial
Countries of recruitment	China
Health condition(s) or problem(s) studied	Schizophrenia
Intervention(s)	Intervention: Lay Health Supporter plus SMS Messaging System Control: Case as ususal (ie. “686” Program)
Key inclusion and exclusion criteria	Inclusion: “686” program participant; diagnosed as schizophrenia; residing in Liuyang Xiang-dialect area Exclusion: Patients who missed past 3 drug refills; currently hospitalized; people physically not capable of using voice or text messaging
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: subject not blinded; caregiver, investigator,

Ver 15-20Oct15

DATA CATEGORY	INFORMATION
	outcomes assessor blinded Primary purpose: improving health Effectiveness study
Date of first enrolment	July 2015
Target sample size	258
Recruitment status	Recruiting
Primary outcome(s)	Medication adherence as measured by pill-counts (medication taken over medication prescribed)
Key secondary outcomes	Symptoms as measured by Clinical Global Impression in Schizophrenia; and functions as measured by 12-item proxy-administered WHO Disability Assessment Schedule 2.0

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Introduction

Background and Rationale

Schizophrenia, characterized by hallucination, delusion, disorganized thinking and negative symptoms, is a chronic and disabling mental disorder which is commonly associated with impairment in social and occupational functioning[1]. Though schizophrenia cannot be cured, most people with schizophrenia can be effectively treated for symptoms with antipsychotic medicines[2]. However, of treated patients, 50% are non-adherent with medication[3]; moreover, even under conditions of compliance, 50% of patients suffer relapse within 1 year of their latest episode[4]. The "686" Program, a massive coutry-wide government effort in China, is a relatively inexpensive and practical model that provides community-based mental health care with limited human and financial resources[5 6]. But the program faces the challenges of poor medication adherence and high relapse - 26% of the program participants never, 39% intermittently, and only 35% regularly take prescribed medications[7]. This research aims to develop, and evaluate, a financially and operationally feasible and sustainable intervention (with the acronym LEAN) to address those "686" program challenges.

Hypothesis

We hypothesize that the LEAN plus "686" solution, as compared to the present "686" standard of care only, will improve medication adherence, reduce the incidence of schizophrenia symptoms, and ultimately result in improved social and occupational functioning for enrollees.

Study Setting

The intervention will be implemented and tested in "686" program particiants in the Xiang-dialect area (a total of 9 towns) of the rural townships of Liuyang Municipality in the Hunan province of China, with an intent to produce solutions that can be adapted and applied in other LMCs with limited mental health resources. Liuyang has developed a three-tier "686" model extending from Liuyang Mental Health Hospital (MHH) to township health centers (THCs) to village clinics that consists of five compnents: 1) patient screening by village doctors (VDs) and mental health administrators (MHAs); 2) registering confirmed cases into"686" with consent; 3) Psychiatrists

touring townships to provide free consultation and medication every two months ("bi-monthly visits"); 4) case management by MHA; and 5) regular monitoring by VDs[8 9 10] (Figure 1).

FIGURE 1 THE "686" PROGRAM SERVICE MODEL

Source: authors.

LEAN

LEAN as an acronym is somehow inspired by Toyota's principle in lean manufacturing[11] although our focus is to add value, minimize waste, and maintain simplicity throughout program implementation. The acronym LEAN summarizes the critical components of the proposed intervention (Figure 2). The LEAN participants can opt out of LEAN anytime by texting us or inform VDs, MHAs by phone or in person.

FIGURE 2 LEAN

LEAN
L: Lay health supporter (LHS)
E: E-platform with e-reminder, e-monitor, and e-educator via mobile text/voice messaging
A: Award system analogous to Taekwondo ranks
N: iNtegrating the L, E and A and "686" Program structure into a lean and coordinated approach

Source: authors.

Lay Health Supporter (LHS)

For each patient in the intervention, LEAN will identify a LHS — a member of the patient's family if possible or a community volunteer (such as a member of the village senior club) — who will perform simple but important roles in support of the patient: 1) facilitate patient medication adherence with prompts from the e-reminders, 2) monitor for early signs of relapse and for medication side effects using checklists from the e-monitor, and 3) team up with the village doctor and the township mental health administrator to facilitate treatment adjustments and, if needed, emergent hospital care.

E-platform

The e-platform employs three main modules: The e-reminder sends the patient up to two reminders either by text or voice messages at 15 minutes interval until the patient responds with confirmation that the scheduled

medication has been taken. Failure to send a confirmation will trigger up to two text alerts to the patient's LHS, prompting the LHS to check in with the patient and text back the result. The e-monitor assists LHSs and patients in detecting signs of relapse and monitoring medication side effects using relevant checklists texted to the patient and LHS at regular intervals (See relapse checklist in appendix. And findally, the e-educator will send periodic SMS messages to the patient, LHS, MHA, and VD educating them on schizophrenia symptoms, medication, adherence strategies, relapse, rehabilitation and social resources.

Award System

Patients and LHSs will accumulate points for responding to SMS messages. Each of their texted confirmation back to the LEAN system will accumulate one point, which will be recorded automatically by the computer system. The points, counted every two months, will advance their Taekwondo-like belt ranking and entitle them to a small gift when they come for the bi-monthly visit to be presented by a LEAN program staff.

iNtegration

The efforts of the patient and LHS to improve medication adherence and reduce relapses will be integrated, facilitated by the e-platform, with those of the VD, MHA and psychiatrist so that the innovations of LEAN strengthens the existing health system. With this integration, non-adherence and relapses detected can then be actually handled with LHS, VDs, MHAs and psychiatrist take concerted effort for prompt treatment adjustments or referrals for emergent hospitalization.

Mechanism of LEAN

The mechanism of LEAN medication adherence is based on an adapted health belief model (HBM) (Figure 3)[12 13]. According to this theory, people with schizophrenia make their medication adherence decisions based on push (patients' self-motivation in improving health) and pull factors that include three elements: 1) Patients' perception of the threat posed by schizophrenia; 2) Patients' perceived net benefit of adhering to therapy, a calculation involving the benefits of therapy minus costs; and 3) Action cues such as the above-mentioned e-reminders or

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mass media health promotion campaigns. Figure 3 illustrates the interface of various LEAN elements with the components of the health belief model.

FIGURE 3 MECHANISM FOR LEAN MEDICATION ADHERENCE

Note: The red dots indicate LEAN components.

Source: adapted from the health belief model.

The development of LEAN has been guided not only by the HBM as a theoretical framework, but was also informed by empirical evidence, particularly in the areas of human resources for health (HRH) and mobile health (mHealth). Much of the literature in HRH suggests that "task shifting" - cascading appropriate tasks from more skilled psychiatrists to less specialized MHAs/VDs and to LHS improves access and efficacy when HRH are lacking or deficient[14 15] (Liuyang has only 1.35 psychiatrists/1.42 specialist nurses versus 8.59 psychiatrists/29.15 nurses for high income countries per 100,000 population in 2011). The e-platform facilitates efficient communication and integration of this network of human resources. Moreover, much evidence supports the use of reminders to improve medication adherence[16 17 18 19 20].

Study Population and the LEAN Sample

People in Liuyang speak three distinct dialects: Gan, Xiang and Hakka. The Xiang-dialect area, located in the west of Liuyang municipality, has 9 townships, 98 villages and a population of 356,900. The "686" Program maintains a roster of patients with schizophrenia in the Xiang-dialect area of Liuyang municipality (total: 631 in 2011) (Figure 4), which forms the study population. The characteristics of this population most relevant to our study are summarized in Table 1. The Xiang-dialect population is selected due to 1). the efficiency to recruit, train and collect data in a more focused population; 2). that Xiang dialect group is the majority group in Hunan province while the oher two dialect-groups in Liuyang are historically immigrants from other provinces; and 3). long and rich past reseach expereince of our group in this area that provides additional data and information for the LEAN study, such as educational levels of all MHAs.

FIGURE 4 MAP OF THE XIANG-DIALECT AREA OF LIUYANG

Note: Yellow-shaded region on the map of China is Hunan Province.

TABLE 1 "686" PROGRAM ENROLLEES WITH SCHIZOPHRENIA IN THE XIANG-DIALECT AREA OF LIUYANG (YEAR 2011)

Township	Popula-tion	No. of village	"686" Enrollees w/ schiz.(1)	Age (mean)	Men (%)	Married (%)	Education < Middle School (%)	Cell Phone (2) (%)	Under Family Care (%)	Fully Functioning(3) (No. / %)		Adhe-rence (4) (%)
1. Beijia	21,000	4	20	47.2	40.0%	55.0%	50.0%	80.0%	100.0%	4	20.0%	0.78
2. Beisheng	52,000	13	111	42.0	45.4%	56.7%	40.8%	55.9%	93.9%	16	14.4%	0.70
3. Dongyang	36,075	5	120	44.6	42.5%	62.6%	41.9%	69.2%	93.5%	45	37.5%	0.62
4. Gejia	20,004	8	33	46.3	51.5%	38.7%	93.9%	63.6%	100.0%	5	15.2%	0.70
5. Guangqiao	26,347	10	14	38.1	50.0%	61.5%	25.0%	78.6%	92.3%	3	21.4%	0.75
6. Puji	41,022	9	109	44.2	32.4%	63.6%	58.0%	56.0%	97.8%	18	16.5%	0.76
7. Yongan	58,883	13	70	43.8	55.4%	61.4%	51.5%	71.4%	98.5%	6	8.6%	0.78
8. Zhengtou	56,000	13	64	43.7	46.0%	69.0%	42.6%	75.0%	96.2%	6	9.4%	0.75
9. Chengchong	43,000	9	90	43.0	40.0%	52.3%	61.4%	68.9%	100.0%	16	17.8%	0.80
Total	**354,331**	**84**	**631**	**43.7**	**43.2%**	**59.1%**	**51.4%**	**65.6%**	**96.6%**	**119**	**18.9%**	**0.725**

(1). "686" enrollees with schizophrenia only, accounting for approximately 80% of all "686" patients in Liuyang

(2). Cell phone ownership by family members of "686" Program enrollees

(3). Function assessed by MHAs using three sub-categories: daily living, social activities and work.

(4). A score of 0-1 calculated as the percentage of prescribed drugs taken by the patient in the month immediately before the survey

Source: author, Liuyang "686" Program Registry (Year 2011)

Inclusion and Exclusion Criteria

The following criteria more precisely define the study population by establishing eligibility requirements for subject recruitment. As villagers and LHSs without a phone will be given a free basic phone and subscription plan, the phone ownership is not included in the inclusion or exclusion criteria. Rationales for inclusion and exclusion criteria are given in parentheses.

Inclusion:

1. "686" Program enrollees.
2. Diagnosed as having schizophrenia according to criteria established in the *Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-5®)[21]
3. Physically reside in the Xiang-dialect area of Liuyang Municipality

Exclusion:

1. Individuals registered in the Xiang-dialect area of Liuyang Municipality, but living elsewhere as migrant workers (as a community-based intervention, LEAN requires residence in the local community)
2. Patients who have missed three immediate consecutive past drug refills (in this case, they have *de facto* dropped out of the "686" Program)
3. People who are currently hospitalized (again, LEAN intervention requires sustained community residence)
4. People physically incapable of using voice or text messaging, e.g. individuals with hearing and/or vision impairment, or who are severely disabled (ability to utilize SMS is necessary for the LEAN intervention)

Sampling Frame, the LEAN Sample and Recruitment

The most recent "686" Program registry of patients with schizophrenia will be used as the sampling frame, from which we aim to draw 258 patients as the LEAN sample. To that end, a statistician otherwise not associated with the project will first create a recruitment list of 400 people drawn at random from the sampling frame. Assuming that 15% of those selected will prove ineligible and that a further 20% will elect not to participate, an initial list of 400 should ensure a final recruitment of no less than 258 subjects. MHAs will provide an initial screening by cross-checking the recruitment list against their own records in order to verify eligibility. Recruitment by project staff will occur during patients' bi-monthly medication refill visits, when psychiatrists will re-confirm the diagnoses of those on the list. Project staff will conduct home visits within one month of their expected bi-monthly visit to recruit those not contacted at the refill visits. At the end of the recruitment, the LEAN sample will be randomly

divided by the same statistician into a treatment group and a control group of equal sizes by a statistician not otherwise involved in the study (Figure 5).

FIGURE 5 THE LEAN POPULATION, SAMPLE AND ASSIGNMENT

Source: authors

Sample Size Calculation

Though the distribution of our primary outcome (adherence, scored as the percentage of drugs taken of those prescribed) is unlikely to be normally distributed, the sample calculation follows standard procedures for the hypothesis of equal population means based on t-test and the comparison of sample means. Since our sample size is large, the central limit theorem ensures that our sample means will be approximately normally distributed, regardless of the underlying distribution of the data.

Assuming a 5% type I error and a 10% dropout ratio for a total sample size of 258 (129 for each of the two comparison groups), the study of 232 participants (after 10% dropping out of 258) will have 85% power to detect an effect size of 0.13 (see appendices). This means that if the adherence score for the control group is 0.72 (SD=0.33), the study will have sufficient power to detect a program effect if adherence for the treatment group is equal to or greater than 0.85. The control adherence of 0.72 used in the sample calculation is based on the self-reported adherence of 0.75 in our study population from the "686" registry.

The proposed sample size of 258 will also satisfy the power requirement for a subgroup analysis of patients who are non-adherent at baseline. Given the ratio of non-adherence to full-adherence (0.55:0.45) of the population reported in the registry, the study will include at least 140 baseline non-adherent subjects available for the sub-group analysis. Again, assuming 5% type I error and a 10% dropout rate, the study will have 85% power to detect an effect size of 0.18 among the sub-group: If the adherence rate for the control is 0.42 (SD=0.35), the study will be powered to detect a program effect if the adherence of the treatment group is equal to or greater than 0.6 (Table 2).

TABLE 2 SAMPLE SIZE CALCULATION SCENARIOS

	Adherence Score		Sample Size Needed[2]		
	Control	**Treat**	**Control**	**Treat**	Total
LEAN Sample	**0.72** (0.33) [1]	**0.85** (0.33)	**129**	**129**	**258**[3]
Non-adherent Subgroup[4]	0.42 (0.35)	0.60(0.35)	70	70	140

(1). Standard deviation in parentheses

(2). Sample calculation assuming power of 0.85, significance level of 0.05, and a 10% dropout rate

(3). See the STATA codes for the sample calculation in appendix

(4). Sample size of the baseline non-adherent sub-group achieved with a LEAN total sample of 258.

Source: authors

Metrics & Measurement

Primary and Secondary Outcomes

The primary outcome will be a continuous medication adherence score from 0 (no adherence) to 1 (complete adherence), calculated as the percentage of drugs taken out of those prescribed over a designated time period (the preceding month). Medication adherence was chosen as the primary outcome on the grounds that 1) adherence correlates with symptom relief, and symptoms correlate with function[22 23]; 2) significant improvement in symptoms, and function, is likely to extend beyond the duration of the study; and 3) improving adherence is valuable in its own right. However, symptoms and functions will also be tracked as the secondary outcomes.

Methods of Assessment and Timeline

Figure 6 summaries how and when we assess outcomes, which piggyback on "686" Program activities, in particular, the bi-monthly meetings with patients. All data will be double-entered into and managed by Research electronic data capture (REDCap) system[24]. All outcome assessors, including psychiatrists and program staff, will be blinded to the control or treatment status of program participants; any inadvertent un-blinding will be noted in order to record the time of the incident and persons involved.

FIGURE 6 RECRUITMENT AND OUTCOME ASSESSMENT

Source: authors

Medication Adherence: Pill counts

Pill counts, to be conducted by project staff when patients bring their pill bottles to the bi-monthly refill, will be used as the primary, objective and inexpensive measurement of medication adherence, to be complemented by pharmacy dispensing records from the "686" registry system. Other objective measures, such serum/urine drug level[25], are clinically and financially impossible to implement. In addition, the Morisky Medication Adherence Scale[26], the Brief Adherence Rating Scale (BARS)[27], and the Drug Attitude Inventory-10 (DAI-10) [28] will supplement the objective assessment. At baseline and again at the end of the study, patients who were no-shows at the bi-monthly visit will be visited and assessed at their homes.

Symptoms – CGI-Sch

From among the "big three" instruments for schizophrenic symptoms[29] we chose the Clinical Global Impression in Schizophrenia (CGI-Sch) primarily due to its brevity and ease of use[30]. "686" Program psychiatrists will assess patients using the CGI-Sch during bi-monthly visits throughout the trial.

Functions – WHODAS 2.0

LEAN will use the 12-item proxy-administered WHO Disability Assessment Schedule 2.0 to assess patient functions, considering its brevity to administer, excellent psychometric properties, and availability of a validated Chinese version[31 32]. Public health students enlisted as program staff will administer the WHODAS to patients and their family members during bi-monthly visits.

Other Measures

As side-effect of anti-antipsychotics may relate to adherence, the brief and self-implemented Glasgow Antipsychotic Side-effect Scale (GASS) will be used to generate a side-effect score[33]. A few other "public health" indicators such as suicide, drug abuse, attacking people, destroying things and wandering will be captured by the existing "686" registry. In addition many process, cost and service utilization indicators will be captured and recorded by the e-platform logs and "686" administrative registry. These process indicators will facilitate analysis of various links in the LEAN mechanism, and surveillance for breaks in the chain.

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Trial Design

We adopt a wait-list design with subjects followed-up for six months after launch of the intervention. The wait-list control design is increasingly used in psychotherapy studies, primarily to address the ethical dilemma involved in withholding a potentially beneficial treatment from the control group. Participants recruited into the study are randomized into a treatment group and a "wait-listed" control group. In stage one (the 6 month period following program initiation), the intervention will be applied to the intervention group only, while the wait-list group will receive usual care per the regular "686" protocol; in stage two (a subsequent 6 month period), the wait-list group will receive the intervention, having "waited" through stage one. Analysis of the intervention will be conducted based on baseline and end-point data collected on both groups during stage one only due to our budget constraint for data collection. Consequently, the only difference between a wait-list design and a traditional two-arm randomized control trial (RCT) is that the control group is also able to benefit from the treatment once the formal study is complete.

Model & Analysis

Unadjusted analysis, ANCOVA and DiD

We mainly considered the issue of efficiency (precision of the estimator) and bias in our choice of the analytical methods. The literature suggests that ANCOVA provides higher efficiency than difference-in-difference (DiD) and the unadjusted model in RCT and is the optimal model for RCT analysis[34] (Figure 7). The LEAN analysis will include as covariates the strong baseline predictors of outcome that are empirically suggested by other studies, and will comprise adherence, WHODAS and CGI-Sch scores, as well as indices of negative symptoms, substance use, medication side effects, and family supervision[35]. It should be noted that while our response variable, expressed as an adherence score from 0-1, may yield values greater than one, those out-of-bound predictions do not invalidate the model since the study's purpose is to produce a "risk difference" (difference in mean adherence between intervention and control groups) rather than an individual prediction. Critically, the large sample size and the central limit theorem ensure that this approach will yield valid inferences of the risk difference despite non-normal adherence outcomes.

FIGURE 7 THREE APPROACHES TO RCT ANALYSIS

Source: adapted from Siyuan Zhang paper[36]

Intent-to-Treat

An intent-to-treat (IIT) analysis will be used to analyze all subjects regardless of treatment actually received. Estimating the IIT effect is more appropriate than the per-protocol or per-treat methods since the LEAN trial is a pragmatic trial, which is to say, it is meant to determine the effectiveness of LEAN as a real-world solution.

Subgroup Analysis

We plan to conduct two subgroup analyses, both with strong theory base and possible interaction effects. The first concerning the non-adherent group at baseline is sufficiently powered (Table 2) (our adherence-focused intervention is more likely to work better for the initially non-adherent group). The other subgroup analyses will be conducted to assess level of functions.

Missing Data

Reasons for missing data will be recorded. Multiple imputation methods will be used so that sensitivity analyses will be conducted to assess the robustness of trial results under different methods.

Monitoring

Considering the short duration of the intervention, we do not have a data monitoring committee. At the mid-point of the trial, outcomes and text messaging data will be analyzed to detect any abnormality. The text messaging system also provides a means for ongoing monitoring of any patient response.

Ethics and Dissemination

The study has obtained IRB approval from University of Washington (49464 G) and Central South University (CTXY-150002-6). Any substantive modification to the protocol will seek a formal approval from the IRBs. Program staff will train and obtain informed consent from both patients and LHSs. Patient data will be securely entered and

stored in RedCap and only de-identified information will be used for analysis. Study results will seek peer-reviewed publications with de-identified data made available on Figshare[37].

Discussion

Several aspects of this study is worth noting. First, the application of mHealth is designed not as a standalone technological solution but a health system strengthening tool that serves to integrate the patient care provided by lay health supporters, village doctors, mental health administrators and psychiatrists.

Second, the active engagement of LHS augment case supervision. Third, the study, evaluating the real world effectiveness of LEAN, emphasizes the implementation parts so as to increase the likelihood of adopting the potentially effective solution. Fourth, the trial is intent to have global implications, especially insofar as the intervention is designed to exclude elements peculiar to China's socio-economic and/or political situation.

The study is faced with several limitations. First, its short duration may not allow sufficient assessment of functional changes and limit analysis of the long-term effect on adherence. Second, our choice of relatively simple assessment tools (pill-counts vs. urinalysis) may create challenges of obtaining accurate adherence level. Third, assuming that improved medication adherence will lead to better patient life-functioning may be problematic. There is concern that the psychiatrists with limited training from Liuyang MHH may deliver inappropriate treatments, adherence to which will be of insufficient benefit. Finally, despite efforts to ensure the generalizability of LEAN, the existing "686" infrastructure may make Liuyang a unique location, although spirit of LEAN should provide useful information for other LMCs.

List of abbreviations

BPRS: Brief Psychiatric Rating Scale

CGI-Sch: Clinical Global Impression in Schizophrenia

DiD: difference-in-difference model

DSM-5® : Diagnostic and Statistical Manual of Mental Disorders-5

HBM: health belief model

HRH: human resources for health

IIT: intent-to-treat

LHS: Lay health supporter

LMC: low and mid-income countries

MHA: mental health administrators

mHealth: mobile health

MHH: mental health hospital

PANSS, Positive and Negative Syndrome Scale

RCT: randomized control trial (RCT)

THC: township health centers

VD: village doctor

Competing interests

The authors declare that they have no competing interests

Authors' contributions

All authors contributed to the conceptualization and the design of the study. WG obtained majority of the funding. DX and WG conceived of the prototype of the intervention, the study design, analytical methods and creation of the team. DX drafted the first manuscript. SX and WG secured the study site. EC and SX contributed significantly to the intervention strategy and the methods of outcome assessment. JH, MN and HH provided critical review and revision to the design and analytical methods of the study. JS contributed to the theoretical framework of the study. KS edited and improved the manuscript. HB helped design and write the economic evaluation part of the

protocol. SG steered the direction of the study and contributed significantly to the revision of the manuscript. All authors read and revised the initial manuscript and approved the final version.

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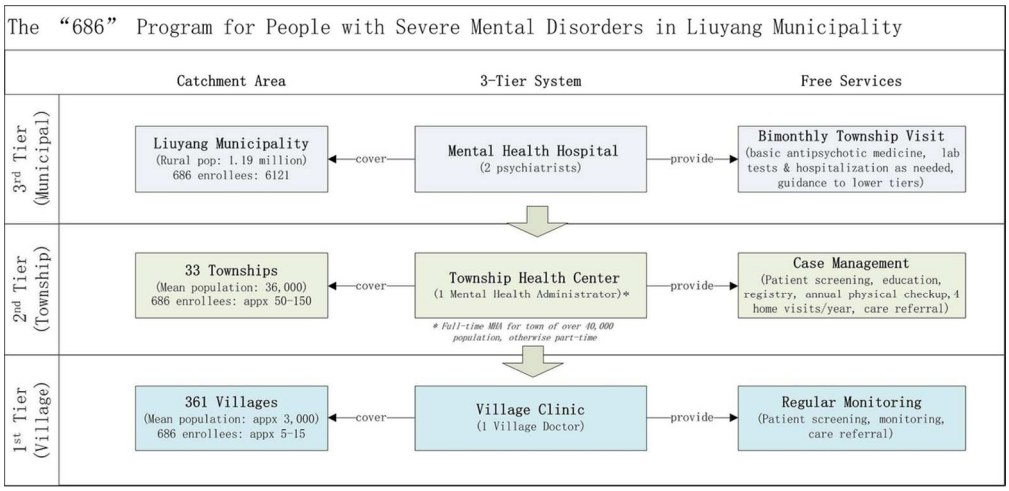

FIGURE 1 THE "686" PROGRAM SERVICE MODEL

Source: authors.
110x53mm (300 x 300 DPI)

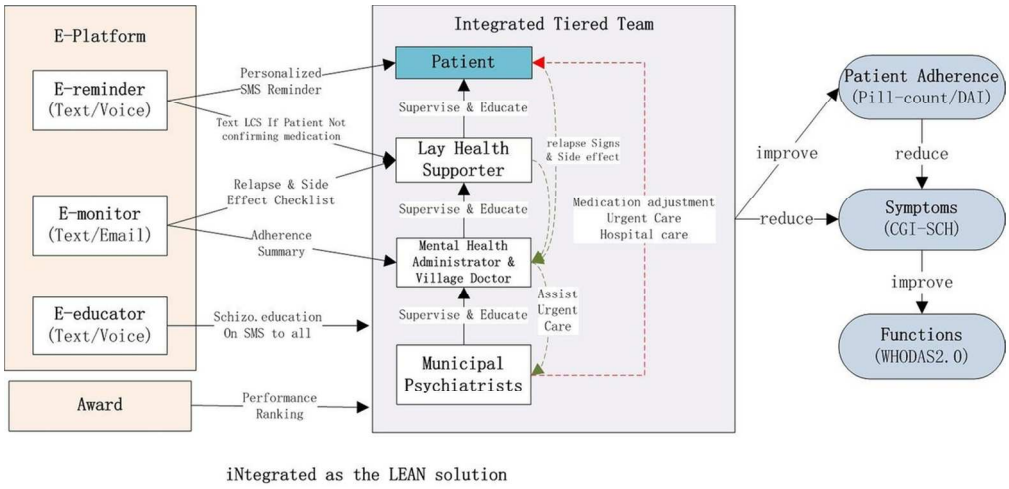

FIGURE 2 LEAN

LEAN
L: Lay health supporter (LHS)
E: E-platform with e-reminder, e-monitor, and e-educator via mobile text/voice messaging
A: Award system analogous to Taekwondo ranks
N: iNtegrating the L, E and A and "686" Program structure into a lean and coordinated approach
Source: authors.

106x51mm (300 x 300 DPI)

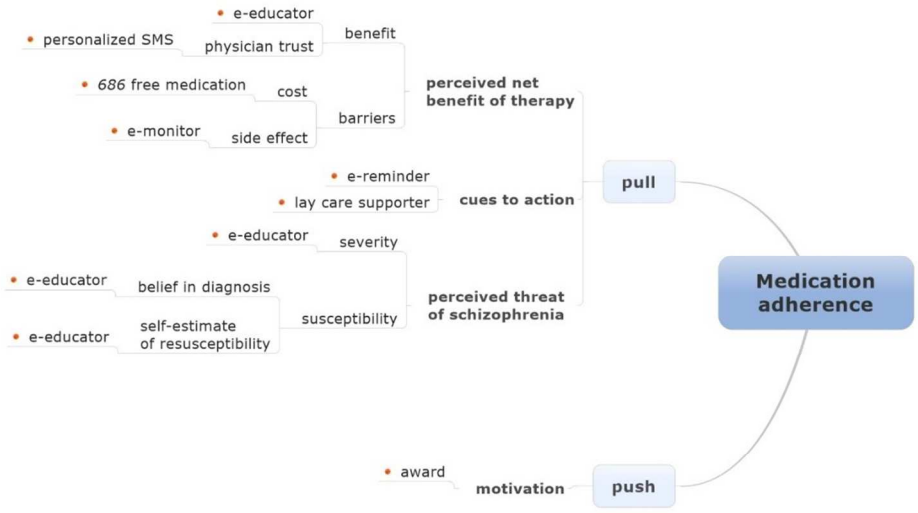

FIGURE 3 MECHANISM FOR LEAN MEDICATION ADHERENCE
Note: The red dots indicate LEAN components.
Source: adapted from the health belief model.

143x85mm (220 x 220 DPI)

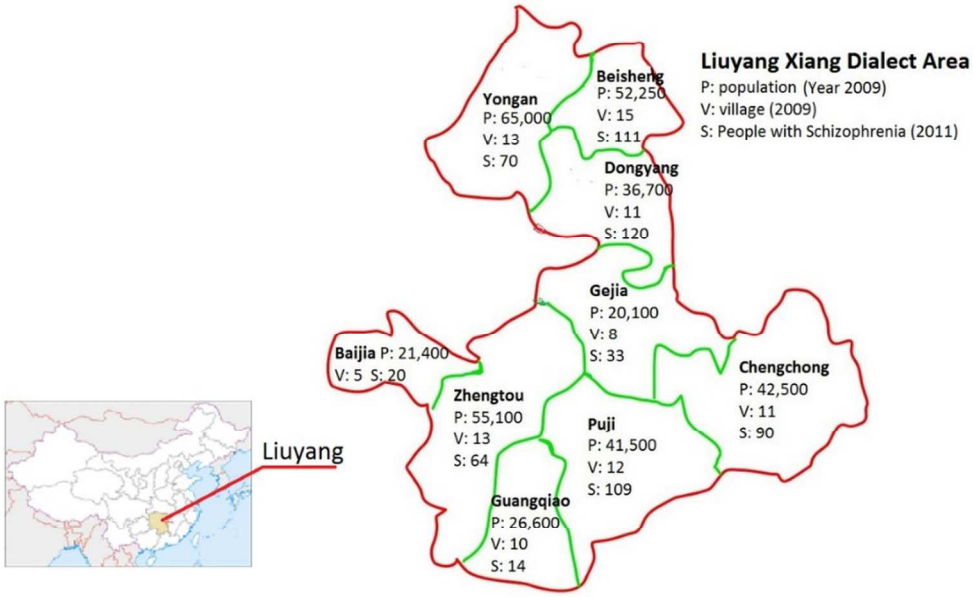

FIGURE 4 MAP OF THE XIANG-DIALECT AREA OF LIUYANG
Note: Yellow-shaded region on the map of China is Hunan Province.

169x115mm (300 x 300 DPI)

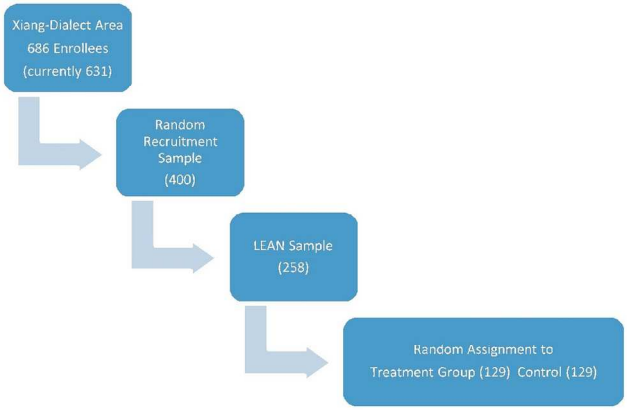

FIGURE 5 THE LEAN POPULATION, SAMPLE AND ASSIGNMENT
Source: authors

156x67mm (300 x 300 DPI)

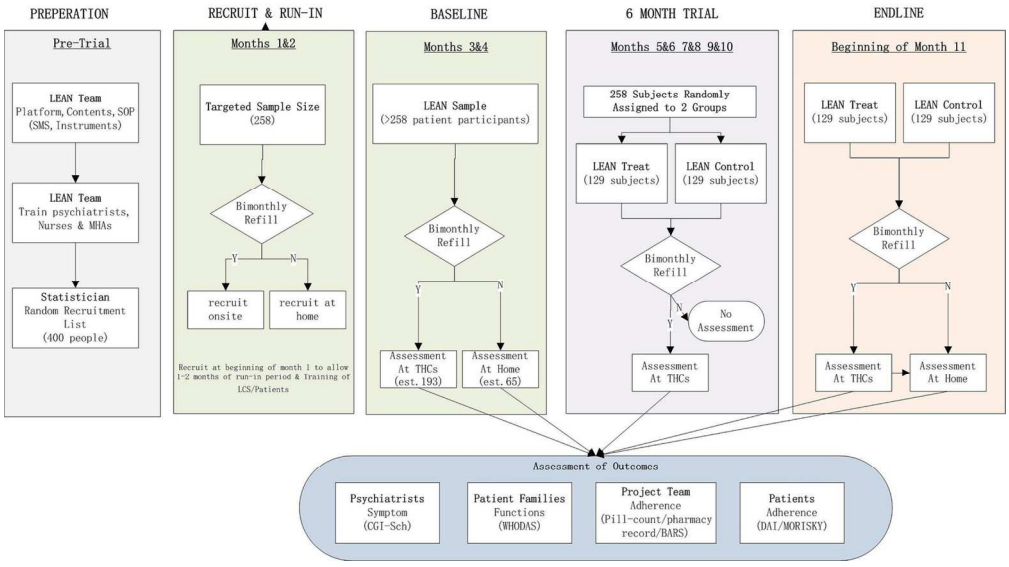

FIGURE 6 RECRUITMENT AND OUTCOME ASSESSMENT
Source: authors

139x77mm (300 x 300 DPI)

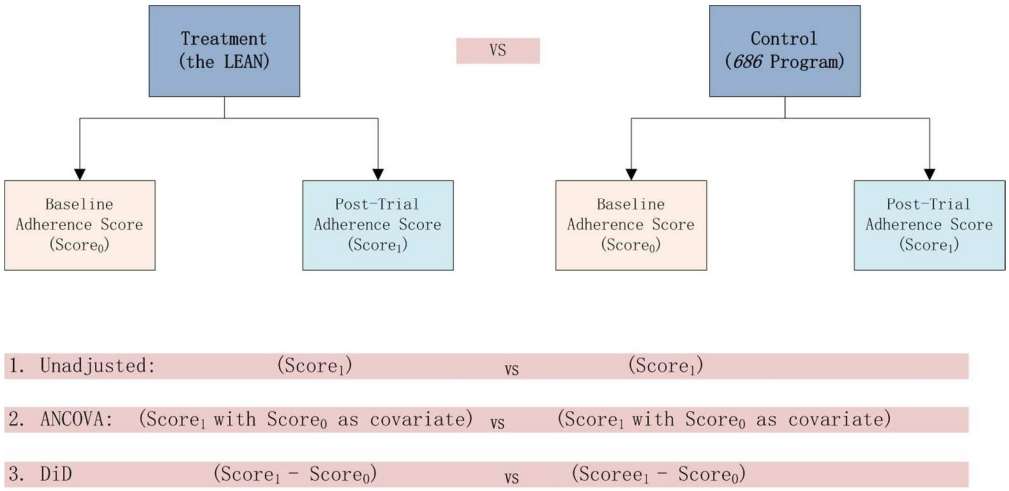

FIGURE 7 THREE APPROACHES TO RCT ANALYSIS
Source: adapted from Siyuan Zhang paper 36

166x80mm (240 x 240 DPI)

Appendices

E-reminder example

"Xiao Wang (Little Wang in Chinese, a diminutive often used in friendly conversation), we have the forecast for two beautiful sunny days and hope you will enjoy some sunshine (or: you may see more and more children in the village as the winter break starts today). We also hope you have taken your meds today. If yes, please text "yes" to let us know. Lao Zhang (Old Zhang)".

Sample Calculation in STATA

```
sampsi .72 .85, sd1(.33) sd2(.33) alpha(0.05) power(.85)
Estimated sample size for two-sample comparison of means
Test Ho: m1 = m2, where m1 is the mean in population 1
                and m2 is the mean in population 2
Assumptions:
        alpha =   0.0500  (two-sided)
        power =   0.8500
           m1 =      .72
           m2 =      .85
          sd1 =      .33
          sd2 =      .33
        n2/n1 =     1.00
Estimated required sample sizes:
           n1 =      116
           n2 =      116
```

Early Signs Questionnaire, Short Form

The following form is reprinted with permission from Marvin Herz, MD. From The University of Rochester.

NAME_____ DATE_____

Compared to last week, has there been an increase in any of the following symptoms?

	YES	NO
1. Problems with sleep	_____	_____
2. Problems with appetite	_____	_____
3. Depression	_____	_____
4. Problems with concentration	_____	_____
5. Restlessness	_____	_____
6. Tension or nervousness	_____	_____
7. Use of alcohol	_____	_____
8. Use of street drugs (includes marijuana)	_____	_____
9. Hearing voices or seeing things that others can't hear or see	_____	_____
10. Less pleasure gained from things you usually enjoy	_____	_____
11. Feeling people were watching you, were against you, or were talking about you	_____	_____
12. Preference for being alone and/or been spending less time with other people	_____	_____
13. Arguments with others	_____	_____
14. Inability to get your mind off of one or two things	_____	_____
Have any other symptoms appeared or increased?	_____	_____

If so, what were they?_____

_____

_____

Did anything specific happen last week which upset you? . . . . _____

_____

If so, what was it?_____

_____

_____

Have you been taking your medication as it is prescribed for you? . . . . _____ _____

Reprinted with permission from Marvin Herz, MD. Clinicians may reproduce this scale for use in their clinical practice. Researchers who wish to use the Early Signs Questionnaire in multi-patient studies should contact Dr. Herz at University of Rochester Medical Center, Strong Ties Community Support Program, 1650 Elmwood Avenue, Rochester, NY 14620, (716)275-0300, x2337, marvin_herz@urmc.rochester.edu

E-educator Example

The example below illustrates a two way and adaptive “conversation” to be directed by the e-educator.

The example below illustrates a two-way adaptive “conversation” to be directed by the e-educator.

Sender: “Have you had challenges lately in persuading (patient name) to take medication? Text “yes” or “no”.”

If the response is “no,” the conversation terminates. The answer “yes” will prompt the following message:

Sender: ”Please choose from among the following four items the reasons why (patient name) is not taking his medicine by texting back the number: 1. He feels good and does not want to; 2. … 3. ….

The chosen items will prompt more detailed information/instruction for the recipient.

Patient informed Consent form

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、

枨冲和镇头九镇开展“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）。现邀请您参加本项目，在参加项目之前，请仔细阅读以下内容，它可以帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

“林项目”的目的是提高资源匮乏地区精神分裂症患者用药依从性，从而提高他们的功能和生活质量；核心内容是为志愿参加国家重症精神病项目管理的精神分裂症患者提供额外的免费服务，服务内容包括：每日为患者提供手机短信用药提醒；选择一位家庭成员或其他患者能接受的人员作为“非专业照看人”（简称“照看人”），照看人将接受简单培训，在手机短信的帮助下，帮助发现患者疾病复发的征兆以及病人用药后的副作用情况，并通过手机短信进行报告；收到报告后，精防专干将协助照看人和患者提高用药依从性，或通过浏阳精神病院医生调整用药，或安排紧急门诊或住院治疗。为了验证试验的效果，参加“林项目”的人员将随机（计算机抽签）分成两组，在头六个月，一组接受“林项目”的手机短信等服务；另一组作为对照，仅接受原有日常服务；六个月后，原仅接受日常服务的对照组也开始接受短信服务（除非当时数据证明干预效果为负面），至少进行六个月。

在项目过程中，我们将收集若干数据用于验证项目的有效性。数据收集将主要在您每两月领药时进行，主要由您的主治医生根据您的诊断状况填写，或通过您自身填报相关表格。我们估计每次占用您 20 分钟左右的额外时间。收集的主要数据包括：您的基本人口学信息（如年龄，性别，民族等）；精神分裂症的症状和功能；服药情况。您的这些数据大部分已经在目前的国家重症精神病项目中采集。项目组将在法律的范围内，严格为您的数据保密，将遵守中国和美国两国给病人隐私安全的保密要求。您的数据将存储在严格加密的“红帽”电子平台；书面信息将保留在加锁的安全之地，保留五年后销毁。我们承诺您的数据将仅作为研究所用。我们所有的研究报告在分析和报告时，您所有的身份信息都将隐去（包括您的所有身份证号码，姓名，所在地，健康档案号等等）。

“林项目”的参与完全是志愿的。您可以在任何时候决定退出“林项目”的服务。退出“林项目”项目不会影响您目前参与的国家重症精神病项目中所享有的任何服务和福利。退出的方式可以是：短信回复退出项目；电话或信件通知村医或精防专干；电话或信件通知中南大学项目团队。

通过参与“林项目”，您可能福利包括：接收到与精神卫生有关的知识性短信；短信用药提醒；可能更快捷的药物调整；可能更快捷的门诊和住院安排。如果您没有手机或手机短信计划，项目组可能会为您提供一台免费的简易手机。与“林项目”有关的所有短信都是

免费的（包括您回复我们的短信）。虽然如前我们将竭尽全力来保护您的隐私数据，参加项目的可能风险主要是您隐私的泄露。

如您对项目有任何疑问，请随时联系项目团队。我们的联系方式如下：龚雯洁（中南大学）13607445252 gongwenjie@csu.edu.cn 徐东（美国华盛顿大学）13910988979 roman.xu@gmail.com

如您在了解以上信息后，决定参加“林项目”，请在下页签字：

研究项目：“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）

课题协作单位：中南大学、美国华盛顿大学

同意申明：

我已经阅读了上述有关本研究的介绍，而且有机会就此项研究与项目成员讨论并提出问题。我提出的所有问题都得到了满意的答复。

我知道参加本研究可能产生的风险和收益。我知晓参加研究是自愿的，我确认已有充足时间对此进行考虑，而且明白：

我可以随时向项目组咨询更多的信息。

我可以随时退出本研究，而不会受到歧视或报复，医疗待遇与权益不会受到影响。

我同意项目组可以在隐匿我身份信息的前提下在研究上使用我在项目过程中被收集的数据。

我将获得一份注明日期的知情同意书副本。

最后，我决定同意参加本项研究，并保证尽量遵从医嘱。

参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

LHS informed consent form

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、枨冲和镇头九镇开展“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）。现邀请您作为患者的照看人参加本项目，在参加项目之前，请仔细阅读以下内容，它可以

帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

“林项目”的目的是提高资源匮乏地区精神分裂症患者用药依从性，从而提高他们的功能和生活治疗；核心内容是为志愿参加国家重症精神病项目管理的精神分裂症患者提供额外的免费服务，包括每日用 SMS（语音或文字短信）的用药提醒。对每个病人而言，项目将培训一个家庭成员或其他人员（在这里就是“您”）作为病人的照看人，以帮助病人提高用药依从性，减少用药副作用，和监测疾病复发。您所担负的角色包括给精防专干或精神科医生发放病人相关的报告，以便与他们可以及时的作出反馈，调整用药，安排门诊和住院服务等。具体而言，这些任务包括

- 如果病人没有回复确认我们给他/她的反复的短信用药提醒，我们将给您发短信，请您去查看一下病人服药的情况并用短信告知我们查看的结果。
- 我们将偶尔用短信给您发送与病人疾病复发或药物副作用相关的核对单，以方便您及时发现和报告病人的疾病复发和副作用情况。
- 我们将偶尔给您用短信发送如何应对疾病的相关资源情况和知识。

为了验证试验的效果，参加“林项目”的人员将随机（计算机抽签）分成两组，在头六个月，一组接受“林项目”的手机短信等服务；另一组作为对照，仅接受原有日常服务；六个月后，原仅接受日常服务的对照组也开始接受短信服务（除非当时数据证明干预效果为负面），至少进行六个月。

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我可以随时向项目组咨询更多的信息。

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我将获得一份注明日期的知情同意书副本。

最后，我决定同意作为_____的照看人参加本项研究，并保证尽量遵从医嘱。

参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

UNIVERSITY of WASHINGTON
HUMAN SUBJECTS DIVISION
Box 359470
Seattle, WA 98195-9470
Phone: 206-543-0098
Fax: 206-543-9218

RESPONSE: Cover Sheet, Conditional Approval

This document contains no hidden branching or guidance.

For HSD Office Use Only

- ☐ Master Copy
- ☐ IRB Working Copy
- ☒ Researcher Copy
- ☒ **YES**: Conditions of IRB approval have been met (verification)
- ☐ **NO**: Conditions of IRB approval are not met. These materials must be reviewed by the IRB.

Date Received:

RECEIVED
Human Subjects Division
APR 20 2015
UW

In response to: Initial review
DORA MOD #: 1

Printed name of verifier: Deborah Dickstein

Date of verification: 4/21/2015

Role/position of verifier:

☒ HSD staff person ☐ IRB member (not HSD staff) ☐ Other (specify):

Notes:

PURPOSE and INSTRUCTIONS

***Purpose**: Use this form to respond to an IRB review letter when your application has received **Conditional Approval**.*

***Instructions**:*

1. *Complete this form.*
2. ***Open the IRB review letter in an electronic format, and then write your answers to IRB questions directly under each question. Please change the date to the date of your response, make it clear that the new letter is from the PI to the IRB (or HSD), and clearly mark your responses with italics, widely separated paragraphs or a contrasting font of some kind.***
3. ***Print out the IRB review letter with your answers.***
4. ***Attach those pages to this form.***
6. *If you are submitting changes to the consent and/or recruitment materials at the IRB's request, please include copies in "tracked changes."*
7. *When preparing double-sided copies, each item (e.g. application, consent form, study instruments, etc.) should begin on the front of a new piece of paper.*
8. *Collate all attachments so that you have three complete "application packets."*
9. *Use clips, not staples, on at least one packet, so that the IRB staff may easily distribute your materials to additional IRB reviewers, as needed.*
10. *Submit the original and two copies.*
11. ***Do not include a revised application form or any part of an application form** unless requested.*

If the instructions above are not followed as stated, the Human Subjects Division will not review your form.

1. Research Study Information

IRB Application Number:	IRB Committee:	IRB Review Date:
49464	G	4/17/2015

IRB Application Title:

Lay Care Supporters Aided by a Mobile Phone Messaging System to Improve Care of Villagers with Schizophrenia in Liuyang China

Lead Researcher Name:	Box #:
Dong (Roman) Xu	

IRB Contact Name (if other than Lead Researcher):	Phone #:	Email:
		romanxu@uw.edu

END PART ONE

2. List of Attachments

- ☐ Assent form(s)

- [ ] Confidentiality Agreement (*1 copy ONLY*)
- [x] Consent form(s) (*Include 1 'clean' copy and 1 'tracked changes' copy per packet*)
- [ ] Consent materials translated into a language other than English
- [ ] Consent materials: addendum consent, information sheets, oral consent scripts
- [ ] Data collection instruments/forms
- [ ] Data safety and monitoring charter and/or report(s)
- [ ] Data Safety Monitoring Plan (DSMP)
- [ ] Data Use Agreement(s)
- [ ] Embryonic Stem Cell Research Oversight committee (ESCRO) approvals/letters/report
- [ ] Environmental Health and Safety (EHS) approvals/letters/report
- [ ] Federal Certificate of Confidentiality
- [ ] GIM 10 Review Letter/Conflict of Interest Management Plan Letter

- [ ] Grant application and title page of grant application (*1 copy ONLY*)
- [ ] HIPAA Authorization Form
- [ ] Implant and Investigational Device Committee (IIDC) approvals/letters/report
- [ ] Individual Investigator Agreements
- [ ] Institutional Biosafety Committee (IBC) approvals/letters/report
- [ ] Investigator brochure (*1 copy ONLY*)
- [ ] IRB Authorization Agreements
- [ ] Letters of cooperation
- [ ] Literature or abstracts supporting the purpose of your research
- [ ] Material Transfer Agreement(s) (MTA)
- [ ] Oral scripts
- [ ] Other funding documentation, only if you have funding that is not a grant application/proposal
- [ ] Other IRB approval letters/notifications
- [ ] Other IRB approvals
- [ ] Other, specify:
- [ ] Protocol (*1 copy ONLY*)
- [ ] Radiation Safety Applications or Radiation Safety Approval Letters (RS)
- [ ] Radioactive Drug Research Committee (RDRC) approvals/letters/report
- [ ] Recruitment-electronic materials: scripts for emails, and/or copies of web pages
- [ ] Recruitment-oral materials: scripts, radio ads
- [ ] Recruitment-written materials: flyers, brochures, newspaper ads, and/or letters
- [ ] Study instruments: surveys, questionnaires, assessment tools, tracking forms, web surveys
- [ ] SUPPLEMENT: Department of Defense (DOD) Involvement
- [ ] SUPPLEMENT: Department of Justice
- [ ] SUPPLEMENT: Devices
- [ ] SUPPLEMENT: Drugs, Biologics, Botanicals
- [ ] SUPPLEMENT: Genetic Research
- [ ] SUPPLEMENT: GWAS dbGaP
- [ ] SUPPLEMENT: Protected and/or Vulnerable Populations
- [ ] SUPPLEMENT: Waiver Request, Consent Requirements
- [ ] SUPPLEMENT: Waiver Request, HIPAA Authorization

END PART TWO

20 April 2015

Deborah Dickstein, MSPH
Administrator, Committee G

Application number: 49464
Application title: *Lay Care Supporters Aided by a Mobile Phone Messaging System to Improve Care of Villagers with Schizophrenia in Liuyang China*
IRB Review date: 4/17/2015
Application type: NEW
Approval type Conditional approval

cc: Stephen Gloyd, MD, MPH

Dear Ms. Dickstein,

I am writing this letter in response to the above-referenced application and CONDITIONAL APPROVAL.

My Response to the IRB Conditions of Approval

1. Please confirm that patients must have Lay Care Supporters (LCS) to be in the study. Also confirm that this is true for both the intervention arm and the control arm.

   Yes, we confirm this. All patients in the study will have LCSs. In majority of the cases, the LCS will be the family members who are already listed on the "686" program who normally accompany the patients to the bimonthly "686" physician visit. Should some patient have no LCS, we will search and identify one for them. This is true for both arms.

2. Please confirm that the LCS are subjects because you collect some data from or about them, and that this is true for both the intervention arm and the control arm.

   Yes, this is true for both control and intervention arms.

3. The application says that you want approval for 250 subjects: 125 in the intervention arm and 125 in the control arm. Please confirm that because the LCS are also subjects, you actually want approval for 250 dyads or a total of 500 individual subjects.

   Sorry for my mistake in the protocol. We confirm we will actually recruit 250 patient subjects and 250 LCS subjects.

4. The LCS consent form sometimes seems to address the patient subject, and it does not tell the LCS enough about their role as study subjects and what you are asking them to do. Please make the following revisions to the LCS consent form. Submit the revised combined form, and a new Chinese-only translation. Add to both a footer showing the revision date, to ensure that you use the correct version. In the second paragraph, delete the current second English sentence and replace it with the following:

   "The core of the LEAN is to provide additional free services for the "686" program enrollees with schizophrenia, including daily medication reminders by SMS (voice or text message). For each

patient, LEAN will also train a family member or other person—you--to help the patient with medication, side effects and relapses. Your role includes sending reports about the patient to the mental health administrator and psychiatrist so that they can respond quickly to adjust medication and/or arrange for outpatient or inpatient services. Specifically:

--If the patient does not respond to repeated medication reminders, we will send you text messages asking you to check on the patient and text back to us.

--We will occasionally send you a checklist for reporting on the patient's relapse signs and side effects.

--We will occasionally send messages with information and resources for dealing with schizophrenia."

We have revised the form. We have enclosed both the Chinese and English version (the clean and tracked-change copies)

After you have made the above revision, at the end of the final sentence of the same paragraph change "your outcome" to "the patient's outcome".

We have revised the form. We have enclosed both the Chinese and English version (the clean and tracked-change copies)

Throughout the rest of the LCS consent form, change "your patient" or "your patients" to "the patient". The LCS is not a care provider in the usual sense of having patients, and in any case is connected to only one patient subject.

We have revised the form. We have enclosed both the Chinese and English version (the clean and tracked-change copies)

LEAN Trial Informed Consent - LCS

We are the Central South University and the University of Washington School of Public Health research team. With the support of a charitable foundation the China Medical Board, we will carry out a project to improve the outcome of the people with schizophrenia with the help of mobile phone messaging (the LEAN Project) in nine townships of Liuyang including Baijia, Beisheng, Dongyang, Gejia, Guangqiao, Puji, Yongan, Chengchong and Zhentou. We cordially invite you as the lay care supporter to participate in the project. Before taking part in the project, please read the following carefully, which can help you understand the purpose, content, duration, and the benefits and risks of your participation in the project. If you like, you are welcome to consult with your relatives or friends to help your decision or to discuss this further with the project team for clarification on any points concerning your participation.

"The LEAN Project" aims to improve medication adherence in patients with schizophrenia in resource poor areas, thereby improving their function and quality of life. The core of the LEAN is to provide additional free services for the "686" program enrollees with schizophrenia, including daily medication reminders by SMS (voice or text message). For each patient, LEAN will also train a family member or other person—you--to help the patient with medication, side effects and relapses. Your role includes sending reports about the patient to the mental health administrator and psychiatrist so that they can respond quickly to adjust medication and/or arrange for outpatient or inpatient services. Specifically:

- If the patient does not respond to repeated medication reminders, we will send you text messages asking you to check on the patient and text back to us.
- We will occasionally send you a checklist for reporting on the patient's relapse signs and side effects.
- We will occasionally send messages with information and resources for dealing with schizophrenia.

In order to test the effect of the project, patient participants of the LEAN will be randomly (drawing lots by a computer) divided into two groups, in the first six months, one group will receive the LEAN services and their regular "686" services; the other group will serve as controls, receiving only existing "686" program services; after six months, both the control group will also receive the LEAN services unless we find the project not useful or even detrimental to improve the patient's outcome at that time.

In the course of the project, we will collect some data to test the effect of the project. Most data related to you will be concerning your demographic information such as sex, age, education; and your interaction with us on the SMS platform. The project team will stick to the strict confidentiality requirement of your data according to both the US and China patient privacy requirement in the scope of the law. Your data will be stored in an encrypted electronic system called "RedCap"; written information will be kept in a locked safe place, to be retain for five years and then will be destroyed. We promise that your data will only be used for our research purposes. In all of our research in the analysis and reporting, all your identifiable information will be de-identified including your ID number, name, location, health record number, etc.).

Participation in the "LEAN Project" is completely voluntary. You can decide to quit the service at any time. Dropping out of the LEAN will not affect any of the services and the welfare you patients have been receiving through the “686” program or other programs. There are also multiple ways of quitting the program including: messaging with SMS to the project team to quit the project; telephone or mail notification of quitting to your village doctors or MHAs or the project team at the Central South University.

By participating in the LEAN project, you may benefit from the following: receiving mental health-related knowledge on SMS; more efficient medication adjustment to the patients; and easier access to urgent outpatient and inpatient care for the patients. All those may help you take better care of the patients. All texting related to the LEAN project is free as well, including your replies on SMS to our SMS. Possible risks involved in the project is mainly your privacy violation, although we will make every effort to protect your privacy and data.

If you have any questions about the project, please feel free to contact the project team. Our contact information is as follows: Gong Wenjie (Central South University) 13607445252 gongwenjie@csu.edu.cn Dong Xu (University of Washington) 13910988979 roman.xu@gmail.com.

If you understand the above information and decide to participate in the "LEAN Project", please sign this document.

Research project: "China Liuyang schizophrenic patients SMS Support Project" (the LEAN project)

Research cooperative units: Central South University, University of Washington

I agree:

I have read the above information about this study, and also have the opportunity to discuss the study with the project members for questions. All my questions have been satisfied with their answers.

I understand the possible risks and benefits of participating in this study. I know that participation in the study is voluntary, and I have adequate time to consider this and make my decision. I understand:

I can always ask for more information to the project team.

I can withdraw from this study at any time, without discrimination or retaliation, and my current benefits to medical treatment will not be affected.

I agree that the LEAN research team can use the data collected in the course of the project on the study while deidentify my personal information.

I will receive a copy of this informed consent.

Finally, I decided to agree to participate in this study as the LCS for _____, and will try to follow the protocols of the intervention.

照看人知情同意书 LCS Informed Consent

signature：_____

Name (print): _____

Date：_____

照看人知情同意书 LCS Informed Consent

LEAN Trial Informed Consent - LCS

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"The LEAN Project" aims to improve medication adherence in patients with schizophrenia in resource poor areas, thereby improving their function and quality of life. The core of the LEAN is to provide additional free services for the "686" program enrollees with schizophrenia, including daily medication reminders by SMS (voice or text message). For each patient, LEAN will also train a family member or other person—you--to help the patient with medication, side effects and relapses. Your role includes sending reports about the patient to the mental health administrator and psychiatrist so that they can respond quickly to adjust medication and/or arrange for outpatient or inpatient services. Specifically:

- If the patient does not respond to repeated medication reminders, we will send you text messages asking you to check on the patient and text back to us.
- We will occasionally send you a checklist for reporting on the patient's relapse signs and side effects.
- We will occasionally send messages with information and resources for dealing with schizophrenia.

~~The core of the LEAN is to provide additional free services for the "686" program enrollees with schizophrenia, including daily SMS to provide you with medication reminders; and training a family member or other person acceptable to you as "Lay Care Supporter" (LCS, ie, "you"), who will help the patient with medication, side effects and relapses by reporting early signs of relapse and side effects to the mental health administrator and psychiatrists so that they can respond quickly to adjust your medication and/or arrange for urgent outpatient or inpatient services.~~

In order to test the effect of the project, patient participants of the LEAN will be randomly (drawing lots by a computer) divided into two groups, in the first six months, one group will receive the LEAN services and their regular "686" services; the other group will serve as controls, receiving only existing "686" program services; after six months, both the control group will also receive the LEAN services unless we find the project not useful or even detrimental to improve the patient's outcome at that time.

In the course of the project, we will collect some data to test the effect of the project. Most data related to you will be concerning your demographic information such as sex, age, education; and your interaction with us on the SMS platform. The project team will stick to the strict confidentiality requirement of your data according to both the US and China patient privacy requirement in the scope of the law. Your data will be stored in an encrypted electronic system called "RedCap"; written

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information will be kept in a locked safe place, to be retain for five years and then will be destroyed. We promise that your data will only be used for our research purposes. In all of our research in the analysis and reporting, all your identifiable information will be de-identified including your ID number, name, location, health record number, etc.).

Participation in the "LEAN Project" is completely voluntary. You can decide to quit the service at any time. Dropping out of the LEAN will not affect any of the services and the welfare you patients have been receiving through the "686" program or other programs. There are also multiple ways of quitting the program including: messaging with SMS to the project team to quit the project; telephone or mail notification of quitting to your village doctors or MHAs or the project team at the Central South University.

By participating in the LEAN project, you may benefit from the following: receiving mental health-related knowledge on SMS; more efficient medication adjustment to ~~your~~ the patients; and easier access to urgent outpatient and inpatient care for ~~your~~ the patients. All those may help you take better care of ~~your~~ the patients. All texting related to the LEAN project is free as well, including your replies on SMS to our SMS. Possible risks involved in the project is mainly your privacy violation, although we will make every effort to protect your privacy and data.

If you have any questions about the project, please feel free to contact the project team. Our contact information is as follows: Gong Wenjie (Central South University) 13607445252 gongwenjie@csu.edu.cn Dong Xu (University of Washington) 13910988979 roman.xu@gmail.com.

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Research project: "China Liuyang schizophrenic patients SMS Support Project" (the LEAN project)

Research cooperative units: Central South University, University of Washington

I agree:

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I understand the possible risks and benefits of participating in this study. I know that participation in the study is voluntary, and I have adequate time to consider this and make my decision. I understand:

I can always ask for more information to the project team.

I can withdraw from this study at any time, without discrimination or retaliation, and my current benefits to medical treatment will not be affected.

I agree that the LEAN research team can use the data collected in the course of the project on the study while deidentify my personal information.

I will receive a copy of this informed consent.

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Finally, I decided to agree to participate in this study as the LCS for _____, and will try to follow the protocols of the intervention.

~~signigure~~signature: _____

Name (print): _____

Date: _____

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[表 004.1]

“林项目”照看人知情同意书

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、枨冲和镇头九镇开展“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）。现邀请您作为患者的照看人参加本项目，在参加项目之前，请仔细阅读以下内容，它可以帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

“林项目”的目的是提高资源匮乏地区精神分裂症患者用药依从性，从而提高他们的功能和生活治疗；核心内容是为志愿参加国家重症精神病项目管理的精神分裂症患者提供额外的免费服务，包括每日用 SMS（语音或文字短信）的用药提醒。对每个病人而言，项目将培训一个家庭成员或其他人员（在这里就是“您”）作为病人的照看人，以帮助病人提高用药依从性，减少用药副作用，和监测疾病复发。您所担负的角色包括给精防专干或精神科医生发放病人相关的报告，以便与他们可以及时的作出反馈，调整用药，安排门诊和住院服务等。具体而言，这些任务包括

- 如果病人没有回复确认我们给他/她的反复的短信用药提醒，我们将给您发短信，请您去查看一下病人服药的情况并用短信告知我们查看的结果。
- 我们将偶尔用短信给您发送与病人疾病复发或药物副作用相关的核对单，以方便您及时发现和报告病人的疾病复发和副作用情况。
- 我们将偶尔给您用短信发送如何应对疾病的相关资源情况和知识。

为了验证试验的效果，参加“林项目”的人员将随机（计算机抽签）分成两组，在头六个月，一组接受“林项目”的手机短信等服务；另一组作为对照，仅接受原有日常服务；六个月后，原仅接受日常服务的对照组也开始接受短信服务（除非当时数据证明干预效果为负面），至少进行六个月。

在项目过程中，我们将收集若干数据用于验证项目的有效性。向您收集的数据主要包括您的人口学信息（如年龄，性别，民族等）；您在短信平台上和我们的互动信息。数据将存储在严格加密的“红帽”电子平台；书面信息将保留在加锁的安全之地，保留五年后销毁。我们承诺您的数据将仅作为研究所用。我们所有的研究报告在分析和报告时，您所有的身份信息都将隐去（包括您的所有身份证号码，姓名，所在地）。

“林项目”的参与完全是志愿的。您可以在任何时候决定退出“林项目”的服务。退出“林项目”项目不会影响患者目前参与的国家重症精神病项目中所享有的任何服务和福利。退出的方式可以是：短信回复退出项目；电话或信件通知村医或精防专干；电话或信件通知中南大学项目团队。

通过参与“林项目”，您将接收到短信平台的简单培训，与精神卫生有关的知识性短信；针对患者的用药短信提醒；对患者的可能更快捷的药物调整；可能更快捷的门诊和住院安排。这些

都可能帮助您照看好患者。与“林项目”有关的所有短信都是免费的（包括您回复我们的短信）。虽然如前我们将竭尽全力来保护您的隐私数据，参加项目的可能风险主要是您隐私的泄露。

如您对项目有任何疑问，请随时联系项目团队。我们的联系方式如下：龚雯洁（中南大学）13607445252 gongwenjie@csu.edu.cn 徐东（美国华盛顿大学）13910988979 roman.xu@gmail.com

如您在了解以上信息后，决定参加“林项目”，请在下页签字：

研究项目：“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）

课题协作单位：中南大学、美国华盛顿大学

同意申明：

我已经阅读了上述有关本研究的介绍，而且有机会就此项研究与项目成员讨论并提出问题。我提出的所有问题都得到了满意的答复。

我知道参加本研究可能产生的风险和收益。我知晓参加研究是自愿的，我确认已有充足时间对此进行考虑，而且明白：

我可以随时向项目组咨询更多的信息。

我可以随时退出本研究，包括我和患者都不会受到歧视或报复，医疗待遇与权益不会受到影响。

我同意项目组可以在隐匿我身份信息的前提下在研究上使用我在项目过程中被收集的数据。

我将获得一份注明日期的知情同意书副本。

最后，我决定同意作为_____的照看人参加本项研究，并保证尽量遵从医嘱。

参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

照看人知情同意书

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[表 004.1]

“林项目”照看人知情同意书

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、枨冲和镇头九镇开展“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）。现邀请您作为患者的照看人参加本项目，在参加项目之前，请仔细阅读以下内容，它可以帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

“林项目”的目的是提高资源匮乏地区精神分裂症患者用药依从性，从而提高他们的功能和生活治疗；~~核心内容是为志愿参加国家重症精神病项目管理的精神分裂症患者提供额外的免费服务，服务内容包括：每日为患者提供手机短信用药提醒；选择一位家庭成员或其他患者说接受的人员作为“非专业看护人”（简称“照看人”，也就是您将担任的角色），照看人将接受简单培训，在手机短信的帮助下，帮助发现患者疾病复发的征兆以及病人用药后的副作用情况，并通过手机短信就行报告；收到报告后，精防专干将协助看护人和患者提高用药依从性，或通过浏阳精神病院医生调整用药，或安排紧急门诊或住院治疗。~~核心内容是为志愿参加国家重症精神病项目管理的精神分裂症患者提供额外的免费服务，包括每日用 SMS（语音或文字短信）的用药提醒。对每个病人而言，项目将培训一个家庭成员或其他人员（在这里就是“您”）作为病人的照看人，以帮助病人提高用药依从性，减少用药副作用，和监测疾病复发。您所担负的角色包括给精防专干或精神科医生发放病人相关的报告，以便与他们可以及时的作出反馈，调整用药，安排门诊和住院服务等。具体而言，这些任务包括

- 如果病人没有回复确认我们给他/她的反复的短信用药提醒，我们将给您发短信，请您去查看一下病人服药的情况并用短信告知我们查看的结果。
- 我们将偶尔用短信给您发送与病人疾病复发或药物副作用相关的核对单，以方便您及时发现和报告病人的疾病复发和副作用情况。
- 我们将偶尔给您用短信发送如何应对疾病的相关资源情况和知识。

为了验证试验的效果，参加“林项目”的人员将随机（计算机抽签）分成两组，在头六个月，一组接受“林项目”的手机短信等服务；另一组作为对照，仅接受原有日常服务；六个月后，原仅接受日常服务的对照组也开始接受短信服务（除非当时数据证明对病人干预效果为负面），至少进行六个月。

在项目过程中，我们将收集若干数据用于验证项目的有效性。向您收集的数据主要包括您的人口学信息（如年龄，性别，民族等）；您在短信平台上和我们的互动信息。数据将存储在严格加密的“红帽”电子平台；书面信息将保留在加锁的安全之地，保留五年后销毁。我们承诺您的数据将仅作为研究所用。我们所有的研究报告在分析和报告时，您所有的身份信息都将隐去（包括您的所有身份证号码，姓名，所在地）。

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如您在了解以上信息后，决定参加“林项目”，请在下页签字：

研究项目：“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）

课题协作单位：中南大学、美国华盛顿大学

同意申明：

我已经阅读了上述有关本研究的介绍，而且有机会就此项研究与项目成员讨论并提出问题。我提出的所有问题都得到了满意的答复。

我知道参加本研究可能产生的风险和收益。我知晓参加研究是自愿的，我确认已有充足时间对此进行考虑，而且明白：

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我同意项目组可以在隐匿我身份信息的前提下在研究上使用我在项目过程中被收集的数据。

我将获得一份注明日期的知情同意书副本。

最后，我决定同意作为_____的照看人参加本项研究，并保证尽量遵从医嘱。

参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

Revised 04.20.15

中南大学临床药理研究所医学伦理委员会

编号:CTXY-150002-6号

中南大学临床药理研究所伦理委员会临床试验审核表

项目名称:	中国浏阳农村精神分裂症患者服药手机短信支持项目		
研究机构	中南大学湘雅医学院、美国华盛顿大学全球卫生系	主要研究者	姜雯洁
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中南大学临床药理研究所医学伦理委员会

单位：中南大学公共卫生学院

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中南大学临床药理研究所医学伦理委员会

2015年02月04日

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

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 0
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	P3-4
Protocol version	3	Date and version identifier	All Pages
Funding	4	Sources and types of financial, material, and other support	P17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P16
	5b	Name and contact information for the trial sponsor	P0
	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	P17
	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)	N/A
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	P5-7
	6b	Explanation for choice of comparators	P5-8
Objectives	7	Specific objectives or hypotheses	P5
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)	P12-13

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	P5-6
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)	P9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P6-8
	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)	P6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P6-7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P5-6
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	P11-12
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)	P11-12
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	P10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P9-10

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	P9-10

	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	P9-10
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9-10
Blinding (masking)		17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P11
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P11
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	P11-12
		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	P11-12
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	P11
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	P13
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P14
		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)	P14
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	P14

	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	P14
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	P14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14
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)	P14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	P14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P16
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	P14
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	P13
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	P14
	31b	Authorship eligibility guidelines and any intended use of professional writers	P16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P14

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	P20-24
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	N/A

*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

Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial

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Keywords:	schizophrenia, medication adherence, mHealth, lay health worker, implementation science, "686" program

Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial

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Abstract

Introduction: Schizophrenia is a severe, chronic, and disabling mental illness. Non-adherence to medication and relapse may lead to poorer patient function. This randomized controlled study, under the acronym LEAN, is designed to improve medication adherence and high relapse among people with schizophrenia in resource poor settings. **Methods/Analysis**: the community-based **LEAN** has four parts: 1) **L**ay health supporters (LHSs), mostly family members who will help supervise patient medication, monitor relapse and side effects, and facilitate access to care, 2) an **E**-platform to support two-way mobile text and voice messaging to remind patients to take medication; and alert LHSs when patients are non-adherent, 3) an **A**ward system to motivate patients and strengthen LHS support, and 4) iNtegration of the efforts of patients and LHSs with those of village doctors, township mental health administrators and psychiatrist via the e-platform. A random sample of 258 villagers with schizophrenia will be drawn from the schizophrenic "686" Program registry for the 9 Xiang-dialect towns of the Liuyang municipality in China. The sample will be further randomized into a control group and a treatment group of equal sizes, and each group will be followed for 6 months after launch of the intervention. The primary outcome will be medication adherence as measured by pill-counts and supplemented by pharmacy records. Other outcomes include symptoms and level of function. Outcomes will be assessed primarily when patients present for medication refill visits scheduled every two months over the 6-month follow-up period. Data from the study will

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be analyzed using ANCOVA for the program effect and an intent-to-treat approach. **Ethics and dissemination**: University of Washington: 49464 G; Central South University: CTXY-150002-6. Results will be published in peer-reviewed journals with deidentified data made available on FigShare. **Trial Registration**: ChiCTR-ICR-15006053

Keywords*:* schizophrenia, medication adherence, mHealth, lay health worker, implementation science, wait-list control, RCT, "686" program

Strengths and Limitations

Strengths:

- The application of mHealth is designed not as a standalone technological solution but a health system strengthening tool that serves to integrate the patient care provided by lay health supporters, village doctors, mental health administrators and psychiatrists.
- The active engagement of family members augments case supervision.
- The study, evaluating the real world effectiveness of LEAN, emphasizes the implementation parts so as to increase the likelihood of scaling up the potentially effective solution.
- The trial is intent to have global implications, especially insofar as the intervention is designed to exclude elements peculiar to China's socio-economic and/or political situation.

Limitations:

- The short duration may not allow sufficient assessment of functional changes and limit analysis of the long-term effect on adherence.
- The choice of relatively simple assessment tools (pill-counts vs. urinalysis) may create challenges of obtaining accurate adherence level.
- Assuming that improved medication adherence will lead to better patient life-functioning may be problematic.

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WHO Trial Registration Data Set

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	ChiCTR-ICR-15006053
Date of registration in primary registry	8 Mar, 2015
Secondary identifying numbers	N/A
Source(s) of monetary or material support	China Medical Board Fogarty International Center, NIH
Primary sponsor	Central South University, China
Secondary sponsor(s)	University of Washington, USA
Contact for public queries	Dong Xu, MPP [+86 20 5969 5071] [romanxu@uw.edu]
Contact for scientific queries	Dong Xu, MPP [+86 20 5969 5071] [romanxu@uw.edu] Sun Yat-sen University
Public title	Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial
Scientific title	Lay health supporters aided by a mobile phone messaging system to improve care of villagers with schizophrenia in Liuyang, China: protocol for a randomized control trial
Countries of recruitment	China
Health condition(s) or problem(s) studied	Schizophrenia
Intervention(s)	Intervention: Lay Health Supporter plus SMS Messaging System Control: Case as ususal (ie. “686” Program)
Key inclusion and exclusion criteria	Inclusion: “686” program participant; diagnosed as schizophrenia; residing in Liuyang Xiang-dialect area Exclusion: Patients who missed past 3 drug refills; currently hospitalized; people physically not capable of using voice or text messaging
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: subject not blinded; caregiver, investigator,

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DATA CATEGORY	INFORMATION
	outcomes assessor blinded Primary purpose: improving health Effectiveness study
Date of first enrolment	July 2015
Target sample size	258
Recruitment status	Recruiting
Primary outcome(s)	Medication adherence as measured by pill-counts (medication taken over medication prescribed)
Key secondary outcomes	Symptoms as measured by Clinical Global Impression in Schizophrenia; and functions as measured by 12-item proxy-administered WHO Disability Assessment Schedule 2.0

Introduction

Background and Rationale

Schizophrenia, characterized by hallucination, delusion, disorganized thinking and negative symptoms, is a chronic and disabling mental disorder which is commonly associated with impairment in social and occupational functioning[1]. Though schizophrenia cannot be cured, most people with schizophrenia can be effectively treated for symptoms with antipsychotic medicines[2]. However, of treated patients, 50% are non-adherent with medication[3]; moreover, even under conditions of compliance, 50% of patients suffer relapse within 1 year of their latest episode[4]. The "686" Program, a massive coutry-wide government effort in China, is a relatively inexpensive and practical model that provides community-based mental health care with limited human and financial resources[5 6]. But the program faces the challenges of poor medication adherence and high relapse - 26% of the program participants never, 39% intermittently, and only 35% regularly take prescribed medications[7]. This research aims to develop, and evaluate, a financially and operationally feasible and sustainable intervention (with the acronym LEAN) to address those "686" program challenges.

Hypothesis

We hypothesize that the LEAN plus "686" solution, as compared to the present "686" standard of care only, will improve medication adherence, reduce the incidence of schizophrenia symptoms, and ultimately result in improved social and occupational functioning for enrollees.

Study Setting

The intervention will be implemented and tested in "686" program particiants in the Xiang-dialect area (a total of 9 towns) of the rural townships of Liuyang Municipality in the Hunan province of China, with an intent to produce solutions that can be adapted and applied in other LMCs with limited mental health resources. Liuyang has developed a three-tier "686" model extending from Liuyang Mental Health Hospital (MHH) to township health centers (THCs) to village clinics that consists of five compnents: 1) patient screening by village doctors (VDs) and mental health administrators (MHAs); 2) registering confirmed cases into"686" with consent; 3) Psychiatrists touring townships to provide free consultation and medication every two months ("bi-monthly visits"); 4) case

management by MHA; and 5) regular monitoring by VDs[8 9 10] (Figure 1). We should note that while Liuyang proivdes free antipsychotics to all its program enrollees, in other parts of China, often only a subset of the program participatnes receive free medication.

FIGURE 1 THE "686" PROGRAM SERVICE MODEL

Source: authors.

LEAN

LEAN as an acronym is somehow inspired by Toyota's principle in lean manufacturing[11] although our focus is to add value, minimize waste, and maintain simplicity throughout program implementation. The acronym LEAN summarizes the critical components of the proposed intervention (Figure 2). The LEAN participants can opt out of LEAN anytime by texting us or inform VDs, MHAs by phone or in person.

FIGURE 2 LEAN

LEAN
L: Lay health supporter (LHS)
E: E-platform with e-reminder, e-monitor, and e-educator via mobile text/voice messaging
A: Award system analogous to Taekwondo ranks
N: iNtegrating the L, E and A and "686" Program structure into a lean and coordinated approach

Source: authors.

Lay Health Supporter (LHS)

For each patient in the intervention, LEAN will identify a LHS — a member of the patient's family if possible or a community volunteer (such as a member of the village senior club) — who will perform simple but important roles in support of the patient: 1) facilitate patient medication adherence with prompts from the e-reminders, 2) monitor for early signs of relapse and for medication side effects using checklists from the e-monitor, and 3) team up with the village doctor and the township mental health administrator to facilitate treatment adjustments and, if needed, emergent hospital care.

E-platform

The e-platform employs three main modules: The e-reminder sends the patient up to two reminders either by text or voice messages at 15 minutes interval until the patient responds with confirmation that the scheduled medication has been taken. Failure to send a confirmation will trigger up to two text alerts to the patient's LHS, prompting the LHS to check in with the patient and text back the result. The e-monitor assists LHSs and patients in detecting signs of relapse and monitoring medication side effects using relevant checklists texted to the patient and LHS at regular intervals (See relapse checklist in appendix. And findally, the e-educator will send periodic SMS messages to the patient, LHS, MHA, and VD educating them on schizophrenia symptoms, medication, adherence strategies, relapse, rehabilitation and social resources.

Award System

Patients and LHSs will accumulate points for responding to SMS messages. Each of their texted confirmation back to the LEAN system will accumulate one point, which will be recorded automatically by the computer system. The points, counted every two months, will advance their Taekwondo-like belt ranking and entitle them to a small gift of USD 2-3 such as soap bars when they come for the bi-monthly visit to be presented by a LEAN program staff.

iNtegration

The efforts of the patient and LHS to improve medication adherence and reduce relapses will be integrated, facilitated by the e-platform, with those of the VD, MHA and psychiatrist so that the innovations of LEAN strengthens the existing health system. With this integration, non-adherence and relapses detected can then be actually handled with LHS, VDs, MHAs and psychiatrist taking concerted effort for prompt treatment adjustments or referrals for emergent hospitalization.

Mechanism of LEAN

The mechanism of LEAN medication adherence is based on an adapted health belief model (HBM) (Figure 3)[12 13]. According to this theory, people with schizophrenia make their medication adherence decisions based on push (patients' self-motivation in improving health) and pull factors that include three elements: 1) Patients' perception

of the threat posed by schizophrenia; 2) Patients' perceived net benefit of adhering to therapy, a calculation involving the benefits of therapy minus costs; and 3) Action cues such as the above-mentioned e-reminders or mass media health promotion campaigns. Figure 3 illustrates the interface of various LEAN elements with the components of the health belief model.

FIGURE 3 MECHANISM FOR LEAN MEDICATION ADHERENCE

Note: The red dots indicate LEAN components.

Source: adapted from the health belief model.

The development of LEAN has been guided not only by the HBM as a theoretical framework, but was also informed by empirical evidence, particularly in the areas of human resources for health (HRH) and mobile health (mHealth). Much of the literature in HRH suggests that "task shifting" - cascading appropriate tasks from more skilled psychiatrists to less specialized MHAs/VDs and to LHS improves access and efficacy when HRH are lacking or deficient[14 15] (Liuyang has only 1.35 psychiatrists/1.42 specialist nurses versus 8.59 psychiatrists/29.15 nurses for high income countries per 100,000 population in 2011). The e-platform facilitates efficient communication and integration of this network of human resources. Moreover, much evidence supports the use of reminders to improve medication adherence[16 17 18 19 20].

Study Population and the LEAN Sample

People in Liuyang speak three distinct dialects: Gan, Xiang and Hakka. The Xiang-dialect area, located in the west of Liuyang municipality, has 9 townships, 98 villages and a population of 356,900. The "686" Program maintains a roster of patients with schizophrenia in the Xiang-dialect area of Liuyang municipality (total: 631 in 2011) (Figure 4), which forms the study population. The characteristics of this population most relevant to our study are summarized in Table 1. The Xiang-dialect population is selected due to 1). the efficiency to recruit, train and collect data in a more focused population; 2). that Xiang dialect group is the majority group in Hunan province while the oher two dialect-groups in Liuyang are historically immigrants from other provinces; and 3). long and rich

past reseach expereince of our group in this area that provides additional data and information for the LEAN study, such as educational levels of all MHAs.

FIGURE 4 MAP OF THE XIANG-DIALECT AREA OF LIUYANG

Note: Yellow-shaded region on the map of China is Hunan Province.

TABLE 1 "686" PROGRAM ENROLLEES WITH SCHIZOPHRENIA IN THE XIANG-DIALECT AREA OF LIUYANG (YEAR 2011)

Township	Popula-tion	No. of village	"686" Enrollees w/ schiz.[1]	Age (mean)	Men (%)	Married (%)	Education < Middle School (%)	Cell Phone[2] (%)	Under Family Care (%)	Fully Functioning[3] (No. / %)		Adhe-rence[4] (%)
1. Beijia	21,000	4	20	47.2	40.0%	55.0%	50.0%	80.0%	100.0%	4	20.0%	0.78
2. Beisheng	52,000	13	111	42.0	45.4%	56.7%	40.8%	55.9%	93.9%	16	14.4%	0.70
3. Dongyang	36,075	5	120	44.6	42.5%	62.6%	41.9%	69.2%	93.5%	45	37.5%	0.62
4. Gejia	20,004	8	33	46.3	51.5%	38.7%	93.9%	63.6%	100.0%	5	15.2%	0.70
5. Guangqiao	26,347	10	14	38.1	50.0%	61.5%	25.0%	78.6%	92.3%	3	21.4%	0.75
6. Puji	41,022	9	109	44.2	32.4%	63.6%	58.0%	56.0%	97.8%	18	16.5%	0.76
7. Yongan	58,883	13	70	43.8	55.4%	61.4%	51.5%	71.4%	98.5%	6	8.6%	0.78
8. Zhengtou	56,000	13	64	43.7	46.0%	69.0%	42.6%	75.0%	96.2%	6	9.4%	0.75
9. Chengchong	43,000	9	90	43.0	40.0%	52.3%	61.4%	68.9%	100.0%	16	17.8%	0.80
Total	**354,331**	**84**	**631**	**43.7**	**43.2%**	**59.1%**	**51.4%**	**65.6%**	**96.6%**	**119**	**18.9%**	**0.725**

(1). "686" enrollees with schizophrenia only, accounting for approximately 80% of all "686" patients in Liuyang

(2). Cell phone ownership by family members of "686" Program enrollees

(3). Function assessed by MHAs using three sub-categories: daily living, social activities and work.

(4). A score of 0-1 calculated as the percentage of prescribed drugs taken by the patient in the month immediately before the survey

Source: author, Liuyang "686" Program Registry (Year 2011)

Inclusion and Exclusion Criteria

The following criteria more precisely define the study population by establishing eligibility requirements for subject recruitment. As villagers and LHSs without a phone will be given a free basic phone and subscription plan, the phone ownership is not included in the inclusion or exclusion criteria. Rationales for inclusion and exclusion criteria are given in parentheses.

Inclusion:

1. "686" Program enrollees.
2. Diagnosed as having schizophrenia according to criteria established in the *Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-5®)[21]
3. Physically reside in the Xiang-dialect area of Liuyang Municipality

Exclusion:

1. Individuals registered in the Xiang-dialect area of Liuyang Municipality, but living elsewhere as migrant workers (as a community-based intervention, LEAN requires residence in the local community)

2. Patients who have missed three immediate consecutive past drug refills (in this case, they have *de facto* dropped out of the "686" Program)

3. People who are currently hospitalized (again, LEAN intervention requires sustained community residence)

4. People physically incapable of using voice or text messaging, e.g. individuals with hearing and/or vision impairment, or who are severely disabled (ability to utilize SMS is necessary for the LEAN intervention)

Sampling Frame, the LEAN Sample and Recruitment

The most recent "686" Program registry of patients with schizophrenia will be used as the sampling frame, from which we aim to draw 258 patients as the LEAN sample. To that end, a statistician otherwise not associated with the project will first create a recruitment list of 400 people drawn at random from the sampling frame. Assuming that 15% of those selected will prove ineligible and that a further 20% will elect not to participate, an initial list of

400 should ensure a final recruitment of no less than 258 subjects. MHAs will provide an initial screening by cross-checking the recruitment list against their own records in order to verify eligibility. Recruitment by project staff will occur during patients' bi-monthly medication refill visits, when psychiatrists will re-confirm the diagnoses of those on the list. Project staff will conduct home visits within one month of their expected bi-monthly visit to recruit those not contacted at the refill visits. At the end of the recruitment, the LEAN sample will be randomly divided by the same statistician into a treatment group and a control group of equal sizes by a statistician not otherwise involved in the study (Figure 5).

FIGURE 5 THE LEAN POPULATION, SAMPLE AND ASSIGNMENT

Source: authors

Sample Size Calculation

Though the distribution of our primary outcome (adherence, scored as the percentage of drugs taken of those prescribed) is unlikely to be normally distributed, the sample calculation follows standard procedures for the hypothesis of equal population means based on t-test and the comparison of sample means. Since our sample size is large, the central limit theorem ensures that our sample means will be approximately normally distributed, regardless of the underlying distribution of the data.

Assuming a 5% type I error and a 10% dropout ratio for a total sample size of 258 (129 for each of the two comparison groups), the study of 232 participants (after 10% dropping out of 258) will have 85% power to detect an effect size of 0.13 (see appendices). This means that if the adherence score for the control group is 0.72 (SD=0.33), the study will have sufficient power to detect a program effect if adherence for the treatment group is equal to or greater than 0.85. The control adherence of 0.72 used in the sample calculation is based on the self-reported adherence of 0.75 in our study population from the "686" registry.

The proposed sample size of 258 will also satisfy the power requirement for a subgroup analysis of patients who are non-adherent at baseline. Given the ratio of non-adherence to full-adherence (0.55:0.45) of the population reported in the registry, the study will include at least 140 baseline non-adherent subjects available for the sub-group analysis. Again, assuming 5% type I error and a 10% dropout rate, the study will have 85% power to detect

an effect size of 0.18 among the sub-group: If the adherence rate for the control is 0.42 (SD=0.35), the study will be powered to detect a program effect if the adherence of the treatment group is equal to or greater than 0.6 (Table 2).

TABLE 2 SAMPLE SIZE CALCULATION SCENARIOS

	Adherence Score		**Sample Size Needed**[2]		
	Control	**Treat**	**Control**	**Treat**	Total
LEAN Sample	**0.72** (0.33) [1]	**0.85** (0.33)	**129**	**129**	**258**[3]
Non-adherent Subgroup[4]	0.42 (0.35)	0.60(0.35)	70	70	140

(1). Standard deviation in parentheses

(2). Sample calculation assuming power of 0.85, significance level of 0.05, and a 10% dropout rate

(3). See the STATA codes for the sample calculation in appendix

(4). Sample size of the baseline non-adherent sub-group achieved with a LEAN total sample of 258.

Source: authors

Metrics & Measurement

Primary and Secondary Outcomes

The primary outcome will be a continuous medication adherence score from 0 (no adherence) to 1 (complete adherence), calculated as the percentage of drugs taken out of those prescribed over a designated time period (the preceding month). Medication adherence was chosen as the primary outcome on the grounds that 1) adherence correlates with symptom relief, and symptoms correlate with function[22 23]; 2) significant improvement in symptoms, and function, is likely to extend beyond the duration of the study; and 3) improving adherence is valuable in its own right. However, symptoms and functions will also be tracked as the secondary outcomes.

Methods of Assessment and Timeline

Figure 6 summaries how and when we assess outcomes, which piggyback on "686" Program activities, in particular, the bi-monthly meetings with patients. All data will be double-entered into and managed by Research electronic data capture (REDCap) system[24]. All outcome assessors, including psychiatrists and program staff, will be

blinded to the control or treatment status of program participants; any inadvertent un-blinding will be noted in order to record the time of the incident and persons involved.

FIGURE 6 RECRUITMENT AND OUTCOME ASSESSMENT

Source: authors

Medication Adherence: Pill counts

Pill counts, to be conducted by project staff when patients bring their pill bottles to the bi-monthly refill, will be used as the primary, objective and inexpensive measurement of medication adherence, to be complemented by pharmacy dispensing records from the "686" registry system. Other objective measures, such serum/urine drug level[25], are clinically and financially impossible to implement. In addition, the Morisky Medication Adherence Scale[26], the Brief Adherence Rating Scale (BARS)[27], and the Drug Attitude Inventory-10 (DAI-10) [28] will supplement the objective assessment. At baseline and again at the end of the study, patients who were no-shows at the bi-monthly visit will be visited and assessed at their homes.

Symptoms – CGI-Sch

From among the "big three" instruments for schizophrenic symptoms[29] we chose the Clinical Global Impression in Schizophrenia (CGI-Sch) primarily due to its brevity and ease of use[30]. "686" Program psychiatrists will assess patients using the CGI-Sch during bi-monthly visits throughout the trial.

Functions – WHODAS 2.0

LEAN will use the 12-item proxy-administered WHO Disability Assessment Schedule 2.0 to assess patient functions, considering its brevity to administer, excellent psychometric properties, and availability of a validated Chinese version[31 32]. Public health students enlisted as program staff will administer the WHODAS to patients and their family members during bi-monthly visits.

Other Measures

As side-effect of anti-antipsychotics may relate to adherence, the brief and self-implemented Glasgow Antipsychotic Side-effect Scale (GASS) will be used to generate a side-effect score[33]. A few other "public health" indicators such as suicide, drug abuse, attacking people, destroying things and wandering will be captured by the

existing "686" registry. In addition many process, cost and service utilization indicators will be captured and recorded by the e-platform logs and "686" administrative registry. These process indicators will facilitate analysis of various links in the LEAN mechanism, and surveillance for breaks in the chain.

Trial Design

We adopt a wait-list design with subjects followed-up for six months after launch of the intervention. The wait-list control design is increasingly used in psychotherapy studies, primarily to address the ethical dilemma involved in withholding a potentially beneficial treatment from the control group. Participants recruited into the study are randomized into a treatment group and a "wait-listed" control group. In stage one (the 6 month period following program initiation), the intervention will be applied to the intervention group only, while the wait-list group will receive usual care per the regular "686" protocol; in stage two (a subsequent 6 month period), the wait-list group will receive the intervention, having "waited" through stage one. Analysis of the intervention will be conducted based on baseline and end-point data collected on both groups during stage one only due to our budget constraint for data collection. Consequently, the only difference between a wait-list design and a traditional two-arm randomized control trial (RCT) is that the control group is also able to benefit from the treatment once the formal study is complete.

Model & Analysis

Unadjusted analysis, ANCOVA and DiD

We mainly considered the issue of efficiency (precision of the estimator) and bias in our choice of the analytical methods. The literature suggests that ANCOVA provides higher efficiency than difference-in-difference (DiD) and the unadjusted model in RCT and is the optimal model for RCT analysis[34] (Figure 7). The LEAN analysis will include as covariates the strong baseline predictors of outcome that are empirically suggested by other studies, and will comprise adherence, WHODAS and CGI-Sch scores, as well as indices of negative symptoms, substance use, medication side effects, and family supervision[35]. It should be noted that while our response variable, expressed as an adherence score from 0-1, may yield values greater than one, those out-of-bound predictions do not invalidate the model since the study's purpose is to produce a "risk difference" (difference in mean adherence

between intervention and control groups) rather than an individual prediction. Critically, the large sample size and the central limit theorem ensure that this approach will yield valid inferences of the risk difference despite non-normal adherence outcomes.

FIGURE 7 THREE APPROACHES TO RCT ANALYSIS

Source: adapted from Siyuan Zhang paper[36]

Intent-to-Treat

An intent-to-treat (IIT) analysis will be used to analyze all subjects regardless of treatment actually received. Estimating the IIT effect is more appropriate than the per-protocol or per-treat methods since the LEAN trial is a pragmatic trial, which is to say, it is meant to determine the effectiveness of LEAN as a real-world solution.

Subgroup Analysis

We plan to conduct two subgroup analyses, both with strong theory base and possible interaction effects. The first concerning the non-adherent group at baseline is sufficiently powered (Table 2) (our adherence-focused intervention is more likely to work better for the initially non-adherent group). The other subgroup analyses will be conducted to assess level of functions.

Missing Data

Reasons for missing data will be recorded. Multiple imputation methods will be used so that sensitivity analyses will be conducted to assess the robustness of trial results under different methods.

Monitoring

Considering the short duration of the intervention, we do not have a data monitoring committee. At the mid-point of the trial, outcomes and text messaging data will be analyzed to detect any abnormality. The text messaging system also provides a means for ongoing monitoring of any patient response.

Ethics and Dissemination

The study has obtained IRB approval from University of Washington (49464 G) and Central South University (CTXY-150002-6). Any substantive modification to the protocol will seek a formal approval from the IRBs. Program staff will train and obtain informed consent from both patients and LHSs. Patient data will be securely entered and stored in RedCap and only de-identified information will be used for analysis. Study results will seek peer-reviewed publications with de-identified data made available on Figshare[37].

Discussion

Several aspects of this study is worth noting. First, the application of mHealth is designed not as a standalone technological solution but a health system strengthening tool that serves to integrate the patient care provided by lay health supporters, village doctors, mental health administrators and psychiatrists.

Second, the active engagement of LHS augment case supervision. Third, the study, evaluating the real world effectiveness of LEAN, emphasizes the implementation parts so as to increase the likelihood of adopting the potentially effective solution. Fourth, the trial is intent to have global implications, especially insofar as the intervention is designed to exclude elements peculiar to China's socio-economic and/or political situation.

The study is faced with several limitations. First, its short duration may not allow sufficient assessment of functional changes and limit analysis of the long-term effect on adherence. Second, our choice of relatively simple assessment tools (pill-counts vs. urinalysis) may create challenges of obtaining accurate adherence level. Third, assuming that improved medication adherence will lead to better patient life-functioning may be problematic. There is concern that the psychiatrists with limited training from Liuyang MHH may deliver inappropriate treatments, adherence to which will be of insufficient benefit. Finally, despite efforts to ensure the generalizability of LEAN, the existing "686" infrastructure (particularly the availability of free basic antipsychotics and the bimonthly physiatrists' visit) may make Liuyang a unique location even within China. We hope the spirit of LEAN should provide useful information for other LMCs. For instance, LEAN may be adapted to manage patients discharged from mental facilities who continue to take free or paid medications.

List of abbreviations

BPRS: Brief Psychiatric Rating Scale

CGI-Sch: Clinical Global Impression in Schizophrenia

DiD: difference-in-difference model

DSM-5® : Diagnostic and Statistical Manual of Mental Disorders-5

HBM: health belief model

HRH: human resources for health

IIT: intent-to-treat

LHS: Lay health supporter

LMC: low and mid-income countries

MHA: mental health administrators

mHealth: mobile health

MHH: mental health hospital

PANSS, Positive and Negative Syndrome Scale

RCT: randomized control trial (RCT)

THC: township health centers

VD: village doctor

Competing interests

The authors declare that they have no competing interests

Authors' contributions

All authors contributed to the conceptualization and the design of the study. WG obtained majority of the funding. DX and WG conceived of the prototype of the intervention, the study design, analytical methods and creation of the team. DX drafted the first manuscript. SX and WG secured the study site. EC and SX contributed significantly to the intervention strategy and the methods of outcome assessment. JH, MN and HH provided critical review and revision to the design and analytical methods of the study. JS contributed to the theoretical framework of the study. KS edited and improved the manuscript. HB helped design and write the economic evaluation part of the protocol. SG steered the direction of the study and contributed significantly to the revision of the manuscript. All authors read and revised the initial manuscript and approved the final version.

Authors' information

A researcher at the Sun Yat-sen University School of Public Health, DX is leading an effort to develop the Sun Yat-sen Global Health Institute; concurrently as the PhD candidate in Global Health (implementation science tract) at the University of Washington (UW) and a Fogarty Global Health fellow, he is conducting LEAN as his dissertation project (DX's LinkedIn profile https://www.linkedin.com/in/romanxu). As a researcher and a clinical doctor of the School of Public Health (SPH) of Central South University (CSU), WG is the principle investigator of this project awarded by the China Medical Board (CMB) through a highly competitive open completion in 2012. SG (health system researcher/professor at UW) chairs the dissertation committee of DX which consists of EC (psychiatrist/professor at University of Rochester), JS (psychologist/professor at UW), JH (bio-statistician/professor at UW), and MN (bio-statistician/assistant professor at UW). SX, a leading public health psychiatrist/professor in China, heads the Mental Health Policy Program of CSU. HH is an associate professor of bio-statistics at Tulane University. KS, a medical dcotor/professor, and HB, an economist specialized in cost-efffectivenss analysis, are both at the Univesity of Texas.

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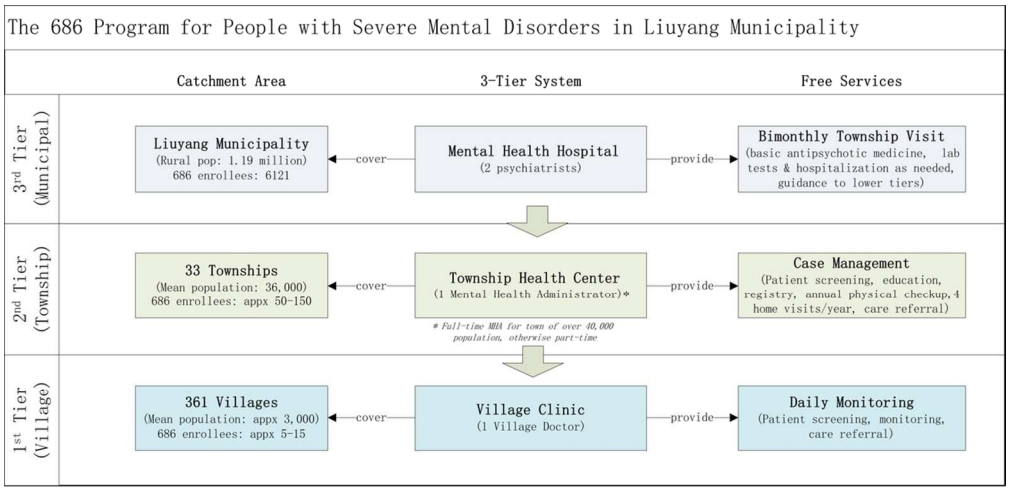

FIGURE 1 THE "686" PROGRAM SERVICE MODEL

Source: authors.
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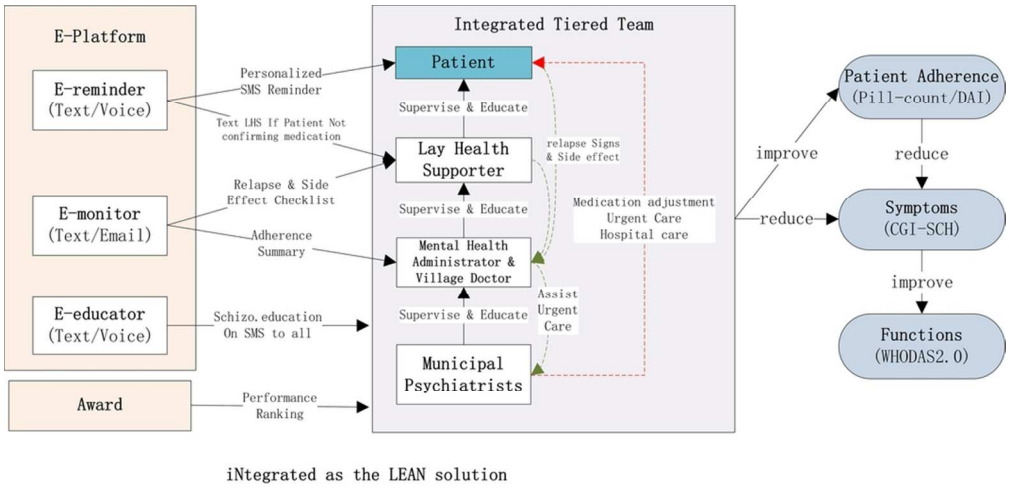

FIGURE 2 LEAN

LEAN
L: Lay health supporter (LHS)
E: E-platform with e-reminder, e-monitor, and e-educator via mobile text/voice messaging
A: Award system analogous to Taekwondo ranks
N: iNtegrating the L, E and A and "686" Program structure into a lean and coordinated approach
Source: authors.

90x43mm (300 x 300 DPI)

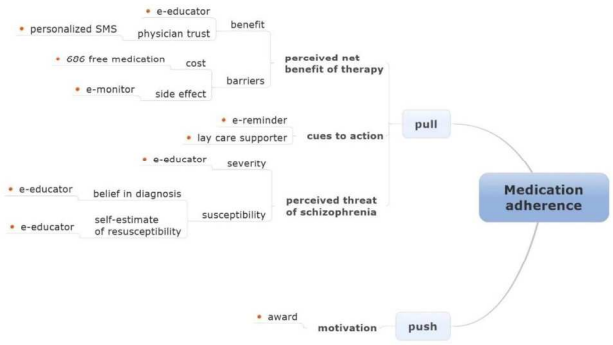

FIGURE 3 MECHANISM FOR LEAN MEDICATION ADHERENCE
Note: The red dots indicate LEAN components.
Source: adapted from the health belief model.

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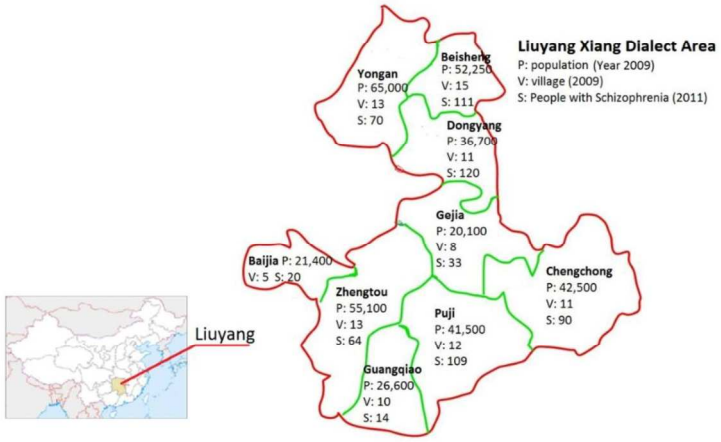


FIGURE 4 MAP OF THE XIANG-DIALECT AREA OF LIUYANG
Note: Yellow-shaded region on the map of China is Hunan Province.

213x149mm (300 x 300 DPI)

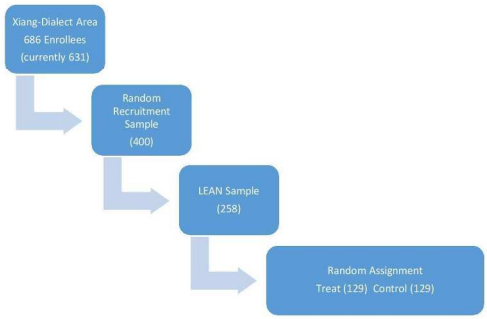
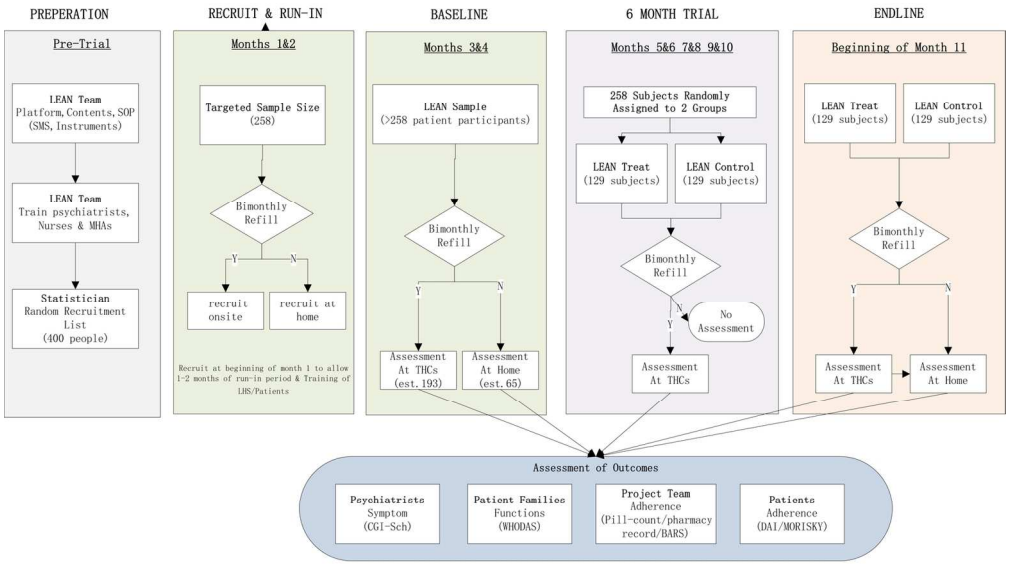


FIGURE 5 THE LEAN POPULATION, SAMPLE AND ASSIGNMENT
Source: authors

215x119mm (300 x 300 DPI)



Source: authors.

FIGURE 6 RECRUITMENT AND OUTCOME ASSESSMENT
Source: authors

149x88mm (300 x 300 DPI)

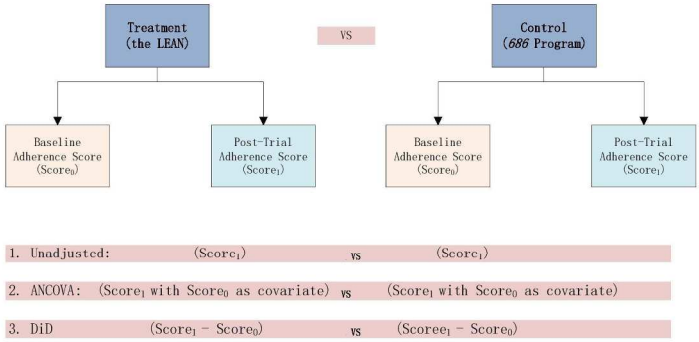


FIGURE 7 THREE APPROACHES TO RCT ANALYSIS
Source: adapted from Siyuan Zhang paper 36

215x119mm (300 x 300 DPI)

Appendices

E-reminder example

"Xiao Wang (Little Wang in Chinese, a diminutive often used in friendly conversation), we have the forecast for two beautiful sunny days and hope you will enjoy some sunshine (or: you may see more and more children in the village as the winter break starts today). We also hope you have taken your meds today. If yes, please text "yes" to let us know. Lao Zhang (Old Zhang)".

Sample Calculation in STATA

```
sampsi .72 .85, sd1(.33) sd2(.33) alpha(0.05) power(.85)
Estimated sample size for two-sample comparison of means
Test Ho: m1 = m2, where m1 is the mean in population 1
                and m2 is the mean in population 2
Assumptions:
        alpha =   0.0500   (two-sided)
        power =   0.8500
           m1 =      .72
           m2 =      .85
          sd1 =      .33
          sd2 =      .33
        n2/n1 =     1.00
Estimated required sample sizes:
           n1 =      116
           n2 =      116
```

Early Signs Questionnaire, Short Form

The following form is reprinted with permission from Marvin Herz, MD. From The University of Rochester.

NAME_____ DATE_____

Compared to last week, has there been an increase in any of the following symptoms?

	YES	NO
1. Problems with sleep	_____	_____
2. Problems with appetite	_____	_____
3. Depression	_____	_____
4. Problems with concentration	_____	_____
5. Restlessness	_____	_____
6. Tension or nervousness	_____	_____
7. Use of alcohol	_____	_____
8. Use of street drugs (includes marijuana)	_____	_____
9. Hearing voices or seeing things that others can't hear or see	_____	_____
10. Less pleasure gained from things you usually enjoy	_____	_____
11. Feeling people were watching you, were against you, or were talking about you	_____	_____
12. Preference for being alone and/or been spending less time with other people	_____	_____
13. Arguments with others	_____	_____
14. Inability to get your mind off of one or two things	_____	_____
Have any other symptoms appeared or increased?	_____	_____

If so, what were they?_____

_____

_____

Did anything specific happen last week which upset you? . . . . _____

_____

If so, what was it?_____

_____

_____

Have you been taking your medication as it is prescribed for you? . . . . _____ _____

Reprinted with permission from Marvin Herz, MD. Clinicians may reproduce this scale for use in their clinical practice. Researchers who wish to use the Early Signs Questionnaire in multi-patient studies should contact Dr. Herz at University of Rochester Medical Center, Strong Ties Community Support Program, 1650 Elmwood Avenue, Rochester, NY 14620, (716)275-0300, x2337, marvin_herz@urmc.rochester.edu

E-educator Example

The example below illustrates a two way and adaptive “conversation” to be directed by the e-educator.

The example below illustrates a two-way adaptive “conversation” to be directed by the e-educator.

Sender: “Have you had challenges lately in persuading (patient name) to take medication? Text “yes” or “no”.”

If the response is “no,” the conversation terminates. The answer “yes” will prompt the following message:

Sender: ”Please choose from among the following four items the reasons why (patient name) is not taking his medicine by texting back the number: 1. He feels good and does not want to; 2. … 3. ….

The chosen items will prompt more detailed information/instruction for the recipient.

Patient informed Consent form

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、

枨冲和镇头九镇开展“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）。现邀请您参加本项目，在参加项目之前，请仔细阅读以下内容，它可以帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

“林项目”的目的是提高资源匮乏地区精神分裂症患者用药依从性，从而提高他们的功能和生活质量；核心内容是为志愿参加国家重症精神病项目管理的精神分裂症患者提供额外的免费服务，服务内容包括：每日为患者提供手机短信用药提醒；选择一位家庭成员或其他患者能接受的人员作为“非专业照看人”（简称“照看人”），照看人将接受简单培训，在手机短信的帮助下，帮助发现患者疾病复发的征兆以及病人用药后的副作用情况，并通过手机短信进行报告；收到报告后，精防专干将协助照看人和患者提高用药依从性，或通过浏阳精神病院医生调整用药，或安排紧急门诊或住院治疗。为了验证试验的效果，参加“林项目”的人员将随机（计算机抽签）分成两组，在头六个月，一组接受“林项目”的手机短信等服务；另一组作为对照，仅接受原有日常服务；六个月后，原仅接受日常服务的对照组也开始接受短信服务（除非当时数据证明干预效果为负面），至少进行六个月。

在项目过程中，我们将收集若干数据用于验证项目的有效性。数据收集将主要在您每两月领药时进行，主要由您的主治医生根据您的诊断状况填写，或通过您自身填报相关表格。我们估计每次占用您 20 分钟左右的额外时间。收集的主要数据包括：您的基本人口学信息（如年龄，性别，民族等）；精神分裂症的症状和功能；服药情况。您的这些数据大部分已经在目前的国家重症精神病项目中采集。项目组将在法律的范围内，严格为您的数据保密，将遵守中国和美国两国给病人隐私安全的保密要求。您的数据将存储在严格加密的“红帽”电子平台；书面信息将保留在加锁的安全之地，保留五年后销毁。我们承诺您的数据将仅作为研究所用。我们所有的研究报告在分析和报告时，您所有的身份信息都将隐去（包括您的所有身份证号码，姓名，所在地，健康档案号等等）。

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通过参与“林项目”，您可能福利包括：接收到与精神卫生有关的知识性短信；短信用药提醒；可能更快捷的药物调整；可能更快捷的门诊和住院安排。如果您没有手机或手机短信计划，项目组可能会为您提供一台免费的简易手机。与“林项目”有关的所有短信都是

免费的（包括您回复我们的短信）。虽然如前我们将竭尽全力来保护您的隐私数据，参加项目的可能风险主要是您隐私的泄露。

如您对项目有任何疑问，请随时联系项目团队。我们的联系方式如下：龚雯洁（中南大学）13607445252 gongwenjie@csu.edu.cn 徐东（美国华盛顿大学）13910988979 roman.xu@gmail.com

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研究项目：“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）

课题协作单位：中南大学、美国华盛顿大学

同意申明：

我已经阅读了上述有关本研究的介绍，而且有机会就此项研究与项目成员讨论并提出问题。我提出的所有问题都得到了满意的答复。

我知道参加本研究可能产生的风险和收益。我知晓参加研究是自愿的，我确认已有充足时间对此进行考虑，而且明白：

我可以随时向项目组咨询更多的信息。

我可以随时退出本研究，而不会受到歧视或报复，医疗待遇与权益不会受到影响。

我同意项目组可以在隐匿我身份信息的前提下在研究上使用我在项目过程中被收集的数据。

我将获得一份注明日期的知情同意书副本。

最后，我决定同意参加本项研究，并保证尽量遵从医嘱。

参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

LHS informed consent form

我们是中南大学和美国华盛顿大学公共卫生学院的研究团队。在慈善基金会美国中华医学基金会的基金支持下，我们将在浏阳柏加、北盛、洞阳、葛家、官桥、普迹、永安、枨冲和镇头九镇开展“中国浏阳乡村精神分裂症患者手机短信支持项目”（简称“林项目”）。现邀请您作为患者的照看人参加本项目，在参加项目之前，请仔细阅读以下内容，它可以

帮助您了解项目的目的，意义，内容，期限，以及对您的益处和风险。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请项目团队给予解释，帮助您作出决定。

“林项目”的目的是提高资源匮乏地区精神分裂症患者用药依从性，从而提高他们的功能和生活治疗；核心内容是为志愿参加国家重症精神病项目管理的精神分裂症患者提供额外的免费服务，包括每日用 SMS（语音或文字短信）的用药提醒。对每个病人而言，项目将培训一个家庭成员或其他人员（在这里就是“您”）作为病人的照看人，以帮助病人提高用药依从性，减少用药副作用，和监测疾病复发。您所担负的角色包括给精防专干或精神科医生发放病人相关的报告，以便与他们可以及时的作出反馈，调整用药，安排门诊和住院服务等。具体而言，这些任务包括

- 如果病人没有回复确认我们给他/她的反复的短信用药提醒，我们将给您发短信，请您去查看一下病人服药的情况并用短信告知我们查看的结果。
- 我们将偶尔用短信给您发送与病人疾病复发或药物副作用相关的核对单，以方便您及时发现和报告病人的疾病复发和副作用情况。
- 我们将偶尔给您用短信发送如何应对疾病的相关资源情况和知识。

为了验证试验的效果，参加“林项目”的人员将随机（计算机抽签）分成两组，在头六个月，一组接受“林项目”的手机短信等服务；另一组作为对照，仅接受原有日常服务；六个月后，原仅接受日常服务的对照组也开始接受短信服务（除非当时数据证明干预效果为负面），至少进行六个月。

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我将获得一份注明日期的知情同意书副本。

最后，我决定同意作为_____的照看人参加本项研究，并保证尽量遵从医嘱。

参加者签名：_____

参加者姓名（正楷）：_____

签名日期：_____

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P 0
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P2
	2b	All items from the World Health Organization Trial Registration Data Set	P3-4
Protocol version	3	Date and version identifier	All Pages
Funding	4	Sources and types of financial, material, and other support	P17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P16
	5b	Name and contact information for the trial sponsor	P0
	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	P17
	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)	N/A
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	P5-7
	6b	Explanation for choice of comparators	P5-8
Objectives	7	Specific objectives or hypotheses	P5
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)	P12-13

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	P5-6
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)	P9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P6-8
	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)	P6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P6-7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P5-6
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	P11-12
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)	P11-12
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	P10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P9-10

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	P9-10

	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	P9-10
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9-10
Blinding (masking)		17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P11
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P11
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	P11-12
		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	P11-12
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	P11
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	P13
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P14
		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)	P14
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	P14

	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	P14
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	P14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14
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)	P14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	P14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P16
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	P14
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	P13
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	P14
	31b	Authorship eligibility guidelines and any intended use of professional writers	P16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P14

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	P20-24
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	N/A

*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.