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Effectiveness of Mobile Text Messaging to Improve Schizophrenia Adherence, Symptoms and
Functioning in a Resource-poor Community Setting: “LEAN” Randomized Controlled Trial

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Abstract

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Objective To evaluate the effectiveness of mobile text messaging to improve medication adherence, symptoms and functioning in community-dwelling people with schizophrenia in a resource-poor setting. **Design** Two-arm randomized controlled trial. **Setting** Rural communities of Hunan Province, China. **Participants** 278 randomly-selected community-dwelling villagers diagnosed with schizophrenia. **Interventions** Participants were randomized 1:1 into two groups. Both the intervention and control groups received a nation-wide community-based mental health program that provided free antipsychotic medications and clinician consultations. The intervention group also received text messages for medication reminders, health education and monitoring of early signs of relapses. The intervention was conducted from November 2015 to July 2016. **Main outcome measures** The primary outcome was the medication adherence

(percentage of dosages taken) assessed by unannounced home-based pill-counts. The secondary outcomes included patient symptoms, functioning, relapses, and re-hospitalization due to schizophrenia. **Results** Medication adherence increased 27% from 0.49 in the control group to 0.63 in the intervention group (adjusted mean difference (AMD) 0.13 [95% CI 0.04 to 0.22]; $p=0.004$; effect size 0.35); The program showed less loss in functioning from 15% loss in the controls to 12% in the intervention (AMD -0.03 [95% CI -0.07 to 0.01]; $p=0.117$; effect size 0.17). No difference in severity of symptoms was found, however, there was substantial reduction in the risks of relapses (26 (21.7%) of 120 interventional participants vs. 40 (34.2%) of 117 controls; risk ratio 0.63 [95% CI 0.42 to 0.97]; NNT 8.0) and re-hospitalizations (9 (7.3%) of 123 interventional participants vs. 25 (20.5%) of 122 controls; risk ratio 0.36[95% CI 0.17 to 0.73]; NNT 7.6). **Conclusions** Texting patients and their family supervisors in a resource-poor community setting was more effective than a free-medicine program alone in improving medication adherence and patient functioning and reducing relapses and re-hospitalizations.

Trial registration ChiCTR-ICR-15006053

Keywords: schizophrenia, medication adherence, text messaging, mHealth, community health worker

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Chapter 1. INTRODUCTION

Schizophrenia is a leading cause of disability, with a global prevalence of 4% [1] and contributing to 1.69% of total Years Lived with Disability. [2] Schizophrenia also leads to a high economic burden [3] and the violation of sufferers' human rights due to the stigmatization of the illness [4] and other causes. The WHO's Mental Health Gap Action Program (mhGAPa) has identified schizophrenia as the top priority for global action, recommending treatment with antipsychotic medicines and psychosocial care. [5] However, in low-and-middle-income countries (LMICs) the treatment gap remains high,[6, 7] and even when treatment is available, adherence to antipsychotics was rather low compared with other patient groups.[8][9] Most people with schizophrenia are prescribed long-term antipsychotic treatment.[10, 11] Nonadherence to antipsychotics is associated with higher risks for relapse, re-hospitalization, violence in society, and suicide, and increased costs and resource use for health systems.[12-14] With limited mental health facilities and healthcare workforce concentrated in large urban centers, the scarcity, inequity, and inefficiency of mental health resources present challenges.[15, 16] As a result, there is a broad consensus for collaborative stepped care that emphasizes community- and family-based treatment, task sharing among human resources, and integrating mental health into existing primary health care.[5, 7, 17]

In community- and family-based healthcare, mobile health (mHealth) has gained increasing traction.[18-20] Short message service (SMS) text messaging, or texting, has been shown to be particularly useful in resource-poor settings due to its wide availability, reliability, ease-of-use, and relative low-cost.[19, 21] Since the first publication of texting for health in 2002,[22, 23] text messaging has been found to benefit diabetes self-management, weight loss, physical activity, smoking cessation, and medication adherence to antiretroviral therapy.[21, 24]

For people with serious mental disorders such as schizophrenia, texting has been used in four areas of application: reminders for medication and clinical appointments,[25, 26] information dissemination, supportive messaging, and self-monitoring procedures.[19] However, despite its recent proliferation, there has been no clear evidence that technology-based prompts improved treatment adherence, symptom and functioning in people with schizophrenia.[27] Most studies to date have been small pilots that focused on feasibility rather than health outcomes,[28] were primarily conducted in high-income countries,[19, 28] did not include informal caregivers who often played important roles in schizophrenia management,^[29] and often served as a stand-alone intervention not integrated with the health system.[30] Also, they gave insufficient attention to user evaluation and appreciation of the program[24] and seldom reported a theoretical basis or the working mechanism for the mobile intervention.^[31]

We conducted this dissertation study as a pragmatic randomized controlled trial, called LEAN Trial (to be explained later), to develop and evaluate a texting system to strengthen family and community care for people with schizophrenia. We intended to address some of the weaknesses of the previous trials mentioned above and to have broad implications for resource-poor settings in LMICs.

This dissertation takes a format of a three-paper rather than the traditional book-length dissertation. We synthesize the three papers into this cohesive dissertation document, which is different in structure to the traditional book dissertation. Those three papers serve different purposes. The first paper, the formal protocol of the study, described the background and rationale of the study, the theory and the empirical evidence that guided the development of our text messaging intervention, the details of the intervention, the targeted population, sampling methods, sample size calculation, the trial design, and the intended statistical methods for data

analysis. The second paper, using data collected throughout the trial, analyzed the measurement concordance of different methods of assessing medication adherence. This paper is important for the dissertation as it highlighted the challenges of assessing adherence (the primary outcome of the study) and justified the measures we used for the study. The final paper evaluated the effectiveness of LEAN in improving patient adherence, symptoms and functioning, relative to care as usual.

Chapter 2. LITERATURE REVIEW

As one of the primary purposes of the study is to improve medication adherence, our review focused on many aspects of adherence. As for our review strategy, we always sought out any available systematic reviews in that subject; if no systematic reviews were identified, we conducted a comprehensive review through Google scholar with relevant search terms and also by checking the reference of the identified papers. The details of the review were reported in our three papers. Here we present a high-level summary of our review.

First, we reviewed the literature regarding the challenges of improving the health of the community-dwelling people with schizophrenia. We found that prevalence of schizophrenia does not vary much across ethnicity, countries, and cultures.[1, 32] The burden is high due to its disabling nature.[3] Mental health resources are insufficient and maldistributed from large urban centers to rural areas.[15] Treatment gaps are high, [6, 7] and adherence to antipsychotic medication remains a challenge.[9] We presented details of the literature throughout the three papers.

Second, we reviewed possible solutions to address the resource and adherence challenges. We found a high level of consensus for a community-based stepped-care approach.[5] There is abundant literature in “task-shifting” that emphasizes delegating appropriate health care roles to people with different levels of training. Family caregivers played a critical role in caring for the patients.[20] The increasing popularity of mobile phones even in remote areas provided new opportunities to facilitate and strengthen family and community-based care.[19, 22, 28, 30] The relevant details of the review were presented in our protocol paper.

Third, we examined theories in behavioral sciences that could guide the development of mobile health (mHealth)-based intervention to improve patient adherence to antipsychotics. In this process, we found that most mHealth studies did not report any theories underpinning the construction of their approaches.[31] We identified health belief model as the appropriate model to guide our development.[33] The details of this review were provided in our protocol paper.

Fourth, as a critical component of improving the health of community-dwelling people with schizophrenia is to address the low adherence to antipsychotics in this population, we reviewed the empirical evidence of the adherence interventions in schizophrenia.[8, 34] There are multiple reasons for non-adherence in schizophrenia, including lack of access to medication, side-effects of the medication, therapeutic alliance, perception about illness and medication, and forgetfulness. Several approaches are available to improve patient adherence. Cognitive behavioral therapy and motivational interviewing address patient perceptions and beliefs about taking medication.[35] Environmental support, such as alarms, pillboxes, and SMS or telephone reminders, intends to resolve cognitive deficiency that causes forgetfulness.[18, 36, 37] The effectiveness of those methods in improving adherence to antipsychotics is inconclusive. We covered this part of the literature in our protocol paper.

Fifth, we specifically reviewed randomized trials that used text messages in schizophrenia. We identified 6 randomized controlled trials that used texting for people with schizophrenia:[19, 34, 38] a recent trial in Finland (n=1139) showed no advantages of texting on any outcomes assessed at 12-month,[39] which conformed to the results of two earlier trials (Netherlands (n=62);[40] Czech Republic (n=146)[41]). One Spain trial (n=254)[42] and two USA trials (n=30 and n=55)[43, 44], however, found significant improvement in medication

adherence and some reduction in symptoms. Few studies reported adequately on outcomes related to patient functioning. Our last paper reported on this aspect of the literature.

Finally, we reviewed different methods of assessing adherence to antipsychotics. While no single measure can be applied to all settings, numerous methods have been used measure adherence.[45-47] These include self-report and informant-report measures (interviews, patient/family diaries, survey instruments) and a variety of so-called “objective” numerical indices (drug level in biologic fluids, direct observation, electronic monitoring, pill counts, pharmacy records).[45-49] Despite advances in measurement methodologies, there has been scant research examining the concordance among measures of adherence to antipsychotics or appraisal of their validity versus a reference standard. We identified only seven relevant studies.[50-57] They reported poor to excellent concordance among adherence measures. We covered more details in the literature of adherence assessment in our concordance paper.

Chapter 3. METHODS

SUMMARY OF THE METHODS

We first explored the concordance and validity of several measures to assess antipsychotic medication adherence. Despite the abundance of measures to assess medication adherence by persons suffering schizophrenia, few studies have evaluated their concordance and validity against a reference standard in resource-poor community settings. Based on the random sample of 278 villagers in LEAN trial, we used a concordance correlation coefficient (r_c) and Kappa statistic to assess agreement among pill counts, refill records, clinician rating, and the Brief Adherence Rating Scale (BARS) and the Morisky Adherence Scale. The validity of various measures was evaluated by their concordance and sensitivity/specificity to home-based unannounced pill count (UPC) as the reference standard. The details of the methods are described in our “concordance” paper.

For the main study, our protocol paper described the methods of our study in details. The paper has been published as an open access paper in *BMJ Open* and can be retrieved at <http://bmjopen.bmj.com/content/6/1/e010120>. [58] We here only provide a summary of our methods. This was a pragmatic two-arm randomized controlled trial. The study, under the acronym LEAN, was designed to improve medication adherence and high relapse among people with schizophrenia in resource poor settings. The community-based LEAN has four parts: 1) Lay health supporters (LHSs), mostly family members who 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 were non-adherent, 3) an Award 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 would be drawn from the schizophrenic “686“ Program registry for the 9 Xiang-dialect towns of the Liuyang municipality in China. The sample would be further randomized into a control group and a treatment group of equal sizes, and each group would be followed for 6 months after the launch of the intervention. The intervention group would receive China’s 686 Program plus LEAN, whereas the control group would receive the 686 Program alone. 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 would be assessed primarily when patients present for medication refill visits scheduled every two months over the 6-month follow-up period or during the follow-up visits to the patients’ homes. Data from the study would be analyzed using ANCOVA for the program effect and an intent-to-treat approach. Ethical approvals were received from the University of Washington (49464 G) and Central South University in China (CTXY-150002-6). The trial registration was ChiCTR-ICR-15006053.

Chapter 4. RESULTS

The details of the results and discussion are presented in our “concordance” and “effectiveness” papers. The concordance paper provided detailed information on the measurement we chose to estimate medication adherence. The effectiveness paper was the main report of the study results. We summarized the results of those two papers below.

SUMMARY RESULTS OF THE CONCORDANCE STUDY

The estimated proportion of adherent patients according to all measures (41%~88%) was substantially higher than identified by UPC (36%). Concordance between any two measures was poor (r_c /Kappa mostly < 0.30). Validity of various measures also was poor against the UPC ($r_c \approx 0.20$; Kappa < 0.16), although refill records and the structured instruments (BARS and Morisky) performed better than office-based pill counts and clinician impression. BARS, DAI and clinician rating were not sensitive to changes in adherence and would likely underestimate any program effect.

SUMMARY RESULTS OF THE MAIN STUDY

Medication adherence increased 27% from 0.49 in the control group to 0.63 in the intervention group (adjusted mean difference (AMD) 0.13 [95% CI 0.04 to 0.22]; $p=0.004$; effect size 0.35); The program showed less loss in functioning from 15% loss in the controls to 12% in the intervention (AMD -0.03 [95% CI -0.07 to 0.01]; $p=0.117$; effect size 0.17). No difference in severity of symptoms was found, however, there was substantial reduction in the risks of relapses (26 (21.67%) of 120 interventional participants vs. 40 (34.19%) of 117 controls; risk ratio 0.63 [95% CI 0.42 to 0.97]; NNT 8.0) and re-hospitalizations (9 (7.32%) of 123 interventional participants vs. 25 (20.49%) of 122 controls; risk ratio 0.36[95% CI 0.17 to 0.73]; NNT 7.6).

Chapter 5. DISCUSSION

The concordance and main paper provided details of the discussion. Here we summarized the discussion. Essentially, we found that texting was widely-available, easy to implement and use, and added little marginal cost. Our trial showed that texting patients and their family supervisors in a resource-poor community setting was more effective than a free-medicine program alone in improving medication adherence and patient functioning and reducing relapses and re-hospitalizations.

The existing evidence of the effect of texting on adherence, functioning, and symptoms is conflicting. We identified 6 randomized controlled trials that used texting for people with schizophrenia. [19, 34] Half of them reported a positive effect on adherence while the other half reported no effect. We discuss three aspects of LEAN relative to prior studies. First, LEAN demonstrated larger adherence improvements than other text message interventions.[29] Three unique features may have contributed to the relative superiority of LEAN: (1) engagement of the lay health supporter; (2) the varying medication reminder embedded in a message with local news and weather forecast; [59] and (3) our use of unannounced home-based pill-counts that were likely more sensitive to changes.[60] Second, like most of the other 5 studies, LEAN did not lead to reported changes in symptoms. Perhaps there was a ceiling effect (program participants with only mild symptoms); or the low adherence, even after LEAN, prevented the medicine from releasing its full potency. Even so, the substantial reduction in relapses (RR=0.63) and re-hospitalization (RR=0.36) may indicate some program effect on symptoms. Finally, we achieved high acceptability to patients and their families, over 90% of whom expressed satisfaction and were willing to continue the program.

The mechanism of LEAN needs further exploration. The mechanism of LEAM improving adherence seemed to be well explained by the Health Belief Model. 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 our reminders or mass media health promotion campaigns. LEAN's education messages may have improved patient and/or family's perception of the illness and treatment and the reminders likely provided strong cues for them to take action. The cues may be particularly useful in our participants due to the cognitive deficiency often associated with schizophrenia.

The mechanism of LEAM reducing relapse and re-hospitalization without significantly improving symptoms and functioning is perplexing. Two explanations seem plausible. First, although the mean level of symptoms of our LEAN participants did not improve, perhaps some individuals with certain patient characteristics may have benefited from LEAN and prevented their symptoms from deteriorating. With the current study, we were not able to identify those possible patient characteristics with certainty. However, we suspect that our texting family members with both reminders and educational information probably increased their level of engagement with the patients or improved their ways of interacting with the patients. The stronger family bond and engagement may benefit patients in improving their symptoms and functioning. In our next phase of LEAN experiment, it is critical to collect information on more details of family engagement with the patients. Second, the "686" clinician assessed patients' symptoms with CGI-sch during their routine "686" consultation. As they normally saw a patient for only 2-3 minutes in a noisy environment without any privacy, we suspect they might not have

sufficient amount of time to give accurate assessment. This possible measurement error alone might not result in the program effect evaluation if the errors randomly occurred for both intervention and control groups. However, we further suspect the clinicians tend to give a more similar assessment to most patients without obvious symptoms, which could reduce the sensitivity of the assessment to the program changes.

Many lessons learned from this trial can be potentially useful for other LMICs that face resource constraints. China's 686 Program successfully implemented many WHO mhGAP recommendations for the resource-poor setting. In particular, the 686 Program in Liuyang had effectively removed access barriers to antipsychotics by providing free medication routinely and conveniently. However, adherence to antipsychotics remained a challenge even for this free medicine program. Our texting further improved the program by addressing the low adherence, functioning, and relapse at marginal cost. Elements of LEAN may be adapted to other resource-poor settings with or without an existing community-based program. However, an adaptation of LEAN should fully consider some implementation details including: (1) keeping program simple and integrated into routine care[36, 61], (2) maintaining low-cost, (3) reliable system to track changes of phone numbers, and (4) choosing right phones.

There are several limitations to our trial. First, the trial was limited to patients in the Liuyang population. Second, we investigated our program cost, but we did not perform a cost-effectiveness analysis. Third, our pursuit of simplicity sacrificed the ability to customize the content, frequency, and timing of the messages to individual patients. Fourth, our trial only had a 6-month follow-up, and thus we could not determine the longer-term effect on adherence, symptoms, and functioning. Lastly, we should have collected caregivers' burden.

Our study points to several future directions for research. Future trials should test the variations of the frequency, timing, and length of the messages. Furthermore, the role of smartphone needs to be further explored in trials. Finally, the potential adverse effect of text messaging on the patients and their families should be more thoroughly investigated.

Chapter 6. THE THREE PAPERS

The full text of the three papers are provided here.

THE PROTOCOL

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.[62] Though schizophrenia cannot be cured, most people with schizophrenia can be effectively treated for symptoms with antipsychotic medicines.[63] However, of treated patients, 50% are non-adherent with medication; moreover, even under conditions of compliance, 50% of patients suffer relapse within 1 year of their latest episode.[64] The “686” Program, a massive country-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.[65, 66] 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.[67] 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.

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.

Methods

Study Setting

The intervention will be implemented and tested in “686” program participants in the Xiang-dialect area (a total of 9 towns) of the rural townships of Liuyang Municipality in the Hunan province of China, with 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 components: 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 (Figure 1). We should note that while Liuyang provides free antipsychotics to all its program enrollees, in other parts of China, often only a subset of the program participants receive free medication.

LEAN

LEAN as an acronym is somehow inspired by Toyota’s principle in lean manufacturing [68] 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.

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. And finally, 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 strengthen 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).[69] 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.

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 [70] [71](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. [72-76]

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 other two dialect-groups in Liuyang are historically immigrants from other provinces; and 3). long and rich past research experience of our group in this area that provides additional data and information for the LEAN study, such as educational levels of all MHAs.

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®)
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).

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).

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; [77, 78] 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. [79] 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.

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 [80] are clinically and financially impossible to implement. Also, the Morisky Medication Adherence Scale,[81] the Brief Adherence Rating Scale (BARS),[54] and the Drug Attitude Inventory-10 (DAI-10) [82] 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 [83] we chose the Clinical Global Impression in Schizophrenia (CGI-Sch) primarily due to its brevity and ease of use.[84] “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.[85] 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.[86] 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 (Figure 7).[87] 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.[88] 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.

Intent-to-Treat.

An intent-to-treat (ITT) analysis will be used to analyze all subjects regardless of treatment actually received. Estimating the ITT 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 (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.

Discussion.

Several aspects of this study are 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 augments 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 psychiatrists' 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.

ADHERENCE MEASUREMENT CONCORDANCE

Background.

Most people with schizophrenia are prescribed long-term antipsychotic treatment.[10, 11] Nonadherence to antipsychotics is associated with higher risks for relapse, re-hospitalization, violence in society, and suicide, and increased costs and resource use for health systems.[12-14] Accurate measurement of adherence is important for effective management of persons diagnosed with schizophrenia, yet reported rates of adherence vary widely. Two meta-analyses reported pooled rates of adherence of 70%[89] and 60%, [90] respectively, and nonadherence is a common finding challenging the meaning of large drug trials.[91] Rates of adherence between individual studies vary even more widely, ranging from 47–95%.[92] The great disparity depends on the population under study and the definition of adherence and measurement methods.[45, 93] While no single measure can be applied to all settings, numerous methods have been used to measure adherence.[45-47] These include self-report and informant-report measures (interviews, patient/family diaries, survey instruments) and a variety of so-called “objective” numerical indices (drug level in biologic fluids, direct observation, electronic monitoring, pill counts, pharmacy records).[45-49] Self and informant-report measures are most commonly used (77% of all antipsychotic adherence studies used subjective measures only).[93] The available tools can also be categorized as direct measures of pill-taking (e.g., drug level, direct observation) versus indirect measures (e.g., office pill counts, self-report tools) that potentially are prone to manipulation. In recent decades, adherence assessment has become more sophisticated. Structured and standardized scales have been developed to improve patient interviews and self-reports, including the Brief Adherence Rating Scale (BARS),[54] the Medication Adherence Rating Scale (MARS),[94] the Brief Evaluation of Medication Influences and Beliefs

(BEMIB),[95] and the Drug Attitude Inventory (DAI).[96] As a presumably more objective measure electronic monitoring via a microchip-imbedded cap to capture each pill bottle opening appeared in the literature during the 1980s[97, 98] and has been used increasingly in addition to pill counts.[99, 100]

Despite advances in measurement methodologies, there has been scant research examining the concordance among measures of adherence to antipsychotics or appraisal of their validity versus a reference standard. In the broader biomedical literature, most studies (68%) reported high or moderate concordance among various measures or against a reference standard.[101, 102] Those related to schizophrenia were few: We identified only 7 relevant studies.[50-57] They reported poor to excellent concordance among adherence measures. All were conducted in high-income countries (US 4; Canada 2; Sweden 1; South Korea 1), with small, convenience samples (64 participants on average ranging from $N = 25$ to 131). Most were conducted in urban hospital settings and failed to include often-used adherence scales such as BARS and DAI in the comparison.

In this analysis, conducted in the context of a large, prospective, community-based intervention, we measured (1) concordance between various antipsychotic adherence measures, and (2) the validity of these measures against home-based unannounced pill counts (UPC) as the reference standard. Our random sample included 278 Chinese consenting villagers who suffered schizophrenia.

Method.

Setting and Participants.

Our analysis of adherence measures was part of a randomized controlled trial[58] designed to test the efficacy of texting reminders to improve medication adherence within the

686 Program, a national community-based program for people with psychosis.[103] By 2016, the 686 Program had covered 5.4 million people (75% of whom had schizophrenia)[104] in 96% of China's counties.[105] In Liuyang County, the program provides its participants at no charge with consultation, prescription and dispensing of antipsychotic medications every two months by psychiatrists traveling to township health centers, follow-up visits quarterly by community health workers (CHWs), and yearly physical exams.[58] The study was conducted in 9 rural townships of Liuyang County, Hunan Province, November 2015–July 2016.

We randomly selected 400 Liuyang residents with a diagnosis of schizophrenia from the 686 Program registry, which included almost all known villagers with the disorder. To reflect real-world context, we applied minimal inclusion/exclusion on program participants, mainly excluding those who were currently institutionalized or not residing in Liuyang, or those not able to provide informed consent. After excluding 56 who did not satisfy our inclusion/exclusion criteria, we successfully recruited 278 consenting participants. The study received approvals from the institutional review boards of both University of Washington in Seattle, US (49464 G), and Central South University in Hunan, China (CTXY-150002-6).

Measures and Definition of Adherence.

We selected 4 commonly used self-report or informant-based measures (“686” clinician impression, DAI, BARS, and Morisky) as well as three presumably less subjective measures (home-based pill counts; office-based pill counts, and refill record).[45, 106] Unless otherwise specified, adherence was defined as a continuous variable (percentage of dosages taken (0-100%) in the past month). For patients on multiple antipsychotics, we took the average of adherence to all antipsychotic medications. Those continuous 0-100% variables also were

dichotomized as adherent versus non-adherent at a cut-point of 75%, an informal convention often used in the schizophrenia literature.[45, 53-56, 107, 108]

Home-Based Unannounced Pill Counts (UPC): Double Counts

The pill count refers to counting dosage units (e.g., tablets, capsules) that remain in pill containers.[45] Most studies have conducted pill counts in clinicians' offices with a single count, which can lead to several methodological limitations, including: 1) patients' intentional or unintentional failure to bring in all or any pill bottles; 2) lack of a baseline count to incorporate residual pills from the last prescription cycle; 3) no consideration of extra refills and pills discarded over the monitoring period; and 4) the Hawthorne effect that participants may change their normal behavior when knowingly under observation.⁹[45, 46, 49] To minimize those problems, we followed the best practices for pill counts.[45, 48, 109] Evaluators made two home-based pill counts 30-days apart; they asked family caregivers and patients to report the "number of additional pills obtained" and "number of pills discarded" intentionally and unintentionally over the same period. The number of pills prescribed for that period was obtained from the 686 Program prescribing system. Adherence was calculated as the ratio of "*(# of 1st count - # of 2nd count + # of additional pills obtained - # of pills discarded) ÷ (# of pills prescribed).*" To verify that all pills were revealed by the family, evaluators inspected the family's usual sites for medication storage with their consent. The counts were unannounced in the sense that although patients knew the general purpose of our study, they did not know on which home visit we would count pills, given that CHWs scheduled those visits for evaluators as part of their routine "686" home visits. The UPC was used as the reference standard for this study.[52]

Office-based Pill Counts: Double and Single Count(s)

On two consecutive visits between the “686” traveling psychiatrist and patients every two months, we asked patients and their family caregivers to bring in their medicine bottles to the prescription site. Pills counts were performed as described above, except that the pill count form posed the additional question, “How many pills have you forgotten to bring in?” The adherence formula was adjusted from the above slightly by the ratio of “(*# of 1st count* - *# of 2nd count* + *# of additional pills obtained* - *# of pills discarded* - *# of pills not brought in*) ÷ (*# of pills prescribed*).” For comparing methods of double count versus single count, we also regarded the second count as if it were the only count and used the following formula for single-count-based adherence: (*# of pills prescribed* - *# of 2nd count*) ÷ (*# of pills prescribed*).

Refill Record

We used the refill record from the “686” psychiatrists bi-monthly visits to the township health centers to calculate a cumulative medication possession ratio (CMPR)[49] (0-100%) over half a year: (*# of days medication obtained*) ÷ (*182 days*).

Brief Adherence Rating Scale (BARS)

The BARS is a 4-item scale specifically developed to measure adherence to antipsychotics in schizophrenia.[54] Three of the items were used to assess patients’ knowledge of their prescribed dosage (...how many pills prescribed?) and missed (...how many days not taking pills?) or altered doses (...how many days taking less than prescribed number of pills?). Based on those 3 items, the evaluator marked the dosage taken over the past month on a 0–100% visual analog scale.

Morisky 8-Item Medication Adherence Scale (Morisky)

The Morisky, initially developed for seniors with hypertension and validated against pharmacy fill data,[81, 110, 111] is the most widely used adherence scale in research.[49, 112] Seven of the 8 items probe patients on their specific medicine-taking behaviors with a yes/no answer while the last item measures patients' "forgetfulness" taking their medication using a 5-point Likert scale. The total score is from 0 to 8 with 8 indicating good adherence, ≥ 6 but < 8 as medium and < 6 as poor adherence.

"686" Clinician Rating (Impression)

The "686" Program has a nationally standardized patient follow-up form, which includes a rating of patient adherence as "routinely taking medicine," "intermittently taking medicine," and "not taking medicine." "686" mental health workers rate patients based on their impressions.

Drug Attitude Inventory (DAI-10)

The DAI-10 is a 10-item scale that assesses subjective experiences, attitude, and beliefs toward antipsychotic medications.[82] The scale has been widely used in schizophrenia studies, sometimes as the gold standard for other subjective scales.[95] Patients respond to 10 true/false items. Scores range from -10 to +10 with positive scores interpreted as a positive subjective response (hence adherence) and a negative score interpreted as a negative subjective response (suggesting nonadherence).

Other Outcome Measures.

Patients' symptoms were assessed by "686" psychiatrists using the Clinical Global Impression in Schizophrenia scale (CGI-SCH), which consists of two categories: severity of illness and degree of change.[84] Each category covers five different aspects of symptoms (positive, negative,

depressive, cognitive and global). Scores range from 1-7 with higher scores indicative of greater severity. Patient functions were evaluated by the 12-item proxy-administered WHO Disability Assessment Schedule 2.0 (WHODAS 2.0).[113] WHODAS scores indicate percentage of functions lost.

Data collection.

The afore-mentioned clinical trial collected data on patient adherence, symptoms and functions at baseline, mid-point (3 months after the launch of the intervention) and end-point (6 months after the launch). Baseline and mid-point data were collected during patients' routine visits with psychiatrists at the township health center, while final data were collected at patients' homes. All evaluators of adherence were Master of Public Health students from Central South University. They received intensive training on the related methods of assessing medication adherence.

Analysis.

Concordance among continuous measures was evaluated with Lin's concordance correlation coefficient (r_c)[114], which indicates how closely pairs of observation fell on a 45° line (the perfect concordance line) through the origin in addition to their correlation.[114-116] The Pearson correlation coefficient (r_p) and Spearman correlation coefficient (r_s) are inappropriate measures of agreement as high correlation does not mean that the two methods agree.[117, 118] We calculated r_p and r_s for comparisons with previous studies. The Kappa statistic[119], which assesses agreement in assessment beyond what is expected by chance alone, was used to evaluate agreement of the dichotomized measurements.

In addition to assessing concordance of measures among one another, we investigated the criterion validity of the measures by assessing their concordance (r_c or Kappa statistics) against

UPC as the reference standard. For the continuous measures, a Bland-Altman plot was used to visualize the concordance.[117, 120] For the dichotomous measures, we also analyzed their sensitivity (strength to detect adherence) and specificity (strength to detect non-adherence) with UPC as the reference.

Results.

Patient Characteristics.

Among the 278 participants, 6 were lost to follow up (2 dropped out; 2 died, and 1 relocated to an unknown address). Table 3 shows that participants had a median age of 45 years; more women, unemployed, poorly educated, with low income, and living with their families. The median duration of illness was 16 years; the median CGI-severity was 3.0, with a median 20% loss of full functions. Eleven antipsychotic medications were prescribed to the participants (Table 3); 79% were taking multiple antipsychotics. Table 4 shows adherence by different measures. The percent of adherent patients identified by UPC (36.4%) was substantially lower than that identified by other measures BARS 68.0%, Morisky 64.4%, DAI 41.9%, refill record 58.1%, office pill counts (55.6% for the 1-count method and 68.6% for the 2-count method).

Concordance and Correlation Among Measures

Overall, there was poor concordance and correlation between any two measures ($r_c / r_s / r_p$ mostly = 0.20–0.30; Kappa mostly < 0.30) (Figure 8). Stronger concordance was found between Morisky and DAI ($r_c=0.43$) and Morisky and BARS ($r_c=0.37$). Office-based pill counts were least concordant with other measures.

Validity (Concordance with UPC)

Criterion validity was poor, with all measures poorly concordant with the UPC as the reference standard ($r_c \approx 0.20$; Kappa mostly < 0.1) (Figure 8). Among all measures, refill record had

relatively better concordance with UPCs ($r_c=0.23$; Kappa=0.16); followed by BARS ($r_c=0.23$; Kappa=0.06), and Morisky. Office-based pill counts and clinician rating performed most poorly. The analysis of sensitivity and specificity revealed similar patterns of the overall strength of the measures (Table 5).

The Bland-Altman plot confirmed the low validity of all studied measures and revealed several patterns (Figure 9): (1) the distributions of the points were diamond-shaped, suggesting various measures were better at correctly detecting the most adherent and most non-adherent patients; (2) the dotted lines (mean-of-all-differences) are all below zero, suggesting a systematic bias of overestimating adherence of those measures; and (3) the distance between the two dashed lines (limits of agreement) was wide, indicating poor agreement between the measures and the UPC. Note that although our data were not normally distributed as assumed by the Bland-Altman plot, non-normality generally does not have a great impact on the limits-of-agreement.[121]

Discussion.

In this study of measures of adherence to antipsychotic medications in a random community sample in China, concordance between any two measures was poor ($r_c / r_s / r_p < 0.3$ in general). More important, all measures had low validity as assessed by their concordance and sensitivity/specificity against UPCs as the reference standard.

Self-report Measures.

Despite the widespread use of self-report and informant measures of adherence,[93] we found poor validity compared to our unannounced home pill count. Several previous studies reported stronger correlation or concordance ($r_s / r_c = 0.54 \sim 0.93$) between subjective measures (patient/family/clinician reports) and pill counts /electronic monitoring in patients with schizophrenia in Canada,[52] Sweden,[50] and the US.[54] However, all three studies involved

self-selected patients, small samples ($n = 60\sim 80$), intensive case management, and a high-income urban setting, which could bias toward participants who may self-report adherence more accurately. Our results were comparable, however, to those of a Korean study in schizophrenia ($r_c = 0.14$ between self-report measures and the reference standard).[53] Another Canadian study reported a negative correlation between self-report and the electronic cap.[56] In the general medical literature, the correlation or concordance between subjective measures and a reference standard tended to be much higher (pooled $r_s = 0.45$ according to a meta-analysis).[101, 118] Patient-reported measures involving persons with schizophrenia are likely less reliable than in other groups, considering the poor insight and impaired cognition linked to schizophrenia. Few earlier studies compare the validity of structured instruments with simpler ratings such as the clinician impression used in this study. In this study, BARS, Morisky, and DAI minimally improved the validity of measuring adherence over clinician impression: Kappa improved from 0.04 in clinician impression to 0.06 in BARS, 0.08 for DAI, and 0.16 for Morisky. Clinician impression had low specificity (12%), suggesting that 686 Program clinicians can barely detect non-adherence. BARS, Morisky and DAI took 5–8 minutes to administer while the clinician rating took less than a minute. Program managers must decide whether any measured improvement is worth the associated effort.

“Objective” Measures.

Pill counts are widely used in adherence studies as a simple and low-cost method of assessment.[122] We provided the details of UPC earlier, which we believe minimized the Hawthorne effect and issues with residual pills and pills not brought in. However, office-based pill counts were affected by these problems: despite two text reminders, only about 75% of participants appeared for the office-based count, among whom approximately 73% failed to

bring in their pills for count. It is also likely that a large portion of patients did not bring in all pills. Because of these irregularities, office-based pill counts proved to be the least valid approach in our study. The UPC was logistically more complicated than office-based counts, but if routine home visits were already a program component, pill counts only took 6–10 minutes once at the patient's home.

The UPC was used as the reference standard in this study despite its limitations to be discussed later. Recent literature proposed electronic caps as the gold standard. We deem electronic caps, while prohibitively expensive, not superior to UPC for this study. In our pilot, we found it common for our patients to transfer pills between bottles, to use original paper boxes rather than bottles, and to take partial or multiple dose (s) for each cap opening. Other studies have reported lost caps (USD 85/cap), “curiosity” cap opening, leaving caps open for a long time,[48] and increased patient anxiety.[123] Electronic caps have an advantage of tracking adherence patterns, [45, 93] but our focus is on overall consumption of dosage over a monitoring period. Finally, though drug level in blood or urine is the most direct reflection of patient adherence, assessment by these methods can be highly affected by patient behavior before the blood draw, and there is considerable individual variability in half-lives or detectability across medications and patients.[124]

Sensitivity to Change.

Medication adherence is often used in clinical trials as an outcome. In the parent study, we detected an improvement of 17 percentage points in the intervention group as measured by the UPC, while the self-report measures showed < 4 percentage points change (

Appendix 2). This finding suggests that by all self-report measures self-report ratings, when used in our rural setting in China, were relatively insensitive to change, and potentially obscured an intervention effect. Of note, self-report measures such as DAI provided additional information regarding patient attitudes toward their medicine, which complemented what we found in our UPC data.

Limitations

Several limitations may exist in this study. We recognize limitations using UPC as the reference standard: (1) there is always the possibility of pills not correctly counted or additional pills not reported; (2) missing either of the 2 counts may lead to missing data; and (3) pills counted may not be equated with pills taken. Second, the level of adherence, concordance, and sensitivity/specificity among dichotomized measures are affected by cut-points. While the conventional choice of 70–80% as cut-points in schizophrenia-related research, [45, 53-56, 107, 108] little evidence supports the clinical efficacy those cuts imply.[92, 125] We chose a 75% cut-point as a convention benchmark, used continuous adherence whenever possible, and recognize that it may be possible to examine various cut-points to assess whether there is a level of adherence that is symptomatically and functionally meaningful. This will be a subject for future examination but is beyond the scope of this paper. We suggest that future studies include an estimate of the percentage of dosages taken to improve comparability across studies on a common scale. Fourth, the refill adherence was calculated over a 6-month period rather than 1-month as other measures. In the 686 Program, patients get their prescription every two months. Adherence as measured by refill records at shorter intervals may improve its accuracy. Lastly, our random sample was drawn from the 686 Program participants in 9 townships in Liuyang County. Extrapolation of the results to the entire 686 Program population in Hunan or other parts

of China requires caution. While we cannot generalize these results to other studies of populations prescribed antipsychotic medications, our results raise important issues regarding the measurement of adherence among persons suffering schizophrenia, especially among less educated individuals.

Conclusion.

We conclude that, in a resource-poor community setting in rural China, the concordance among various measures for documenting adherence to antipsychotic medications was poor, and the validity of various measures was low when assessed by their concordance and sensitivity/specificity against UPC as the reference standard. Office-based pill counts were misleading, and for the community-based patients we studied, they could adversely affect patient management by over-estimating the amount of prescribed medications patients are consuming. Given our results, self-report measures should not be used alone. They overestimated adherence, underestimated program effect, and showed poor validity. A combination of UPC and self-report measures may prove more useful for future clinical trials and for assessing the impact of mental health programs.

THE MAIN STUDY

Introduction

Schizophrenia is a leading cause of disability, with a global prevalence of 4%^[1] and contributing to 1.69% of total Years Lived with Disability.^[2] Schizophrenia also leads to a high economic burden^[3] and the violation of sufferers' human rights due to the stigmatization of the illness^[4] and other causes. The WHO's Mental Health Gap Action Program (mhGAPa) has identified schizophrenia as the top priority for global action, recommending treatment with antipsychotic medicines and psychosocial care.^[5] However, in low-and-middle-income countries (LMICs) the treatment gap remains high,^[6, 7] and even when treatment is available, adherence to antipsychotics was rather low compared with other patient groups.^[8]^[9] With limited mental health facilities and healthcare workforce concentrated in large urban centers, the scarcity, inequity, and inefficiency of mental health resources present challenges.^[15, 16] As a result, there is a broad consensus for collaborative stepped care that emphasizes community- and family-based treatment, task sharing among human resources, and integrating mental health into existing primary health care.^[5, 7, 17]

In community- and family-based healthcare, mobile health (mHealth) has gained increasing traction.^[18-20] Short message service (SMS) text messaging, or texting, has been shown to be particularly useful in resource-poor settings due to its wide availability, reliability, ease-of-use, and relative low-cost.^[19, 21] Since the first publication of texting for health in 2002,^[22, 23] text messaging has been found to benefit diabetes self-management, weight loss, physical activity, smoking cessation, and medication adherence to antiretroviral therapy.^[21, 24] For people with serious mental disorders such as schizophrenia, texting has been used in four areas of application: reminders for medication and clinical appointments,^[25, 26] information

dissemination, supportive messaging, and self-monitoring procedures.[19] However, despite its recent proliferation, there has been no clear evidence that technology-based prompts improved treatment adherence, symptom and functioning in people with schizophrenia.[27] Most studies to date have been small pilots that focused on feasibility rather than health outcomes,[28] were primarily conducted in high-income countries,[19, 28] did not include informal caregivers who often played important roles in schizophrenia management,[29] and often served as a stand-alone intervention not integrated with the health system.[30] Also, they gave insufficient attention to user evaluation and appreciation of the program[24] and seldom reported a theoretical basis or the working mechanism for the mobile intervention.[31]

We conducted this study as a pragmatic trial to evaluate a texting system to strengthen family and community care for people with schizophrenia. We intended to address some of the weaknesses of the previous trials mentioned above and to have broad implications for resource-poor settings in LMICs.

Methods

Study design and participants

We designed a two-prong individually-based randomized controlled trial. Details of the study design, methods, and analysis plan have previously been published.[58] The study took place between February 2015 and September 2016 in 9 rural townships of Liuyang County (population 356,900), Hunan Province, in central China.

We applied minimum inclusion and exclusion criteria.[58] The study population comprised community-dwelling enrollees of China's Management of Major Psychoses Program, known as the "686 Program," with a primary diagnosis of schizophrenia. Trial participants were randomly selected from the 686 Program patient registry, which included almost all known

villagers diagnosed with schizophrenia in Liuyang County. Although the diagnosis of schizophrenia in the 686 Program used the Chinese Classification of Mental Disorders (CCMD-3),[126] the relevant CCMD-3 diagnosis is highly concordant with that of the Diagnostic and Statistical Manual of Mental Disorders-3 (DSM-3).[127, 128] Trained interviewers obtained written informed consent from both the patient and a family member who agreed to serve as a lay health supporter.

Randomization and masking

After all patients were recruited, a statistician not otherwise associated with the project allocated participants (1:1) by simple randomization to receive either the 686 Program plus LEAN (intervention group) or the 686 Program alone (control group). It was not possible to blind the participants and their family caregivers to allocation. However, outcome assessors were blind to group assignment and were physically separated from the intervention group who operated LEAN and monitored user experiences. The psychiatrists who treated these patients were also blind to allocation status. Unmasking was reported immediately, and a make-up assessment was scheduled with separate assessors.

Procedures

The development of LEAN was guided by theory, empirical evidence, and our trial and error. In early 2015, challenged by low medication adherence in 686 Program enrollees, we piloted a program in rural Liuyang that tasked “village doctors” (paraprofessionals with rudimentary medical training) to directly deliver and monitor medication ingestion in patient homes.[129] However, these doctors were already over-burdened, and had neither time nor incentive for more work. After rounds of consultation with policy-makers, clinicians, and patients and their families, we reached a consensus that only a low-cost, low-burden, easy-to-

implement, and easy-to-use intervention was acceptable. Subsequently, with the guidance of the health belief model (HBM),[33] we selected components of LEAN from empirical literature in “task-sharing,” medication adherence and mHealth, and arranged them as “pull” or “push” factors to improve patient adherence to medication (details elsewhere[58]). We piloted LEAN from September to November 2015 which resulted in several design and implementation changes. The official form of LEAN was conducted December 15, 2015 to June 15, 2016.

The acronym LEAN reflects our intention to add value, minimize costs, and maintain simplicity, and also summarizes the 4 program components: Lay health supporters, E-platform, Award, and integration. In our trial, a lay health supporter was selected from each patient family who followed phone-texted instructions to perform simple tasks: supervising patient medication, monitoring side effects and relapse, and facilitating urgent care. The e-platform (use of an existing commercial telemarketing system) texted two daily messages to both the patients and their lay health supporters: one at 9:00 am for educational information on schizophrenia and a reminder at 7:00 pm to take medicine (see Appendix 4 for sample messages). All messages were phrased to be caring, polite, and personal as those are patient-preferred.³⁰ To reduce user fatigue, the medication reminder was embedded in a message about local weather and news (for example, “Good evening. Tomorrow: Sunny, 23 degrees. Go out and enjoy the Temple Fairs with shows in ... village. Please text back 1 if you’ve taken your medicine.”). We also sent occasional messages with a 14-item checklist for early signs of relapse[130] and medication side effects. The lay health supporter was expected to text back “1” if any item was checked, to which a project coordinator would follow up with a phone call. Every month we awarded families who improved their SMS-based responses to confirm medication with a token gift such as a bar of soap and a congratulatory text message. Finally, text messaging also served as a communication

tool that integrated the efforts of lay health supporters into the existing health system—one example of this being an arrangement between village doctors, the project coordinator, and patient psychiatrist that if signs of relapse were detected, village doctors were texted to assess severity and the project coordinator then scheduled and texted appointment details with the psychiatrists to the patients' families.

While the intervention group received the 686 Program plus LEAN, the control group received the 686 Program alone. The 686 Program is a national public program covering 5.4 million people with psychosis in China, 3/4 of whom were schizophrenic.[131] Despite some local variations, the basic structure of the 686 Program remains the same across the country. In Liuyang, a psychiatrist served as the full-time program director, supported by two other psychiatrists and several staff members working part-time (all “psychiatrists” were internists who converted their roles through on-the-job training). The psychiatrists together with several staff members traveled every two months to each township health center (THC) to provide patient consultation and free medication. The township mental health administrators (MHAs), supervised by both the psychiatrists and local THCs, coordinated the work of village doctors to provide regular services which included yearly physical exams, assessment of risk levels, ≥ 4 home visits, health education, and urgent care.

Outcomes

Our trial protocol provided details on measurements.[58] In brief, the primary outcome was a score of adherence to antipsychotic medication, which consisted of a percentage of dosages taken over the past 30 days measured by unannounced home-based pill counts. Trained assessors performed two pill-counts at the 30-day interval. The counts were unannounced to minimize a potential “Hawthorne effect.”[132] We developed specific procedures to handle

multiple bottles, discarded pills, and additionally acquired pills in between the two counts. Adherence was calculated as the ratio of “(*# of 1st count - # of 2nd count + # of additional pills obtained - # of pills discarded*) ÷ (*# of pills prescribed*)”; details of our pill-count method were described in our related working paper.[60] Secondary outcomes were patient symptoms and functioning measured by clinical global impression-schizophrenia (CGI-sch)[84] and the WHO Disability Assessment Schedule 2.0 (WHODA 2.0),[85] respectively. Also, rating scales, including the Morisky Medication Adherence Scale,[81] the Brief Adherence Rating Scale (BARS),[54] and the Drug Attitude Inventory-10 (DAI-10),[82] were used to provide additional information on adherence. ³⁴ 686 Program psychiatrists administered CGI-sch on patients and public health Master’s students assessed other outcomes. Outcomes were assessed at baseline, 3 months, and 6 months. Routine 686 Program registry provided additional and routine data on patient attendance for clinical appointments, insight, incidence of re-hospitalization due to schizophrenia, medication side effects, treatment effects, and incidence of attacking people, destroying things, self-harm, and suicide attempts. We also captured information on program cost, service utilization and user experiences from various program operation channels and patient surveys. All data were double-entered into and managed by RedCap, a web-based secured data management tool.[79]

Statistical analysis

Based on the adherence data based on the clinician impression from the 686 Program management system, we determined that an increase of medication adherence from 0.72 to 0.85 (SD 0.33) would be a minimally important difference after consultation with 686 Program policy-makers. Following a standard procedure for the hypothesis of equal population means based on t-test, we calculated that a total sample size of 258 participants (129 per group) would

have 85% power to detect an increase of medication adherence from 0.72 to 0.85, assuming a 5% type I error and a 10% attrition ratio. All analyses including the sub-group analyses were conducted as pre-specified in the protocol.[58] Statistical package R was used for the analysis.

We first performed a descriptive analysis of the data: social demographic information, key covariates, and outcomes at baseline were compared between the intervention and control groups to assess the randomization and participant characteristics. For the analysis of the program effect, the intent-to-treat (ITT) analysis was used for all participants with the use of multiple imputations for missing outcomes (Appendix 3). We used a nonparametric generalized estimating equation (GEE) model to analyze program effect on adherence, symptoms, and functioning (i.e., medication adherence scores, WHODAS scores, and CGI-sch severity scores) at the endpoint. Adherence analysis was adjusted for baseline adherence, WHODAS and CGI-Sch scores, substance use, medication side, and family supervision, all of which are empirically-suggested strong baseline predictors of adherence and pre-specified in our protocol. WHODAS and CGI-sch analyses were adjusted for baseline WHODAS and SGI-sch scores, respectively. We used the same GEE models for the analyses of two subgroups identified by the baseline levels of adherence (cut-off at 0.75) and functioning (cut-off at 22), respectively. To enable cross-study comparison, we calculated the program effect size as Cohen's d.[133]

Patients' involvement

The development of the intervention and the frequency and content of texting reflected our extensive consultation with the patient and their family caregivers. The patient experiences and appreciation of the program were tracked throughout the trial as well. We also focused on the outcomes such as symptoms and functioning that are important to the patients and their families.

Results

Figure 10 shows the trial profile. 278 enrolled patients were randomized 1:1 into the intervention and control groups. 12 people refused the enrollment and most did not provide a specific reason for refusal. Recruitment and follow-up took place between May 1, 2015 and July 31, 2016. 6 participants (4%) from the intervention group and 1 (0.7%) from the control group were lost to follow-up at the 6-month assessment. No outcome interviews were unmasked throughout the trial. The sociodemographic and clinical profiles were comparable by group at baseline (Table 6). Typical patients were married, in their mid-forties, poorly-educated, living with family, unemployed with low income, and had minimum to mild symptoms and 15% loss of functioning.

A range of process indicators related to training, program implementation, user experiences, and content of family care were collected. For training, we were able to assess 103 out of 139 patients for their ability to use three basic phone functions: turning on/off the phone, charging the phone, and reading/returning text messages. 72 (70%) patients were deemed in need of training, and 62 patients subsequently received training up to 30 minutes. 29 (47%) trainees were capable of using the three phone functions after the training. Information on phone ownership and maintenance, frequency of phone number changes, and users' experiences and satisfaction are summarized in Table 8. At the same time, following the same protocol, 8 Master's or doctoral students in public health produced a total of 237 educational text messages, which covered self-care, medication, symptoms, relapse prevention, rehabilitation, and social resources; 2 messages on relapse signs and medication side effects; and about 150 unique messages of reminders (Appendix 4). On average, 27% of the families responded to the medication reminders by texting back "1" every day; 47% responded at least once over a week.

The Family members and patients were surveyed at 6 months to check their understanding of the changes and content of family-based care for the patients. No statistical differences were noted across 6 domains of family care between the intervention and control groups (Figure 11).

We noted strong evidence of an intervention effect on adherence to antipsychotic medications. Medication adherence measured by unannounced home-based pill counts increased 27% from 0.49 in the control group to 0.63 in the intervention group (adjusted mean difference (AMD) 0.13 [95% CI 0.04 to 0.22]; $p=0.004$; effect size 0.35; Table 7). Our study was underpowered to detect the treatment interaction with baseline adherence (p for interaction 0.20), although we found stronger intervention effect on adherence within the non-adherent subset at baseline (mean adherence 0.44 in the intervention group vs. 0.63 in the control group; AMD 0.20 [95% CI (0.07 to 0.33)]; $p=0.003$; effect size 0.516; Appendix 5) while the program effect disappeared for the baseline adherent group (AMD 0.04 [95% CI -0.10 to 0.17]; $p=0.591$). Meanwhile, participants in LEAN attended a mean of 83% of scheduled appointments, higher than the 76% in controls ($p=0.066$).

There was less loss of functioning in the LEAN intervention group, though not statistically significant (WHODAS scores 0.12 in the intervention group and 0.15 in the control group; (AMD -0.03 [95% CI -0.07 to 0.01]; $p=0.117$; effect size 0.17, Table 7). There is, however, substantial evidence of effect modification with baseline medication adherence (p for interaction 0.018): for the subset with good medication adherence at baseline, the WHODAS scores improved from 0.19 in the control to 0.09 in the intervention (AMD -0.08 [95% CI [-0.15 to -0.01]; $p=0.017$; effect size 0.57; Appendix 5); however, there was no significant difference in patient functioning between the groups for the subset with poor baseline adherence.

We did not note any significant improvement in severity of symptoms for the overall group and the pre-specified subgroups (Table 7). However, there was strong evidence of substantial reduction in risk of relapses (26 (21.67%) of 120 interventional participants vs. 40 (34.19%) of 117 controls; risk ratio 0.63(0.42 to 0.97); NNT 8.0) and re-hospitalizations (9 (7.32%) of 123 interventional participants vs. 25 (20.49%) of 122 controls; risk ratio 0.36(0.17 to 0.73); NNT 7.6) (Table 7).

Discussion

Texting was widely-available, easy to implement and use, and added little marginal cost. Our trial showed that texting patients and their family supervisors in a resource-poor community setting was more effective than a free-medicine program alone in improving medication adherence and patient functioning and reducing relapses and re-hospitalizations.

Comparision with prior studies

The existing evidence of the effect of texting on adherence, functioning, and symptoms is conflicting. We identified 6 randomized controlled trials that used texting for people with schizophrenia:[19, 34] a recent trial in Finland (n=1139) showed no advantages of texting on any outcomes assessed at 12-month,[39] which conformed to the results of two earlier trials (Netherlands (n=62);[40] Czech Republic (n=146)[41]). One Spain trial (n=254)[42] and two USA trials (n=30 and n=55)[43, 44], however, found significant improvement in medication adherence and some reduction in symptoms. Few studies reported adequately on outcomes related to patient functioning. We discuss four aspects of LEAN relative to prior studies. First, LEAN demonstrated a 27% improvement in adherence which is substantially larger than the 15–18% range of adherence improvements reported in other text message interventions.[29] Meanwhile, our program improved patients' attendance to the scheduled clinical appointments.

Prior studies found mixed effects of the use of technological prompts on appointment attendance in psychological settings.[134, 135] Three unique features may have contributed to the relative superiority of LEAN: (1) engagement of the lay health supporter; (2) the varying medication reminder embedded in a message with local news and weather forecast that perhaps helped reduce receivers' fatigue in other studies;[59] and (3) our use of unannounced home-based pill-counts that were likely more sensitive to changes in adherence than the subjective measures commonly used in other studies.[60] In line with the theory of HBM,[33] text reminders and lay health supporters may have provided "cues to action" to address forgetfulness and reluctance to take medicine,[58] while the texted education may have improved the perceived net benefits of the medications. We did note improved attitude toward medication on DAI scores, although the action cues probably played a bigger role -- 46% of patients regarded text reminders as most useful while only 24% considered educational messages most useful. Second, like most of the other 5 studies, the improvement in medication adherence, however, did not lead to significant reported changes in symptoms. Perhaps there was a ceiling effect, as the program participants in those studies including ours on average had only mild symptoms at baseline (Table 6). It may also be possible that the low adherence, even after LEAN, prevented the medicine from releasing its full potency. Even so, the substantial reduction in relapses (RR=0.63) and re-hospitalization (RR=0.36) may indicate some program effect on symptoms. Third, prior studies in texting for schizophrenia seldom reported the global functioning level of the patients. Our program had a small effect on reported patient functioning for the overall group (effect size is 0.169; p=0.117), but it had a medium and statistically significant effect for the subset with good baseline adherence (effect size is 0.574; p=0.017). As this improvement in the subset was not accompanied by the improvement in medication adherence, the text messages may have served

as a rudimentary psychosocial intervention that improved functioning. Earlier studies indicated even simple messages asking “how are you” or saying “thank you” reduced social isolation and improved functions.[136, 137] Finally, we achieved high acceptability to patients and their families, over 90% of whom expressed satisfaction and were willing to continue the program. Our program attrition was only 4.3%, compared with an overall rate of 20% (95% CI: 17–24%)[138] in interventional trials for schizophrenia.

Implications

Many lessons learned from this trial can be potentially useful for other LMICs that face resource constraints. China’s 686 Program successfully implemented many WHO mhGAP recommendations for the resource-poor setting. In particular, the 686 Program in Liuyang had effectively removed access barriers to antipsychotics by providing free medication routinely and conveniently. However, adherence to antipsychotics remained a challenge even for this free medicine program. Our texting further improved the program by addressing the low adherence, functioning, and relapse at marginal cost. Elements of LEAN may be adapted to other resource-poor settings with or without an existing community-based program. However, adaptation of LEAN should fully consider some implementation details including: (1) keeping program simple and integrated into routine care[36, 61] (LEAN required minimum training and leveraged existing resources such as a commercial telemarketing platform and 686 Program structures), (2) maintaining low-cost (The 686 Program in Liuyang cost approximately USD 100 person/year and LEAN added USD 11 per patient participant/6-month including texting fees for patients and their lay health supporters, message development and management, and additional time cost for health workers), (3) reliable system to track changes of phone numbers (participants

frequently changed numbers (Table 8)), and (4) choosing right phones (some cheap phones' small storage filled up quickly and prevented incoming messages).

Limitation

There are several limitations to our trial. First, the trial was limited to patients in the Liuyang population. To counteract this limitation, we tried to report as much as possible sample characteristics and contextual elements of our study so that any extrapolation to other populations and settings can at least have solid reference points. Second, we investigated our program cost, but we did not perform a cost-effectiveness analysis. This partially reflected the preference of local policy-makers for low-cost rather than cost-effectiveness. Third, our pursuit of simplicity sacrificed the ability to customize the content, frequency, and timing of the messages to individual patients. Individual tailoring is considered more effective[19, 21] but would have significantly increased program complexity and cost. Fourth, our trial only had a 6-month follow-up, and thus we could not determine the longer-term effect on adherence, symptoms, and functioning. Neither did we evaluate the effect of text messaging on adherence after stopping the messaging, albeit the effect may linger if the patient acquired the habit of taking medicine after repeated external stimuli from our text messaging. Lastly, we should have collected caregivers' burden, as they play a crucial role in supporting people with schizophrenia and can be subject to distress.[139] In particular, using family supervisors for medication might negatively affect family-patient relations if coercion was used to take medicine.

Future research

Our study points to several future directions for research. Although >80% of participants were satisfied with the frequency, timing, and length of our messages, some non-schizophrenia studies suggested less frequent messages are more effective.[19] Future trials should test those

variations. Furthermore, 33% of lay health supporters and 29% of patients used a smartphone. Smartphones, with their sensor technologies and apps, may have considerable potentials in promoting health in schizophrenia.[140] However, complicated apps may create barriers as well, considering that 29% and 48% of our patients could not even master the simple task of reading and replying to messages, respectively. The role of smartphone needs to be further explored in trials. Finally, the potential adverse effect of text messaging on the patients and their families should be more thoroughly investigated. 4 (6%) patients and 10 (11%) lay health supporters did report.

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TABLES

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

Note: (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.

Table 2 Sample Size Calculation Scenarios

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

Note: (1). Standard deviation in parentheses; (2). Sample calculation assuming power of 0.85, significance level of 0.05, and a 10% dropout rate; (3). Sample size of the baseline non-adherent sub-group achieved with a LEAN total sample of 258.

Table 3 Patient and Family Characteristics

Variable	Count(%)/Median(IQR)
Sex	
Female	154(55.60%)
Male	122(44.04)
Missing	1(0.36%)
Marriage	
Married	177(63.90%)
Unmarried	99(35.74%)
Missing	1(0.36%)
Employment	
Employed	92(33.21%)
Unemployed	184(66.43%)
Missing	1(0.36%)
Living	
Living alone	13(4.69%)
Living with family/friends	262(94.58%)
Missing	2(0.72%)
Age (years)	45(36-54)
Education (years)	8(6-9)
Patient income last month (RMB)	80(0-600)
Family annual income (RMB)	20000(10000-50000)
Duration of Schizophrenia (years)	16(10-25)
Clinical Global Impression-severity^a	
Overall severity	3(2-4)
Positive symptoms	2(1-4)
Negative symptoms	3(2-4)
Depressive symptoms	2(1-3)
Cognitive symptoms	3(1-4)
WHO Disability Assessment Schedule 2.0^b	0.13(0.04-0.29)
Antipsychotics Prescribed	
Clozapine	84(30.32%)
Risperidone	74(26.71%)
Quetiapine	38(13.72%)
Sulpiride	36(13.00%)
Perphenazine	22(7.94%)
Aripiprazole	15(5.42%)
Chlorpromazine	10(3.61%)
Penfluridol	4(1.44%)
Olanzapine	2(0.72%)
Other antipsychotics	3(1.08%)

^a. Higher scores indicate worse symptoms (possible range 1–7 for both total and domain scores).

^b. Scores indicate percent of functions lost

Table 4 Rates of Adherence as Assessed by Various Measures

Measures^a	Mean Adherence^b (SD)	No. Adherent Subjects (%)
PC Home ^b	0.56(0.35)	83/228(36.40%)
PC Office1 ^b	0.41(1.14)	94/169(55.62%)
PC Office2 ^b	0.96(1.39)	116/169(68.64%)
Refill record ^b	0.79(0.31)	158/272(58.09%)
BARS ^b	0.70(0.22)	147/216(68.06%)
Morisky1 ^c	5.83(2.10)	123/191(64.40%)
Morisky2 ^c	5.83(2.10)	49/191(25.65%)
DAI ^d	3.55(4.20)	80/191(41.88%)
Impression ^e	1.15(0.42)	227/258(87.98%)

^a. PC Home: unannounced home-based pill-count; PC Office1: office-based pill-count with 1

count; PC Office2: Office-based pill-count with 2 counts; BARS: Brief Adherence Rating Scale;

Morisky: Morisky 8-Item Medication Adherence Scale; DAI: Drug Attitude Inventory-10;

Impression: “686” clinician impression

^b. For pill-counts, refill and BARS, adherences are percentage of dosages taken over the past month or dichotomized as adherent and non-adherent at the cut-point of 0.75

^c. Morisky adherence is from 0 to 8 (8=good adherence, 6-8=medium, <6=poor adherence);

Morisky1 and Morisky2 are also dichotomized at <6 and <8, respectively.

^d. DAI adherence is from -10 to +10 (higher score=more positive attitude toward medication).

Also dichotomized at ≥ 6

^e. Clinician impression is from 1 to 3 (1=routinely taking medicine, 2=intermittently taking medicine, 3=not taking medicine); Also dichotomized at ≤ 2 .

Table 5 Sensitivity and Specificity of Various Measures

Measures	Sensitivity	Specificity
<i>Objective Measures (Cut-point ≥ 0.75)</i>		
Office-based Pill Count (1 count)	48.33%	41.66%
Office-based Pill Count (2 counts)	73.33%	30.95%
Refill Record	72.29%	45.77%
<i>Subjective Measures</i>		
Brief Adherence Rating Scale (BARS) (Cut-point ≥ 0.75)	72.73%	34.65%
Morisky1 (Cut-point at <6)	77.61%	40.71%
Morisky2 (Cut-point at <8)	26.87%	74.34%
Drug Attitude Inventory (DAI) (Cut-point ≥ 6)	46.97%	60.87%
Clinician Impression (Cut-point at ≤ 2)	93.75%	11.94%

* Reference standard: home-based Unannounced Pill Count (Cut-point at ≥ 0.75).

Table 6 Baseline Characteristics

	Intervene(n=139)	Control(n=139)
	Count(%) / Median(IQR)	Count(%) / Median(IQR)
Female	77(55.4%)	77(55.4%)
Married	87(62.6%)	90(64.8%)
Employed	44(31.7%)	48(34.5%)
Living alone	7(5.0%)	6(4.3%)
Age (years)	46(37-54)	44(35-52)
Education (years)	8(6-9)	9(6-10)
Patient income last month (RMB)	66(0-500)	95(0-800)
Family annual income (RMB)	20,000(10,000-50,000)	20,000(10,000-50,000)
Duration of Schizophrenia (years)	15(10-24)	16(10-26)
CGI-severity ^a	3(2-4)	3(2-5)
WHODAS ^b	0.13(0.02-0.29)	0.15(0.05-0.27)

^a. Higher scores indicate worse symptoms (possible range 1–7)

^b. Scores indicate percentage of functioning lost

Table 7 Primary and Secondary Outcomes at 6-Month

Measures	Intervene (n=139) mean(SD) or n/N(%)	Control (n=138) mean(SD) or n/N(%)	Mean difference(95%CI) or relative risk(95%CI)	P value
Primary outcome				
Adherence ^a	0.63(0.34)	0.49(0.35)	0.133(0.043 to 0.224) ^h	0.004
Secondary outcomes				
WHODAS ^b	0.116(0.15)	0.145(0.19)	-0.031(-0.069 to 0.008) ^h	0.117
CGI-severity of illness ^c	2.844(1.37)	2.756(1.24)	0.105(-0.209 to 0.419) ^h	0.51
negative	2.944 (1.46)	2.975 (1.43)	0.018(-0.286 to 0.322)	0.908
positive	2.704 (1.62)	2.672 (1.55)	0.174(-0.140 to 0.490)	0.277
depression	2.312 (1.29)	2.107 (1.26)	0.746(-0.152 to 0.302)	0.517
cognition	2.856 (1.50)	2.852 (1.44)	0.074(-0.217 to 0.364)	0.617
CGI-degree of change ^d	3.09(1.15)	3.024(1.08)	0.027(-0.248 to 0.302)	0.848
Relapse ^e	26/120(21.7%)	40/117(34.1%)	0.634(0.415 to 0.967)	0.033
Re-hospitalization ^f	9/123(7.3%)	25/122(20.5%)	0.357(0.174 to 0.733)	0.004
686 Program registry^g				
Dead	2/139(1.4%)	1/134(0.8%)	1.928(0.177 to 21.015)	0.958
Wander	2/138(1.5%)	2/134(1.5%)	0.971(0.139 to 6.795)	0.976
Violence	1/137(0.7%)	2/134(1.5%)	0.489(0.045 to 5.330)	0.557
Damaging goods	2/138(1.5%)	5/134(3.7%)	0.388(0.077 to 1.968)	0.252

^a. Percentage of antipsychotic dosage taken over a month assessed by unannounced home-based pill-counts

^b. WHO Disability Assessment Schedule; Scores indicate percentage of functioning lost

^c. Clinical Global Impression-severity; Higher scores indicate worse symptoms (possible range 1–7)

^d. CGI-degree of change in symptoms (1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse)

^e. Incidences reported by the 686 Program registry

^h. Adjusted mean difference

Table 8 User Experiences

	Patients	Lay health supporters
Phone status		
Owned a smartphone	33(29.0%)	35(33.3%)
Used a phone given by LEAN	58(51.8%)	19(18.8%)
Changed phone numbers over past 2 months	13(12.4%)	92(92.0%)
Phone fully functioning	77(77.8%)	92(92.0%)
User evaluation		
Overall satisfied with the program	62(98.4%)	77(100.0%)
Willing to continue receiving messages	52(91.2%)	80(94.1%)
Messages very useful	61(59.1%)	47(60.3%)
Messages bothered you	4(6.3%)	9(10.7%)
Time of texting appropriate	57(91.9%)	70(90.9%)
Frequency of texting appropriate	53(86.9%)	66(83.5%)
Length of messages appropriate	59(98.3%)	71(92.2%)
Most useful part of the messages		
Treatment and medication education	10(17.0%)	18(24.7%)
Family care in schizophrenia	5(8.5%)	8(11.0%)
Medication reminders	27(45.8%)	39(53.4%)
Local news	2(3.4%)	1(1.4%)
Weather forecast	15(25.4%)	7(9.6%)
User capability		
Able to navigate phones to read messages	52(71.2%)	74(84.1%)
Able to reply messages	38(52.1%)	55(64.0%)
Did not understand messages	12(17.7%)	4(4.9%)
Some physical disability that prevent using a phone	12(18.5%)	9(10.7%)
User experiences		
Always received messages last month	44(62.0%)	65(77.4%)
Always or often read messages	39(54.9%)	65(76.5%)
Frequently replied to texted reminders	15(22.4%)	27(31.8%)
Concerned about cost of messages	7(10.9%)	4(4.8%)

FIGURES

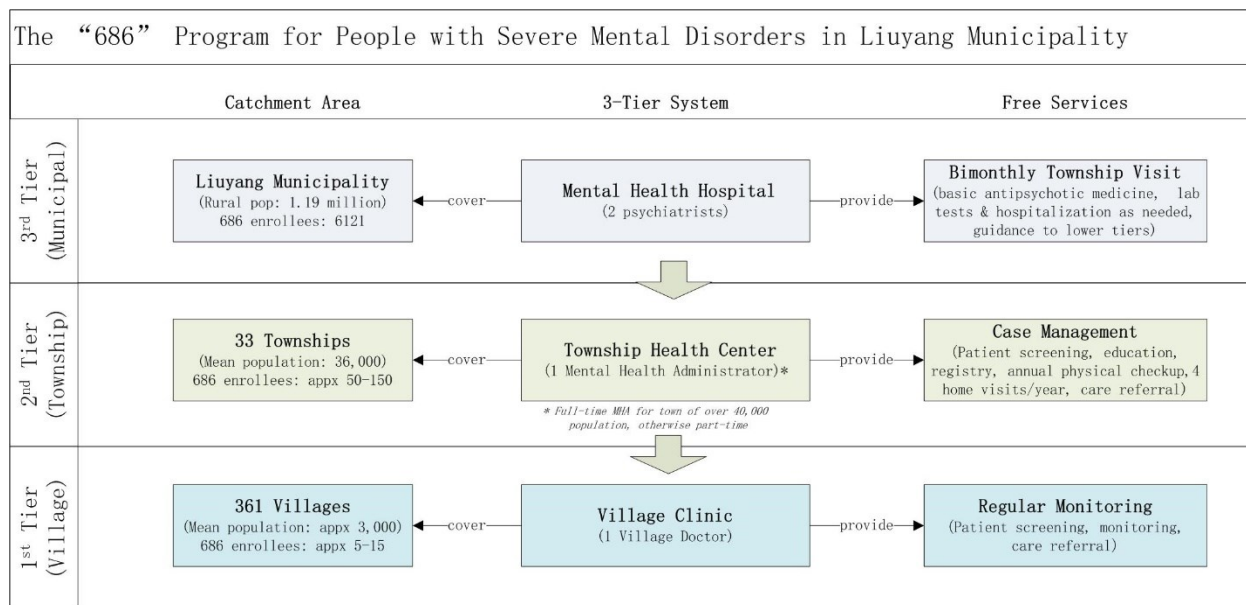
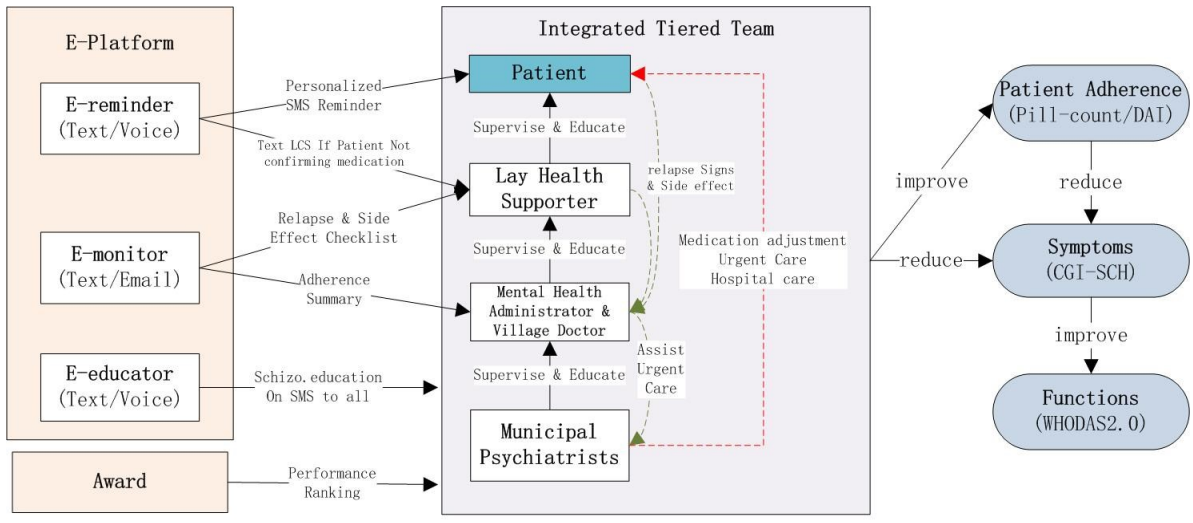


Figure 1 The “686” Program in Liuyang



iNtegrated as the LEAN solution

Figure 2 LEAN Component

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

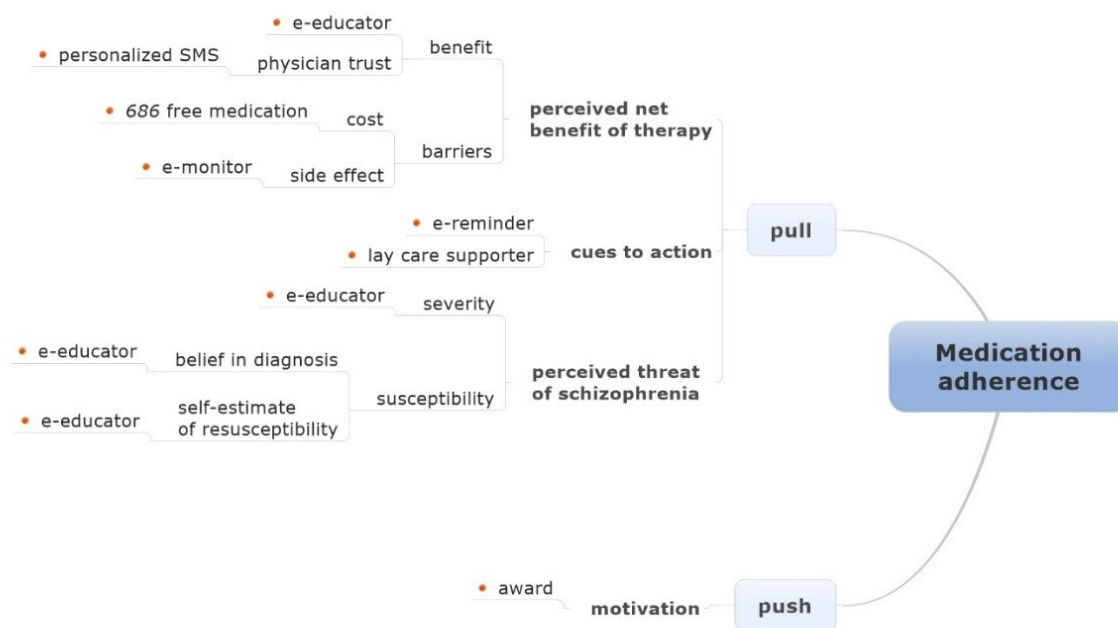


Figure 3 LEAN Mechanism

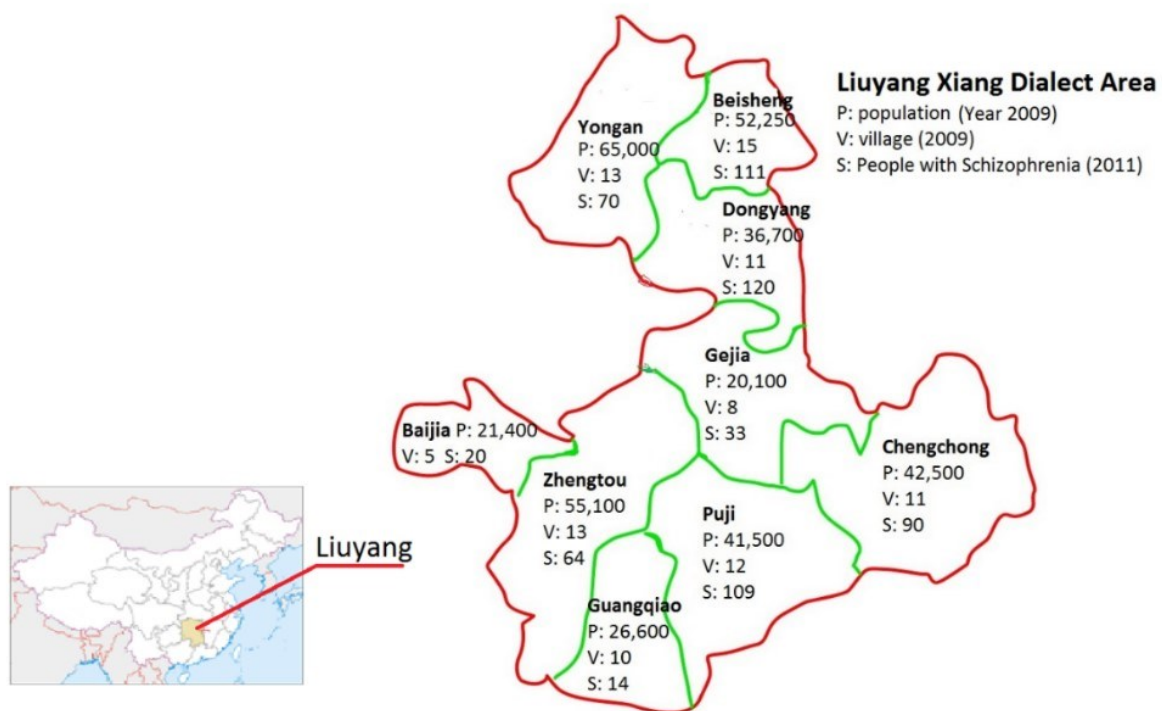


Figure 4 Liuyang Map

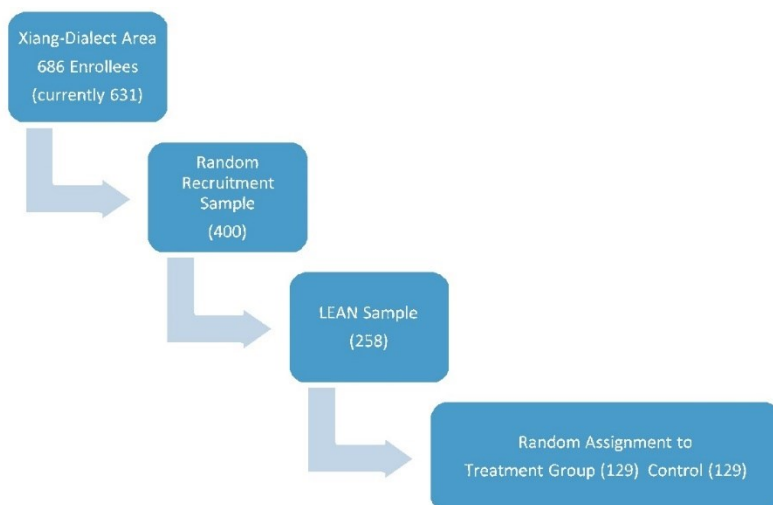


Figure 5 The Lean Population, Sample and Assignment

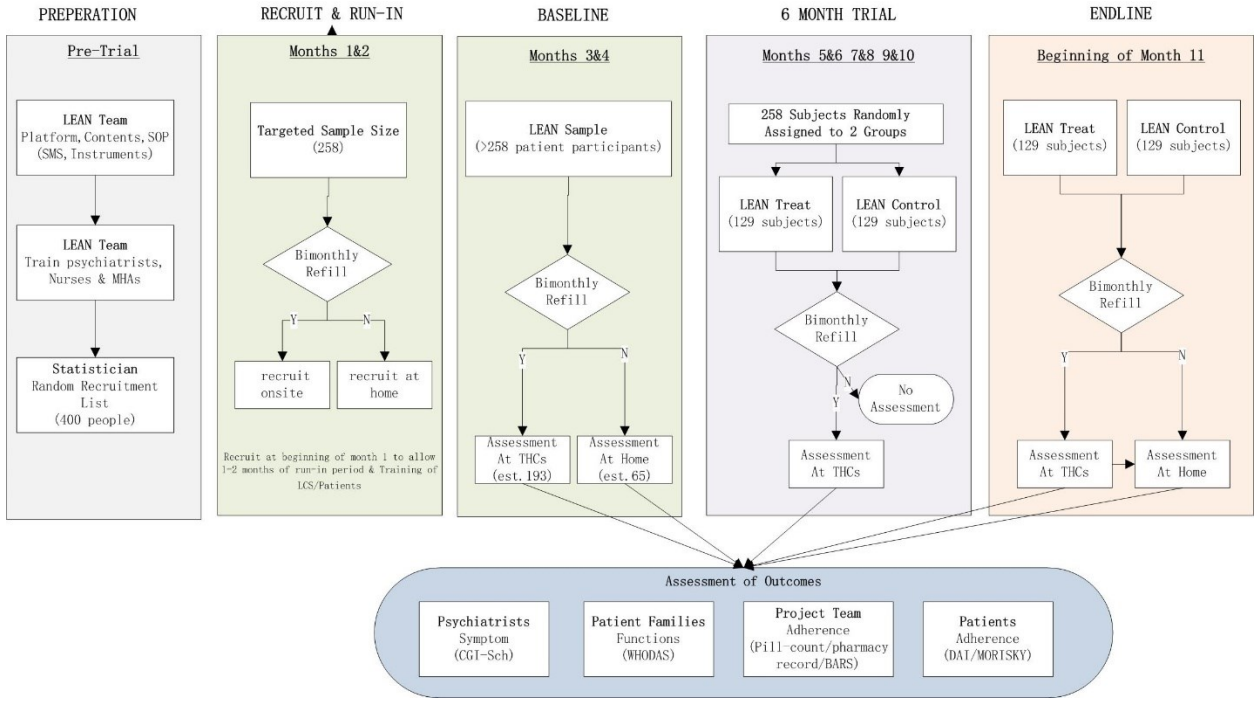
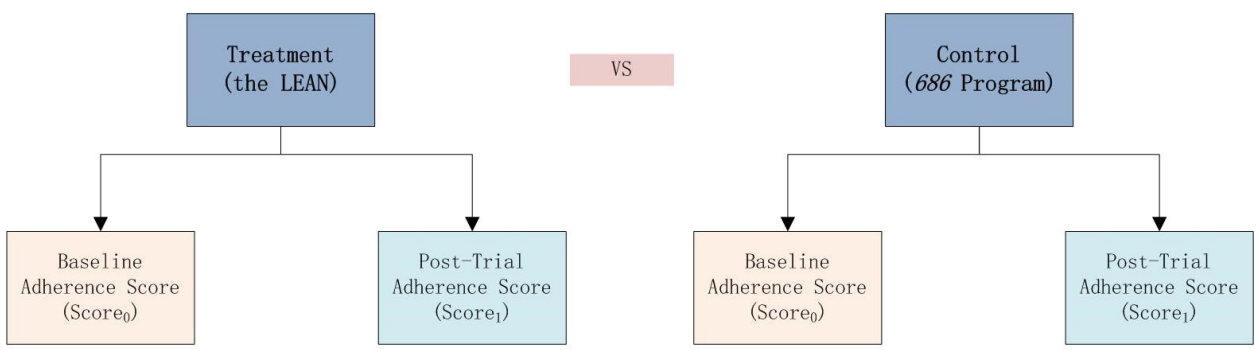


Figure 6 Recruitment and Outcome Assessment



- 1. Unadjusted: (Score₁) vs (Score₁)
- 2. ANCOVA: (Score₁ with Score₀ as covariate) vs (Score₁ with Score₀ as covariate)
- 3. DiD (Score₁ - Score₀) vs (Score₁ - Score₀)

Figure 7 Three Approaches to RCT Analysis

Source: adapted from Siyuan Zhang paper



Figure 8 Concordance and Correlation of Measuring Adherence between Different Measures

*PC home: Home-based unannounced pill-count; Refill: refill record; BARS: Brief Adherence Rating Scale; Morisky: Morisky Adherence Scale; DAI: Drug Attitude Inventory; PC Office 1: Office-based pill-count (1 count); PC Office 2: Office-based pill count (2-count); Impression: Clinician Impression

**For Kappa, following cut-points were used: ≥ 0.75 for pill-counts, refill and BARS; < 6 for Morisky; and ≥ 6 for DAI.

**Size of the circle indicates the strength of the association; blue color indicates positive association while red indicates inverse association.

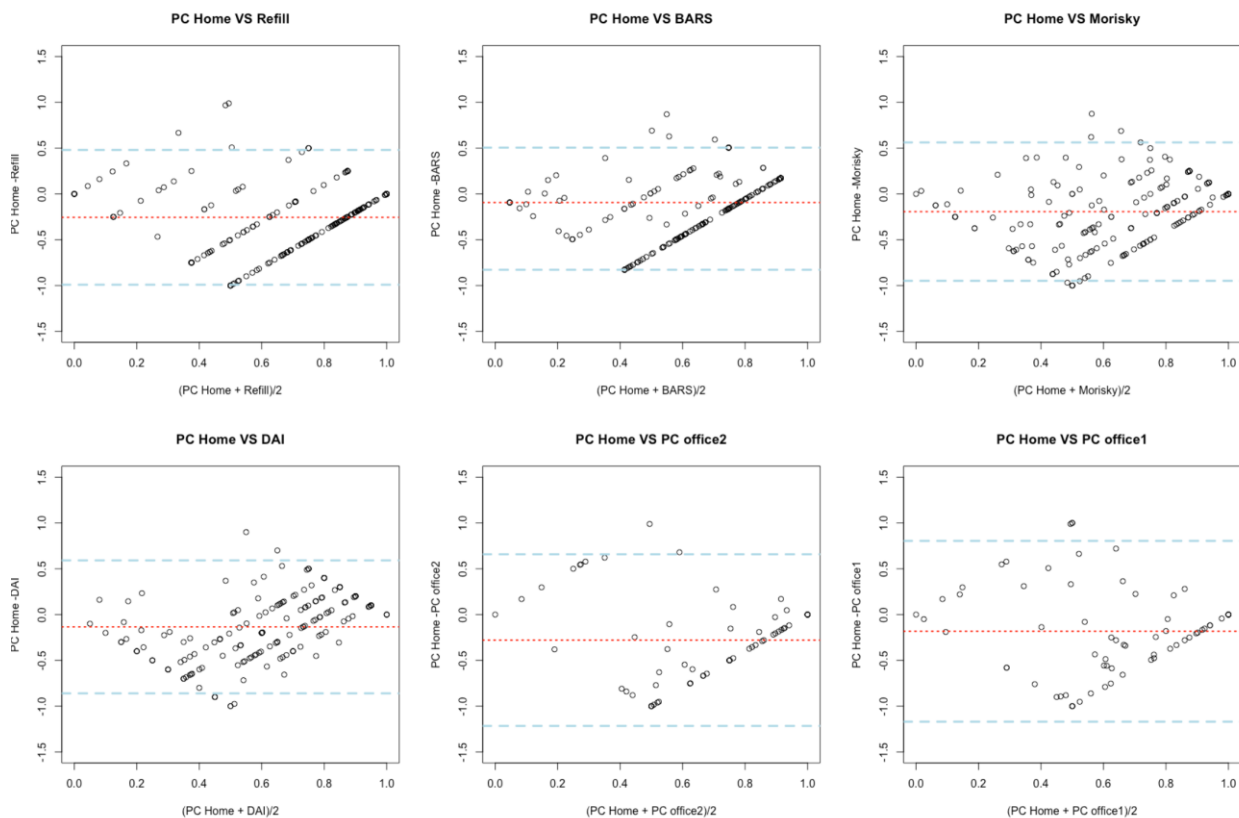


Figure 9 Bland-Altman Plot

*PC home: Home-based unannounced pill-count; Refill: refill record; BARS: Brief Adherence Rating Scale; Morisky: Morisky Adherence Scale; DAI: Drug Attitude Inventory; PC Office 1: Office-based pill-count (1 count); PC Office 2: Office-based pill count (2-count)

**X-axis: mean of the adherence rates assessed by the two measures for each subject; Y-axis: differences of the adherence rates between the two measurements for each subject; Dotted red line: “mean-of-all-differences” line; Dashed blue lines: “limits of agreement” lines indicating 1.96 standard deviations of the measured differences between the two measurements above or below the mean-of-all-difference line

***Morisky and DAI scores were rescaled to range from 0-1 for comparative purposes.

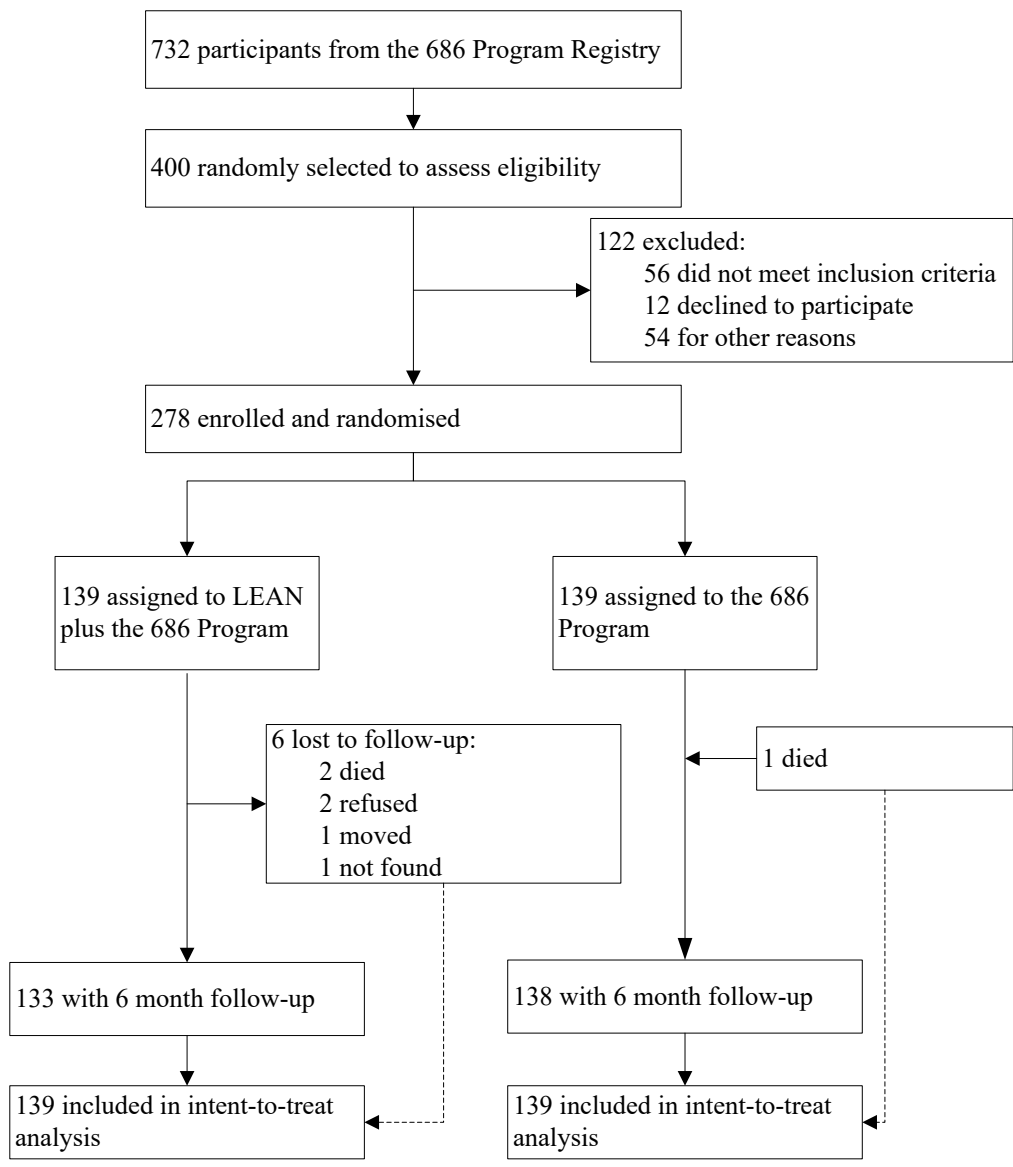


Figure 10 Trial Profile

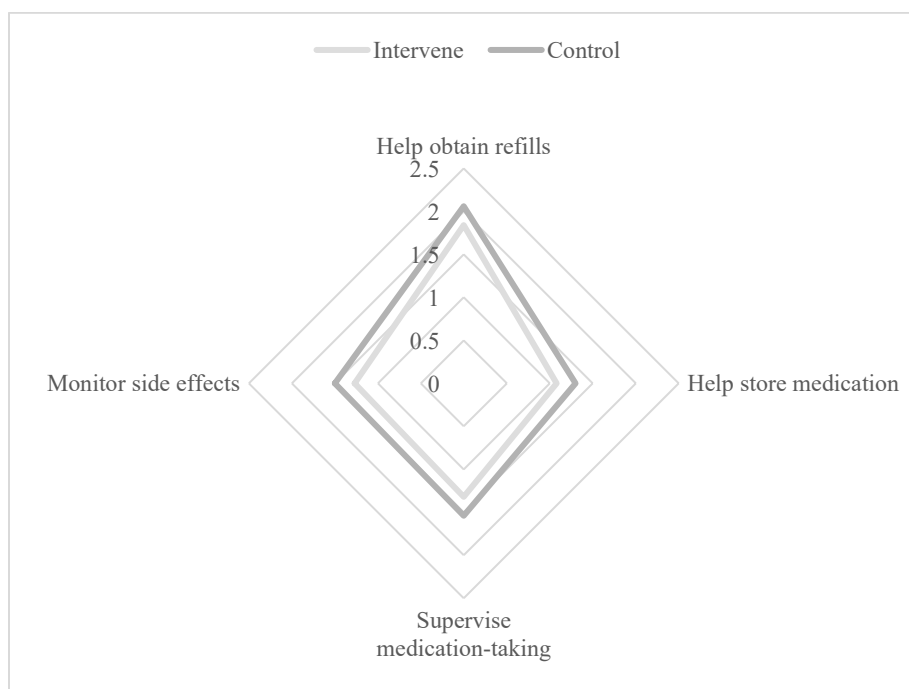
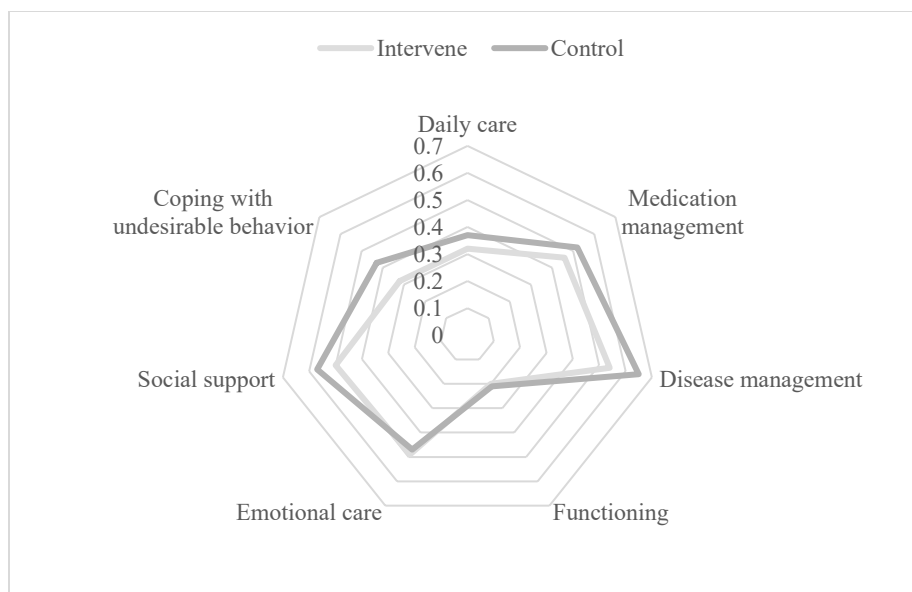


Figure 11 Care provided to person with schizophrenia by their family caregivers at 6-month

The upper figure shows percentage of items of care by the family to the patient for one of the 7 domains of care; the lower figure shows the mean level of efforts (0=never; 1=seldom; 3=sometimes; 4=often) by the family caregivers for each item of care for the domain of “supervising medication-taking”.

SUPPLEMENTARY MATERIALS

Appendix 1 Spearman Correlation Between Adherence Measures and CGI-Severity / WHODAS

Measures	Spearman Correlation Coefficient (P)	
	CGI-Severity	WHODAS
Home-based unannounced pill-count	-0.07(0.31)	-0.09(0.20)
Refill record	-0.03(0.70)	-0.10(0.13)
Brief Adherence Rating Scale (BARS)	0.08(0.24)	-0.01(0.90)
Morisky Adherence Scale	0.04(0.62)	-0.17(0.02)
Drug Attitude Inventory-10 (DAI)	-0.10(0.17)	-0.14(0.09)
Office-based pill-count with 2-count	0.13(0.25)	-0.03(0.78)
Office-based pill-count with 1-count	0.01(0.91)	0.02(0.88)
“686” Clinician Impression	-0.08(0.37)	0.03(0.75)

Appendix 2 Rates of Adherence for the Intervention and Control Groups as Assessed by Various Measures

Measures ^a	Intervene		Control		Program Effect(P)
	Mean Adherence ^b (SD)	No. Adherent Subjects (%)	Mean Adherence (SD)	No. Adherent Subjects (%)	
PC Home ^b	0.63(0.34)	51/114(44.74%)	0.49(0.36)	32/114(28.07%)	0.14(0.0013)
PC Office1 ^b	0.24(1.42)	41/86(47.67%)	0.58(0.72)	53/83(63.86%)	-0.34(0.0232)
PC Office2 ^b	0.84(1.68)	55/86(63.95%)	1.08(0.99)	61/83(73.49%)	-0.24(0.1773)
Refill record ^b	0.83(0.28)	85/135(62.96%)	0.76(0.34)	73/137(53.28%)	0.07(0.0659)
BARS ^b	0.71(0.21)	79/113(69.91%)	0.68(0.23)	68/103(66.02%)	0.03(0.4192)
Morisky1 ^c	6.04(1.97)	73/100(73.00%)	5.61(2.23)	50/91(54.95%)	0.43(0.1948)
Morisky2 ^c	6.04(1.97)	26/100(26.00%)	5.61(2.23)	23/91(25.27%)	0.43(0.1948)
DAI ^d	3.66(4.04)	42/99(42.42%)	3.44(4.39)	38/92(41.30%)	0.22(0.9418)
Impression ^e	1.13(0.42)	114/127(89.76%)	1.16(0.43)	113/131(86.26%)	-0.03(0.4167)

^a PC Home: home-based pill-count; PC Office1: office-based pill-count with 1 count; PC

Office2: Office-based pill-count with 2 counts; BARS: Brief Adherence Rating Scale; Morisky:

Morisky 8-Item Medication Adherence Scale; DAI: Drug Attitude Inventory-10; Impression:

“686” clinician impression

^b For pill-counts, refill and BARS, adherences are percentage of dosages taken over the past month or dichotomized as adherent and non-adherent at the cut-point of 0.75

^c Morisky adherence is from 0 to 8 (8=good adherence, 6-8=medium, <6=poor adherence);

Morisky1 and Morisky2 are also dichotomized at <6 and <8, respectively.

^d DAI adherence is from -10 to +10 (higher score=more positive attitude toward medication).

Also dichotomized at ≥ 6

^e Clinician impression is from 1 to 3 (1=routinely taking medicine, 2=intermittently taking medicine, 3=not taking medicine); Also dichotomized at ≤ 2 .

Appendix 3 Data Imputation

In the analysis process, we mainly use the R package mice, gee, norm. (MICE: Multivariate Imputation by Chained Equations). In the multiple imputations, we imputed 10 complete datasets. The GEE model is then applied for each dataset, and the synthetization of 10 GEE model results is done with the norm R package. We describe the specific steps below, using the analysis of the effect of the program on medication adherence:

1. Assessing the missing data pattern: We visualized the pattern of missing data in order to discern any systematic pattern of missing (Figure 1 and Figure 2). As we did not find any clear pattern, we assume that data are missing at random in our analysis.
2. Selecting the data imputation model: If the variable with missing value is a continuous variable, the predictive mean matching (PMM) method is used; if the variable with missing value is a binary variable, Logistic regression is then used; while for a multi-level categorical missing variable, the polytomous regression is applied..
3. Determining the independent variables used in the imputation model: all other variables except for the dependent variable were used in the imputation model. In order to improve the accuracy of the imputation, in addition to the variables used for the GEE model including the variables of intervention assignment, adherence, functioning, substance use, drug side effects, family supervision, we also used other social-economic and demographic variables such as sex, age, education, income, living alone, duration of illness, symptoms severity etc.in the imputation model.
4. Determining the order of imputation: From left to right: demographic/social-economic information and other variables, the independent variables used in the GEE model, dependent variables used in the GEE model.

5. Ten complete datasets generated were generated: Figure 3 shows the original observed data and the imputed data. The imputed data sets show a similar pattern of data distribution to the original dataset.
6. GEE model was performed for each of the 10 complete data sets.
7. Using norm R package to synthesize the results from the 10 GEE models to obtain the overall an estimate of the effect of the program.

References: MICE: Multivariate Imputation by Chained Equations in R

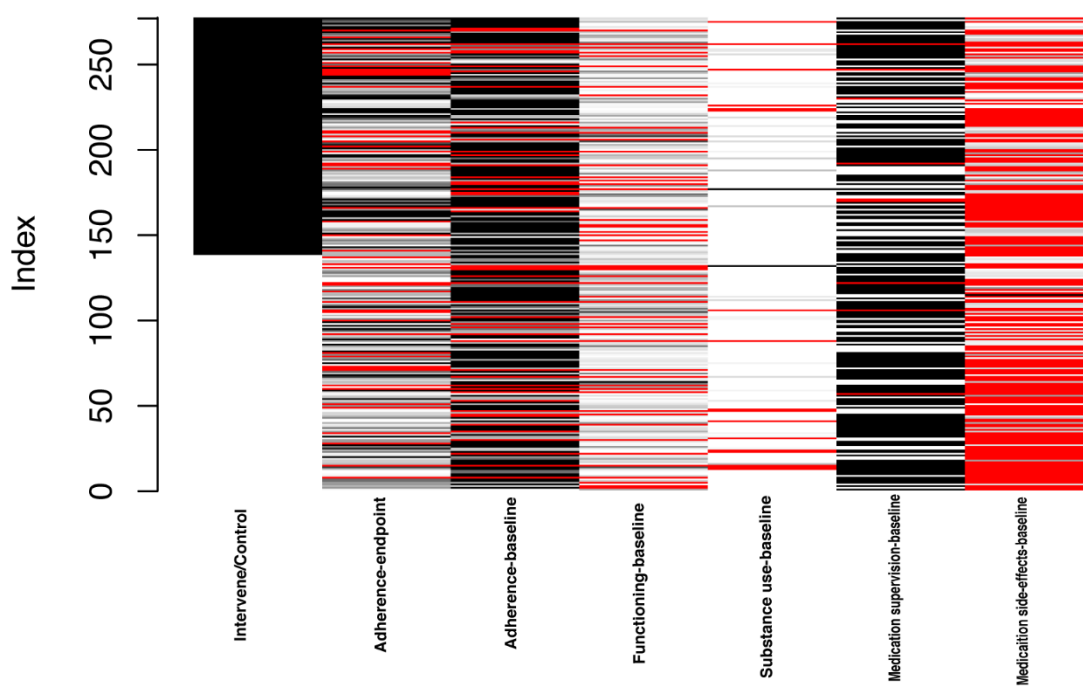


Figure 1: missing data comparison: control vs. intervention groups; Red indicting missing; gray and black indicating available data; darker color indicting greater value.

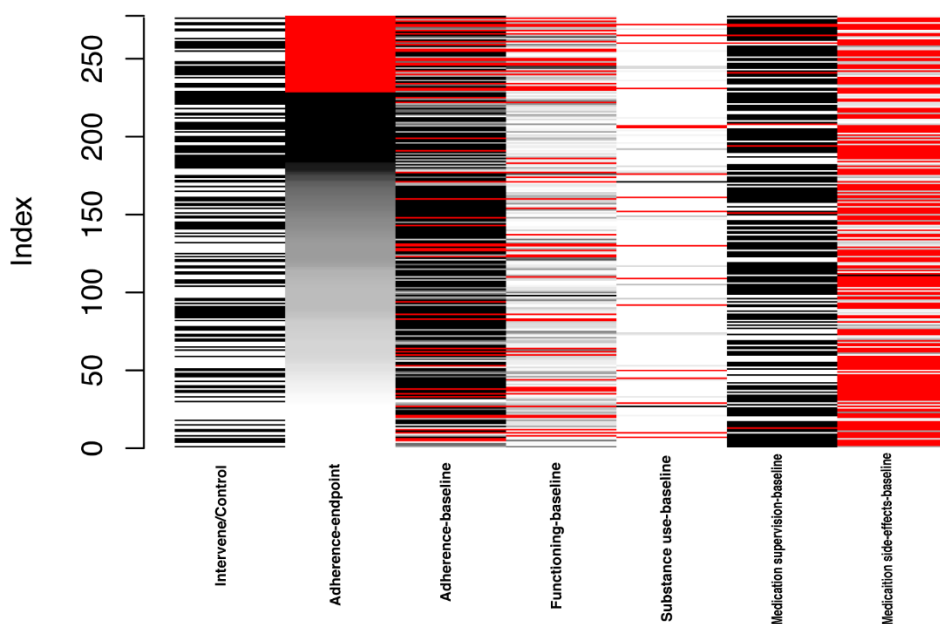


Figure 2: Missing data (sorted in order of medication adherence level)

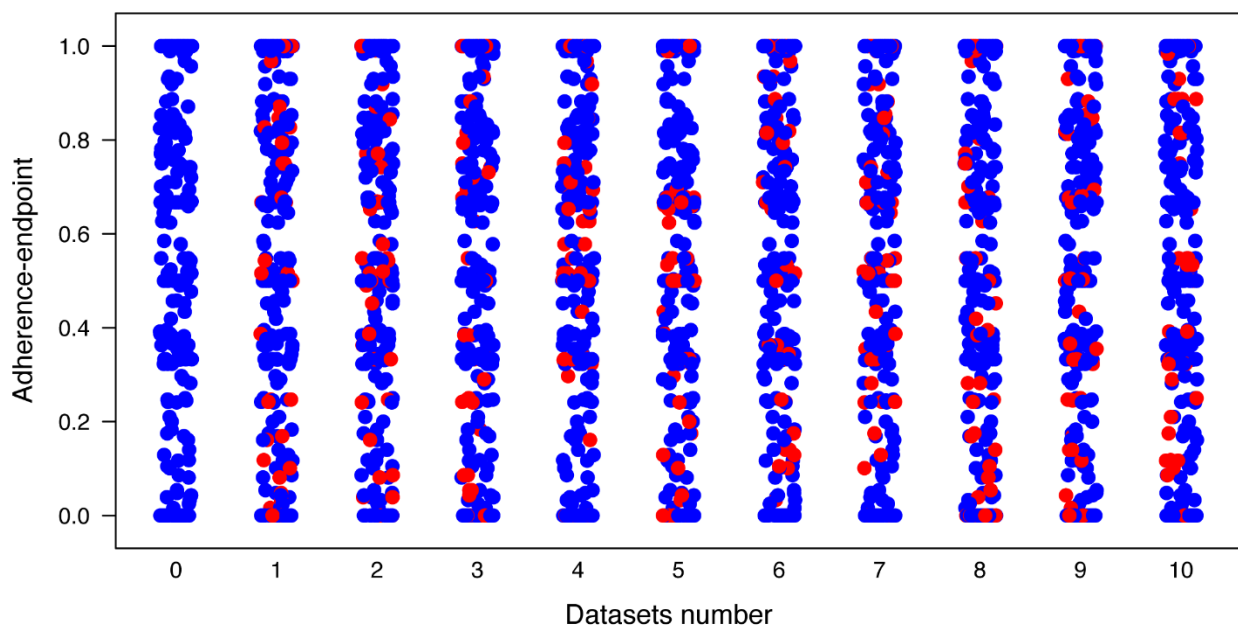


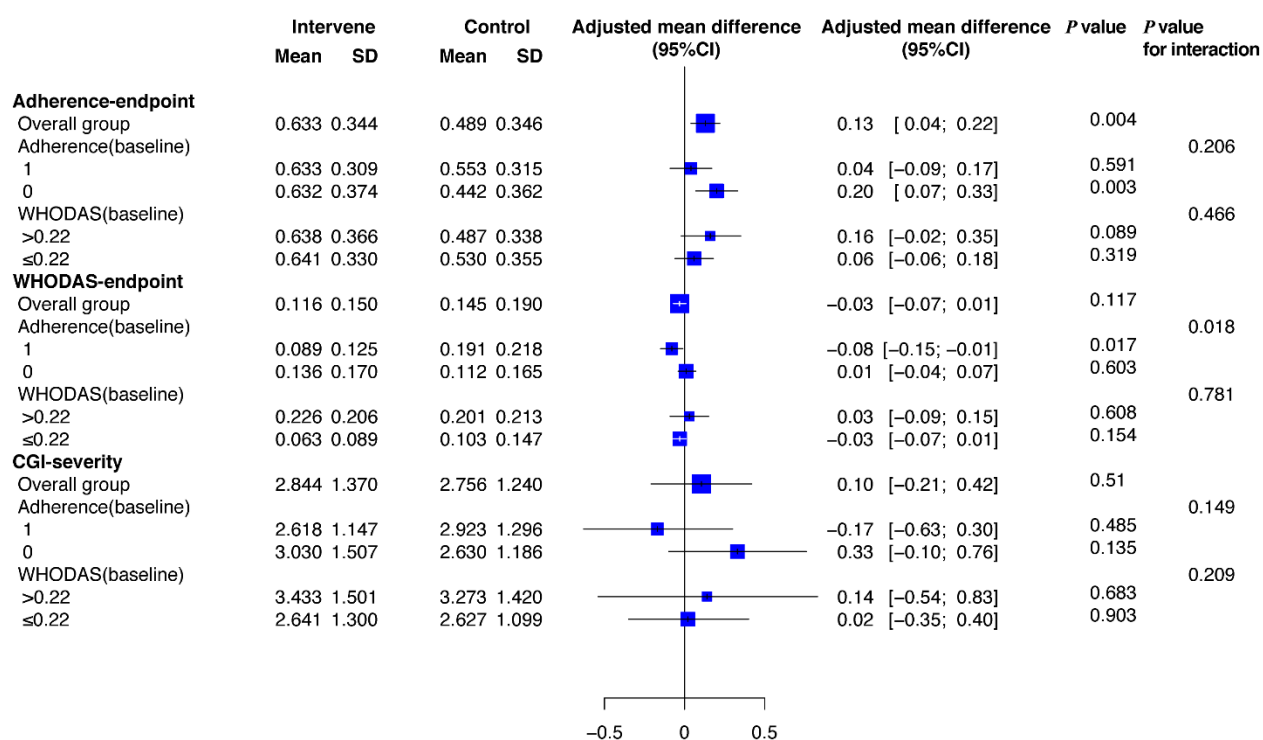
Figure 3 Imputed datasets, using medication adherence as an example; 0 represents the original observed data; 1-10 represent datasets after multiple imputation, with the blue dot indicating the original observed value, the red dot representing the imputed value

Appendix 4 Sample Text Messages

1. **Daily medication reminder:** Good evening! Tomorrow there is a temple fair in Baisheng township and weather will be great at 23 centigrade, sunny. Please remember to take your medicine and text back “1”.
2. **Education message (to family member):** Hello, one common sign of relapse is lack of interests in things that they used to like. Please pay attention to those early signs and prevent the disease from recurring. Caring for the patients is a lot of work and we will work with you for their health.
3. **Education message (to patients):** Have you seen the movie "Beautiful Mind"? The film is based on a real story: John Nash, a professor of economics, suffering from schizophrenia, pursued his study in game theory and won the Nobel Prize in economics. For your dreams, please adhere to the treatment and remember to take medicine on time.
4. **Education message:** Psychological, art, and music therapies can only complement rather than replace your medication therapy. Remember that adhering to your medication on time and on the prescribed dose is the key to control your symptoms. We here at LEAN are with you and for your help.
5. **Education message (to family member):** People with schizophrenia may hear voices not heard by others, or think others can see their thoughts, control their own thinking, or attempt to harm themselves. These experiences can lead to fear, withdrawal or emotional agitation. As you care for your patients, try to understand them and get their trust.
6. **Monitoring messages:** If any of the following happens or worsens, please text back “1”:
problem with sleep, appetite, or concentration; depression; restlessness; tension or nervousness; hearing voices or seeing things that others can't hear or see; less pleasure

gained from things you enjoy; feeling people were watching you; preferring being alone; arguments with others; inability to get your mind off of something.

Appendix 5 Sub-group Analysis



^a. Adherence: percentage of antipsychotic dosage taken over a month assessed by home-based unannounced pill-counts; ^b. WHODAS: WHO Disability Assessment Schedule; Scores indicate percent of functioning lost; ^c. CGI-severity: Clinical Global Impression for severity of illness; Higher scores indicate worse symptoms (possible range 1–7)

VITA

Dong (Roman) Xu is the executive deputy director of the Sun Yat-sen Global Health Institute (SGHI) of the Sun Yat-sen University and a research professor in global health and health systems. His research focuses on developing and evaluating health system innovations in the global health context, particularly those related to primary health care, payment systems, health quality assessment and mHealth. He is leading a large 18-province multi-center research in quality of primary care, using unannounced standardized patient and smartphone-based virtual patients. Roman published in leading journals such as the Lancet and Implementation Science. Before his SGHI work, he held leadership positions at the China Medical Board (CMB), Harvard Medical School's Harvard Medical International, Medtronic Inc., and the Chinese Medical Association. Roman is expected to obtain his Ph.D. in Global Health (implementation science) from the University of Washington in 2017. He had a master in public policy (health policy) from Harvard University in 2004, and bachelor in medical English from West China University of Medical Sciences in 1996.