Cluster randomized trial of a medication monitor in the treatment management of patients with pulmonary tuberculosis

Protocol version 3.1, 24 June 2020

Amendments since version 3.0: Minor amendment to definition of primary outcome on page 26 based on discussion during finalisation of statistical analysis plan. Change to MDR TB and Adverse reaction added as poor outcomes. Definition of LTFU secondary outcome corrected

Funder: Bill & Melinda Gates Foundation

Sponsor: Chinese Center for Disease Control and Prevention, China

Clinical trial registration number: http://www.isrctn.com/ISRCTN35812455

Research ethics committee reference numbers:
Chinese Center for Disease Control and Prevention, China: 201603
London School of Hygiene & Tropical Medicine, UK: 10665

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Study summary

Background: China has the second highest number of TB cases globally and ensuring adequate adherence to treatment for all TB patients is a priority. In our previous study we compared three intervention approaches, utilising text message reminders, a medication monitor, or both to standard of care. The results showed that the medication monitor approach greatly reduced non-adherence, but problems with the medication monitor were reported frequently. The medication monitor now has a second version and we would like to see how well this performs and whether the impact on adherence translates into better clinical outcomes for patients.

Aim: To determine a composite poor outcome among adults with drug sensitive pulmonary TB, managed using a treatment strategy including a medication monitor for reminding daily drug dosing and monitoring adherence patterns, and targeted intensive management of patients with poor adherence patterns; and to compare this outcome among adults with drug sensitive pulmonary TB managed according to standard of care.

Methods: Open-label, pragmatic cluster-randomised trial, with districts/counties as the unit of randomisation. Adults (at least 18 years) who are Gene Xpert positive (rifampicin sensitive), have no communication impairment and able to use the medication monitor after training will be eligible. In intervention communities, the medication monitor will be used to remind patients to take the medication each day and to attend their monthly follow-up visits. The monitor will also collect the date and time of opening and these data will be used by the doctor to determine whether the patient requires more intensive management. Patients in control communities will be managed according to standard of care.

Participants in both arms will be followed up to 18 months after the start of treatment. The primary outcome is a composite outcome measured 18 months from the start of treatment and based on: (i) treatment lost to follow-up; (ii) treatment failure (culture positive); (iii) death during treatment; (iv) culture positive or started TB treatment during months 6-18 months after the start of treatment. Secondary outcomes include poor outcome at the end of treatment, loss to follow-up during treatment and adherence outcomes. We will also explore the cost-effectiveness of this treatment management strategy.

Significance: If the treatment management strategy proves effective in reducing the composite poor outcome, this approach could be implemented in other provinces in China.

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1. Background

Tuberculosis (TB) remains one of the world's deadliest communicable diseases. In 2014, an estimated 9.6 million people developed TB and 1.5 million died from the disease (1). Incident cases of TB are declining at an average rate of 1.5% per year from 200-2014. China is one of the 22 high burden countries, where incident cases in 2014 were 0.89 million, accounting for 10% of all estimated incident cases worldwide, making China second only to India in numbers of TB cases. Globally, an estimated 3.3% of new cases and 20% of previously treated cases have multi-drug resistant TB (MDR-TB). In 2014, there were an estimated 480 000 new cases of MDR-TB worldwide, and approximately 190 000 deaths from MDR-TB. If all TB cases notified in 2014, were tested for drug resistance an estimated 300 000 would have been found to have MDR-TB. More than half of these patients were in India, China and the Russian Federation. Ensuring adequate adherence to treatment for drug susceptible TB is key to curing the patient and to preventing the emergence of drug resistant TB (2).

1.1 Tuberculosis treatment for drug sensitive TB

1.1.1 Treatment length and regimens

According to the guidelines of TB treatment from China, the treatment length is 6 months, the anti-TB drugs include isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) (3). The treatment regimen for new sputum smear positive (SS+) and new sputum smear negative (SS-) TB patients is as following:

(1) 2H3R3Z3E3/4H3R3
Intensive phase: H, R, Z, E, every other day, two months, 30 doses.
Continuation phase: H, R, every other day, four months, 60 doses.
A total number of 90 doses for a full course of treatment.

(2) 2HRZE/4HR
Intensive phase: H, R, Z, E, daily, two months, 60 doses.
Continuation phase: H, R, daily, four months, 120 doses.
A total number of 180 doses for a full course of treatment.

There are two categories of patients who have to extend their treatment:

1. Patients who are sputum smear-positive at the end of their second month of treatment have to be treated for an additional month in their intensive phase;
2. Patients whose treatment has been interrupted for side effects would extend their treatment.

The 12th Five-year National TB Control Program (2011-2015) Issued by Chinese State Council suggested the anti-TB fixed-dose combination (FDC) be gradually being expanded for TB treatment in all counties in 2015 to improve patients' adherence on treatment.

1.1.2 Measurement of treatment outcomes

Reporting for TB takes a cohort approach with outcomes at the end of treatment described for all patients. Microbiological results are used to confirm cure and in most of the World this is based on microscopy results from collected sputum. In China sputum is collected as following:

1 For new TB patients, one early morning sputum sample and one evening sputum sample should be collected and examined by sputum smear microscopy respectively at the end of the 2nd, 5th and 6th month (completion of therapy) after the treatment initiation (3).
2 An additional sputum smear microscopy should be performed at the end of the 3rd month for new SS+ TB patients who have one positive sputum smear result at the end of the 2nd month.

The outcomes of TB treatment are defined as following:
1 Cured: SS+ TB patients complete full course of treatment and have two consecutive negative smear results including one after completion of therapy.
2 Completed treatment: SS- TB patients complete the prescribed course of treatment and have a negative sputum smear microscopy result or do not receive smear examination after completion of therapy; and SS+ TB patients complete the prescribed course of treatment, have one negative sputum for the last sputum smear microscopy and do not receive smear examination after completion of therapy.
3 Death of TB: Active TB patients die due to disease progression or such complication as haemoptysis, spontaneous pneumothorax, corpulmonale, systemic failure or extra-pulmonary TB.
4 Death of non-TB: TB patients die due to other reasons than TB.
5 Failure: SS+ TB patients have positive sputum smear microscopy results at the end of the 5th month or after completion of therapy; and SS- TB patients have conversion to SS+ during therapy.
6 Lost: TB patients discontinue therapy for more than two months or cannot be reached through tracing within two months after being transferred out by TB control institutions or are reregistered in other areas.
7 Adverse events: Serious adverse events associated with TB drugs lead to impossibility of continuing therapy.
8 Changed diagnosis: TB is excluded during therapy.
9 Refusal: Confirmed TB patients refuse to take TB drugs. Patients receiving at least one dose should be excluded. Discontinuation of therapy cannot be classified as "Refusal".
10 Transferred to MDR treatment: Patients are confirmed as MDR TB based on DST results during therapy and transferred to MDR treatment regimens.

1.1.3 Recurrence

The outcome of “cured” relies on negative smear results, yet the majority of patients may be smear negative at the start of treatment and so this does not represent strong evidence for long-term cure. As such, the long term impact of TB treatment is the relapse rate after treatment through follow up of more than 2 years. The relapse rate is about 1%-5%.

Yan Biya et al reported the relapse results of short course chemotherapy in 1993.The regimens was as following:①6HRE,②9HRE,③3HSP/15HP. Total cases observed was 481 which were observed for 5 years. The relapse rates of smear positive were 5.8%, 1.1% and 3.9% respectively (4).

Cao Jiping et al reported the relapse results of short course intermitted chemotherapy regimen in 1995.The regimens was 2H3R3Z3E3（S3）/4H3R3. Total cases observed was 481 which were observed for 2 years. The relapse rate of smear positive was 3.4% (5).

Geng Huarui reported the study results of treatment relapse in 2014. He observed 184 cases of smear positive cases, the treatment regimen was 2H3R3Z3E3/4H3R3. The cases were observed for 2 years. The relapse rate of smear positive was 1.6% (6).

Three recently published studies investigated whether treatment could be shortened to four months, compared to the standard six month treatment. All three confirmed that the shorter regimen was not non-inferior and so the standard six-month regimen is still recommended. In addition, they all presented relapse/recurrence data. Gillespie et al. used a control regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks, followed by 18 weeks of isoniazid and rifampin. The relapse after culture-negative status was 2.4% (12/510) in this control arm (7). Merle et al. and Jindani et al. both used a control regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks, followed by 16 weeks of isoniazid and rifampin. Recurrence in the control arm was reported for 47/662 (7.1%) by Merle et al. (8) and relapse in the control arm was reported for 6/188 (3.2%) by Jindani et al. (9).

1.2 Delivering DOT in China

The WHO declared a global TB control emergency in April 1993 and the solution to this situation was a global Directly Observed Treatment Short course (DOTS) strategy. A key point of this strategy is Directly Observed Treatment (DOT), which is designed specifically for strengthening treatment adherence. The WHO defines DOT as six to eight-months' worth of regular treatment for TB patients who have already been found to be infectious, along with direct observation of patients' drug intakes every time during the intensive phase, at the very least. Implementation of the Directly Observed Treatment Short course (DOTS) strategy started in China in 1992 and covered the entire country by 2005.

1.2.1 Uptake of DOT in China

According to the China Tuberculosis Control Program Implementation Guide (2008) (3), supervision of smear positive TB patients should be carried out during the entire course of chemotherapy. Based on the report issued by National Center for TB Control and Prevention of China CDC, 90% of smear positive TB patients received their entire treatment under the DOT system, about 8% began treatment under the DOT system sometime during the intensive phase of chemotherapy, and about 2% of patients did not receive DOT treatment (10). However, according to the on-site supervision and domestic researchers' reports, the enrolment rate of DOT in some areas was lower, especially in those poverty stricken areas that lack healthcare facilities. In September 2000, an assessment group formed by the WHO and the Chinese Anti-Tuberculosis Association launched a site assessment in China. Four provinces were randomly selected, and forty patients from each of four counties from each province took part in the investigation. In this assessment, 64.7% of smear positive TB patients received chemotherapy under DOT guidelines during the whole course of treatment and an additional 7% enrolled in DOT during the intensive phase of treatment only, for a total rate 71.7% (11).

The World Bank /DFID China TB Control Project was carried out the evaluation in Liaoning, Fujian, Henan, and Xinjiang provinces in 2004, reported that only 57.2% of the patients received fully supervised treatment, while 42.8% received no supervision during the treatment (12). A study conducted in Chongqing in 2004 showed that only 16% (64/401) of patients were enrolled in the DOT system and 72% (289/401) had no supervision at all (13).

W-L. Hou, F-J. Song, N-X. Zhang et al systematically reviewed (in meta-analyses using reported and imputed data) that provided information about DOTS implementation in China in terms of actual observation and treatment. Actual DOT and adherence Of the 12 implementation survey studies, 8 reported numbers of patients by type of treatment observer and 8 reported numbers of patients who had ever missed doses. The pooled analysis showed that 52% of the TB patients were on SAT,

27% were observed by family members and only 20% were observed by health workers. The occurrence of missed doses was much more frequent among urban patients (41%) than rural patients (14%) (14). In the 2010 National TB Prevalence Survey, 20% of TB patients treated by the public health system – using national TB case-management approaches – were lost to follow-up or were not taking their medications regularly. Thus more effective case-management approaches are needed in China.

1.2.2 Elements that deter the use of DOT in China

The problems that have occurred over the years point to the difficulty of comprehensively instituting DOT in China. The elements that inhibit DOT performance in China are described below.

(1) Regional Variation

China is a large developing country with a multitude of different economic and geographic regions, and varying transportation and healthcare infrastructures. In the expansive western region of China where the means of transportation are limited, it is difficult to implement DOT for a six to eight month course of treatment. In a study of 401 TB smear positive patients in four counties in Chongqing, Hu et al. found that the implementation rate of DOT varied by region (from 7.6% in Xiushan county to 25.3% in Rongchang county) because of economic and geographic differences (13).In other regions with well-developed healthcare systems, such as Jiangsu Province, the implementation rate of DOT was more than 90% (15).

(2) Difficulties of Promoting DOT among Patients

Attitudes towards DOT differ among patients. Most patients believe that it is not necessary to be supervised when taking medication (12, 13). Some think that taking medication is their own business, and that they can do it conscientiously on their own. Others fear that a visit from the doctor could infringe upon their privacy or interfere with their work, so they refuse supervision. However, older patients and patients who have difficulty taking medications on their own readily accept supervision (16). Management measures should be adapted according to a patient's attitude toward medical staff visits and treatment.

(3) Total Implementation of DOT Will Increase the Burden on Both the Patient and the Healthcare System

China has the second highest number of TB patients in the world (1). To fully implement DOT and visit each and every patient several times a week would require a very large number of treatment supervisors in a country with limited healthcare resources. This becomes particularly problematic in cases where patients live far from health centers or have work schedules that conflict with those of the medical staff. In some areas the proportion of medical staff supervisors to patients is very low (17, 18). In these cases family members become the first choice to act as supervisors (19). In rural areas many farmers work long hours, so it is not possible for them to perform treatment supervision duties, in which case fully supervised treatment exists in name only. Lienhardt and Ogden proposed that many factors such as different attitudes towards TB, rapidly changing healthcare practices, the high cost of treatment, and social discrimination still faced by TB patients, make DOT unsuitable for continuous TB prevention without external financial support (20). Therefore, they questioned the universal application of DOT. Similar conclusions were drawn from a randomized controlled trial of TB drug resistance (21). Khan et al. showed that the implementation of DOT is less cost-effective than self-medication management (22).

It is difficult to fully implement DOT management for the treatment of TB in many developing countries; it is complicated by the high cost of healthcare and differences in economic levels, geography, availability of transportation, and patient preferences. Though DOT is considered the best management strategy currently available and is widely recommended by the WHO (23), its effectiveness is still controversial. It was shown in ten self-treatment management trials that DOT is not more effective than self-treatment (24).

Research also suggested that it is not possible to achieve the WHO's aim that 85% of TB patients complete their treatment without other treatment support measures (25).

There are about 1 million active TB patients diagnosed each year in China. When dealing with such a large epidemic, it would seem reasonable to target different populations and patients with different management strategies instead of employing a single strategy across the board, even one as well-established as DOT.

1.3 Study results in phase 1 project

In response to these problems of implementing the DOT, current developments in treatment management involve utilizing new technology and research to discover more effective and efficient ways of ensuring that patients take their medication. In 2010, China began a TB control study on the feasibility and operability of new treatment methods for the TB patients. The study, organized and implemented by The National Center for TB Control and Prevention of the China CDC, was conducted in 36 counties in Chongqing, Jiangsu, Heilongjiang and Hunan provinces, with funding from the Bill &Melinda Gates Foundation (26).

1.3.1 Brief description of the trial

Mobile text messaging and medication monitors have the potential to improve adherence to tuberculosis (TB) treatment and reduce the need for directly observed treatment (DOT), but they have not been properly evaluated in TB patients. We assessed the effectiveness of text messaging and medication monitors to improve medication adherence in TB patients.

In a pragmatic, cluster-randomised trial, 36 districts/counties (each with at least 300 active pulmonary TB patients registered in 2009) within the provinces of Heilongjiang, Jiangsu, Hunan, and Chongqing, China, were randomised to one of four case-management approaches and received reminders from text messages, a medication monitor, both, or neither (control) using stratification and restriction. The intervention arms had reminders for drug intake, reminders for monthly follow-up visits, and a recommendation to switch patients with adherence problems to more intensive management or DOT. In all arms, patients took medications out of a medication monitor box, which recorded when the box was opened. Patients were followed up for six months. The primary outcome was the percentage of patient-months on TB treatment where at least 20% of doses were missed as measured by pill count and failure to open the medication monitor. Secondary outcomes included additional adherence and standard treatment outcome measures. Interventions were not masked to study staff and patients.

1.3.2 Main findings

From June 2011 – March 2012, 4292 new pulmonary TB patients were enrolled across 36 clusters. A total of 119 patients (by arm: 33 in control, 33 text messaging, 23 medication monitor, 30 combined) withdrew from the study in the first month because they were reassessed as not having TB by their managing doctor (61 patients) or were switched to a different treatment model due to hospitalisation or travel (58 patients), leaving 4173 TB patients (by arm: 1104 in control, 1008 text

messaging, 997 medication monitor, 1064 combined). The percentage of patient-months on TB treatment where at least 20% of doses were missed was 29.9% in the control arm, 27.3% in the text messaging arm (adjusted mean ratio [aMR] of 0.94, 95% confidence interval [CI]: 0.71, 1.24), 17.0% in the medication monitor arm (aMR 0.58, 95% CI: 0.42, 0.79), and 13.9% in the combined arm (aMR 0.49, 95% CI: 0.27, 0.88).

Table 1: Summary of results from the first trial.

Study arm	**Number of patients**	**Geometric mean of cluster level endpoint**	**Unadjusted analysis**		**Adjusted analysis**[1]	
			Mean ratio (95% CI)	**p-value**	**Mean ratio (95% CI)**	**p-value**
Primary endpoint – Percentage of months with at least 3/15 doses missed						
Control	1091	29.9%	1		1	
Text messaging	996	27.3%	0.91 (0.66, 1.25)	0.536	0.94 (0.71, 1.24)	0.622
Medication monitor	992	17.0%	0.57 (0.40, 0.81)	0.004	0.58 (0.42, 0.79)	0.002
Combined	1059	13.9%	0.46 (0.25, 0.86)	0.018	0.49 (0.27, 0.88)	0.020
Poor treatment outcome (any of failure, death, patient loss to follow-up)						
Control	1066	8.6%	1		1	
Text messaging	966	3.9%	0.45 (0.18-1.16)	0.092	0.44 (0.17-1.13)	0.084
Medication monitor	955	6.1%	0.70 (0.32-1.53)	0.264	0.71 (0.33-1.51)	0.346
Combined	992	8.8%	1.01 (0.46-2.22)	0.973	1.00 (0.45-2.20)	0.991
Patient loss to follow-up						
Control	1057	8.5%	1		1	
Text messaging	954	3.6%	0.42 (0.18-1.00)	0.050	0.42 (0.18-0.98)	0.046
Medication monitor	946	5.0%	0.58 (0.23-1.51)	0.243	0.61 (0.25-1.51)	0.264
Combined	982	7.6%	0.90 (0.38-2.08)	0.783	0.90 (0.38-2.09)	0.784

CI=confidence interval;

[1] adjusted for individual level variables of gender, age category, occupation, living in household registration place or not, distance from nearest TB clinic, education level, income category, smear result at start of treatment and cluster level variable of pre-randomisation strata (rural/urban).

Patient loss to follow-up was lower in all three intervention arms, but there was only statistical evidence for this reduction in the text messaging arm (aMR 0.42, 95% CI: 0.18-0.98).

Equipment malfunction or operation error was reported in all study arms. Analyses separating those with and without medication monitor problems did not change results. Initiation of intensive management was underutilized [34].

1.3.3 Limitation of end-points

Based on our results, the use of medication monitor shows great promise. In a setting such as China where universal use of DOT is not feasible, innovative approaches to enable patients to adhere to TB treatment are needed. Widespread use of medication monitors in national TB control programs can benefit from the development of a low-cost and reliable medication monitor as well as evidence that its use can improve clinical outcomes.

However, the improvements in adherence seen in the medication monitor and combined arms may not translate directly into improvements in patient cure. Our endpoint of poor treatment outcome

was underpowered and was only measured at the end of treatment and almost no patients failed treatment (based on smear microscopy). Hence, we want to observe the long-term impact of using medication monitors on a clinical endpoint using culture-confirmed cure.

2. Aims and objectives

The overall aim of the trial is to investigate whether drug-sensitive pulmonary adult TB patients managed using a treatment strategy including a medication monitor for reminding daily drug dosing and monitoring adherence patterns, and targeted intensive management of patients with poor adherence patterns (intervention arm) have better clinical and adherence outcomes compared with patients managed according to standard of care (control arm).

Specific objectives are:

Primary objective
To compare, among drug sensitive pulmonary TB adult patients, a composite poor outcome measured 18 months from the start of treatment between intervention and control arms.

Secondary objectives:

1. To compare poor treatment outcome at the end of treatment between intervention and control arms
2. To compare a composite poor outcome measured 12 months from the start of treatment between intervention and control arms
3. To compare lost to follow-up during treatment between intervention and control arms
4. To compare adherence outcomes, measured using the medication monitor, between intervention and control arms
5. To compare the costs and cost-effectiveness of the intervention and control arms

Exploratory objectives

1. To compare two month smear conversion among patients smear positive at the start of treatment between intervention and control arms

3. Methods

3.1 Study design

Open (unblinded) pragmatic cluster-randomised trial, with districts/counties as the unit of randomisation.

Districts/counties (clusters) will be selected based on pre-defined inclusion criteria.

TB patients satisfying the inclusion criteria and diagnosed in the selected clusters will be recruited into the study and followed up for 18 months after the start of treatment (that is during treatment period [usually 6 months] and a period following the end of treatment, giving a total follow-up time of 18 months). Patients in clusters randomised to the control arm will receive current standard of care which includes a decision by patient and managing doctor on who observes treatment. Patients in clusters randomised to the intervention arm will receive a treatment strategy including a medication monitor for reminding daily drug dosing and monitoring adherence patterns, and targeted intensive management for patients with poor adherence patterns.

3.2 Study sites

The study will be conducted at TB dispensary/hospitals in districts/counties in a mixture of urban and rural settings in three provinces of Zhejiang, Jiangxi, Jilin in China.

Inclusion criteria for participating districts/counties:

- at least 300 pulmonary TB patients in 2014
- access to Gene Xpert & culture
- TB services supplied by a TB designated hospital or TB dispensary
- Implementing the daily chemotherapy scheme

Exclusion criteria for participating districts/counties:

- Participating in another study
- Be unwilling to participate in the study

3.2.1 Randomisation of districts/counties

Randomisation of clusters to intervention or control arm will be conducted by stratification and restriction. Type of provider, province & number of TB cases in 2014 will be considered in the randomisation.

3.3 Study population

The study population comprises adults with pulmonary TB. In order to maximise generalisability, we plan to make the trial as inclusive as possible.

3.3.1 Patient selection criteria

Inclusion criteria:

- New pulmonary TB case
- Gene Xpert-positive and rifampicin-sensitive
- Likely to be in the study area for next 18 months; or able to attend the 12 and 18 month follow-up visits after the start of treatment
- Patient agrees to fixed-dose combination (FDC)
- Patient is receiving treatment from TB designated hospital or TB dispensary at the county (district) level and treatment management in the community health service centers
- Receiving daily chemotherapy regimen

Exclusion criteria:

- Aged <18 years;
- Communication impairment
- Gene Xpert negative, or Gene Xpert positive and rifampicin resistant, or Gene Xpert invalid/not known
- Travel planned during the intensive phase
- Patients known at the start of treatment to require greater than 6 months of treatment (for example patients with tuberculous pleuritis, diabetes, silicosis, extra-pulmonary TB, trachea and bronchus tuberculosis)
- Known to be HIV-positive
- Custody patients (prison and medicine rehabilitation center)

- Patients who have been hospitalised continuously for the first two months of treatment

3.4 Patient selection procedures

Consecutive adult patients starting TB treatment at the TB dispensary/hospital in the county/district will be offered enrolment into the study. A base form will be completed for all active new pulmonary TB patients whether they are screened or not.

3.5 Intervention and control arms

National TB Control Programme guidelines in China require drug sensitive TB patients to take fixed-dose combination tablets daily for six months.

Patients in both the control and intervention arms will be asked to keep their medication in a medication monitor box, which records the date and time of each opening. Patients in the intervention arm will bring the box to each monthly follow-up visit, at which time the doctor will connect it to the computer and download the data.

Data from the box for patients in the control arm will be downloaded once, at the end of treatment or earlier if patient stops using the medication monitor before the end of treatment; the doctor will not be able to access these adherence data.

3.5.1 Control arm

In brief, patients, in consultation with the doctor, choose whether to take their tablets under direct observation by a healthcare worker, direct observation by a family member, or self-administered. (See appendix 3 for more details). After each dose is taken, a mark is put on a TB treatment record card, which is shown to the doctor at the monthly follow-up visit as a way of determining adherence.

During the treatment period the CDC, township & village doctors make visits to the patient as defined by current practice.

Details are summarised in table 2.

3.5.2 Intervention arm

In brief, the medication monitor will beep to remind the patient (i) to take their daily medication and (ii) when their next monthly follow-up visit is due. In addition, the doctor will be able to see how often the medication monitor has been opened and can then use these data to determine whether the patient needs additional support.

During the treatment period the CDC, township & village doctors make visits to the patient as defined by current practice.

Details are summarised in table 2.

Table 2: description of the control and intervention arms

Service Contents	Intervention arm	Control arm
Supervision method for daily dosing	The patient is supervised by the medication monitor for daily dosing. The medication monitor will alert the patient to take their next dose using a buzzer sound and light: the buzzer sound rings and green light flashes for 5 minutes, followed by 5 minutes where both alerts stay off; followed by the buzzer sound ringing and green light flashing for 5 minutes, followed by 5 minutes where both alerts stay off; followed by the buzzer sound ringing and green light flashing for 5 minutes. If the box is opened during this period then the alarm is cancelled until the next day. If the box is opened four hours before the set time the alarm is cancelled until the next day. The time of daily medicine reminders are set by doctors in designated medical institutions at the county (district) level at enrolment and may be changed at subsequent follow-up visits.	Patients choose one of the following methods of treatment adherence supervision in consultation with their doctor at the start of treatment: (1) Medical staff's supervision; (2) Family members' supervision; (3) Self-administration. (see appendix 3)
Reminding of follow-up visits	A yellow (amber) light is used to remind patients to attend their monthly follow-up visit – this is set to a date before the scheduled clinic visit, and turning on daily up to the actual visit date (refill) to obtain monthly medications. The yellow light comes daily during this period at the agreed time for 30 minutes.	If a patient does not attend the scheduled follow-up visit, the hospital/dispensary doctor, nurse or other staff member contacts the patient (using patient or family member phone) and asks him/her to return to the hospital/dispensary for follow-up. If a patient does not attend a follow-up visit three days after the scheduled date the

	A pictogram label is attached to the monitor indicating to the patient that sputum should be collected before returning to the clinic at months 2, 5 and 6. If a patient does not attend the scheduled follow-up visit, the hospital/dispensary doctor, nurse or other staff member contacts the patient (using patient or family member phone) and asks him/her to return to the hospital/dispensary for follow-up. If a patient does not attend a follow-up visit three days after the scheduled date the hospital/dispensary doctor immediately informs the CDC. The CDC and township hospitals inform the village doctor. The village doctor is required to visit the patient and supervise them to visit the designated medical institution to get medications or receive sputum examination within 24 hours after receiving the follow-up notice from the higher-level agency. This is the same approach as described in the control arm.	hospital/dispensary doctor immediately informs the CDC. The CDC and township hospitals inform the village doctor. The village doctor is required to visit the patient and supervise them to visit the designated medical institution to get medications or receive sputum examination within 24 hours after receiving the follow-up notice from the higher-level agency.[1] A pictogram labels will not be used for patients in the control arm.
Monthly follow-up visit by the patient to the doctor	At the monthly follow-up visits (months 1-6) the TB doctor at the county (district) level exports and saves the medicine-taking log from the electronic medication monitor. The doctor shows the drug-intake summary to the patient, and discusses the patient's drug-intake summary and the importance of timely drug-intake. A summary of the patient's monthly adherence data will be printed out and given to the patient at each follow-up visit. Based on the log for the last month from the electronic medication monitor the doctor will determine whether an adjustment to the	Patients are seen at the monthly follow-up visits (months 1-6) by the TB doctor at the county (district) level. If the TB treatment record card indicates doses have been missed the doctor asks the patient about why drugs have been missed and educate him/her about the important of taking timely and regular drug intake. This is current NTP practice.

	way of managing patients' medication is required. Actions are described below. The Doctor also checks if there has been any malfunction and /or low battery (indicated by the red light), and if so resolves the problem.	Data from the box will be downloaded once, at the end of treatment or earlier if patient stops using the medication monitor before the end of treatment; the doctor will not be able to access these adherence data. In the event of the red light (indicating to the user a malfunction and /or low battery) turning on, the patient will be encouraged to bring the medication monitor to the follow-up visit for the Doctor to resolve the problem.
Visit by doctor to the patients	(1) The CDC doctor visits every patient once during the intensive and continuous phases. During the visit, patients' medicine-taking situation and the use of electronic medication monitor shall be understood, and if some patients are reluctant to take drugs, the reason shall be understood and they should be educated about keeping healthy. (2) Doctors from community service centers will visit the patient once a month to confirm use of electronic medication monitor, monitor adverse reactions. If any errors in using the electronic medication monitor these are reported to the organization for tuberculosis prevention at the county (district) level immediately.	Same activity as the NTP: (1) The CDC doctor visits each patient once during the intensive and continuous phases. During the visit, the doctor asks about the patient's drug-adherence, gives advice about timely & regular drug intake and educates the patient about keeping healthy. (2) Doctors from community service centres doctor will visit the patients who are self-supervised or have family member supervision every 10 days in the intensive phase, and once a month in the continuous phase.
Judgment and handling of missing doses	The TB doctor at the county (district) level assesses medication adherence based on the medicine -taking log recorded by the electronic medication monitor, excluding time periods when the patient had been in hospital or travelling, as follows:	No specific requirement

	<20% doses missed: reasons for doses missed will be ascertained and the patient educated about keeping healthy. There will be no change to the management of the patient. 20-50% doses missed (first occasion): the township hospital doctor will be informed. Township doctors will be asked to visit the patients every two weeks and village doctors will be asked to visit the patients every week. There will be no change to the management of the patient. >50% doses missed or 20%-50% doses missed (second occasion): the management mode of taking medications is changed into "taking medicine in the presence of medical staff", namely, village doctors are required to directly supervise patients to take medicine in person.	

NTP National TB Control Program; CDC Center for Disease Control and Prevention

[1]The description for the control arm for this component will become NTP policy in mid-2016.

[2]The NTP guidelines are that patients are required to visit the doctor at the end of 2,5,6 month during the treatment at least. However, in approximately one third of clinics, the patient is asked to return monthly. For the purposes of the study all patients in the control arm are seen by the doctor every month over the treatment period in order to help ensure the medication monitor is being used.

A red light on the medication monitor is used to alert the user to a malfunction and /or low battery.

3.6 Withdrawals and exclusions

3.6.1 Post-enrolment exclusions

The following lists the limited reasons for post-enrolment exclusions:

(i) Participants whose Xpert result was not known at enrolment and found to either be Xpert-negative or Xpert-positive and rifampicin resistant
(ii) Participants who stopped taking the FDC within the first 1 month due to an adverse reaction.
(iii) Participants who permanently stopped the treatment management model within the first 1 month due to, for example, travel, hospitalisation, etc.
(iv) Participant subsequent found to be HIV-positive
(v) Participants who were subsequently required to extend their treatment for greater than 6 months due tuberculous pleuritis, diabetes, silicosis, extra-pulmonary TB, trachea or bronchus tuberculosis

Participants satisfying the exclusion criteria listed above will be withdrawn from the study and not contribute to study outcomes. The reason for exclusion will be documented and care will be taken not to inappropriately exclude patients who are in fact lost to follow-up.

3.6.2 Patient-initiated withdrawals

Participants are free to withdraw from the study at any time. In the case of patient-initiated withdrawal, not fulfilling any of the post-enrolment exclusion criteria listed above, the study team will request the patient allows access to data on end of treatment outcomes and, where possible, sputum samples collected at the end of treatment, and 12 and 18 months from starting TB treatment.

3.7 Outcome measures

3.7.1 Primary endpoint:

Composite poor outcome measured over 18 months from start of TB treatment.

The composite poor outcome is defined as poor outcome at the end of treatment (death, treatment failure or loss to follow-up) or subsequent recurrence (culture positive for TB or (re-)starting TB treatment in the follow-up period.

3.7.2 Secondary outcomes:

Clinical outcomes:

1. Poor outcome at the end of treatment (death, treatment failure or loss to follow-up)

2. Composite poor outcome measured over 12 months from start of TB treatment.
3. Lost to follow-up during treatment

Adherence outcomes:

4. The percentage of months in which the patient missed at least 20% of doses, measured using data from medication monitor box.
5. The percentage of doses missed, measured using data from the medication monitor box each month.

3.7.3 Exploratory outcomes:

1. Two-month smear conversion among patients smear positive at the start of treatment

3.7.4 Cost effectiveness outcomes:

1. Mean cost per patient treatment month for each arm
2. Mean cost for each arm, and incremental cost of the intervention compared to control arm per patient completing treatment
3. Mean cost for each arm, and incremental cost of the intervention compared to control arm per death and DALY averted
4. Mean number for each arm, and incremental number of the intervention compared to the control of cases of catastrophic cost

3.8 Study procedures

National TB Control Programme guidelines in China require drug sensitive TB patients to take fixed-dose combination tablets daily for six months, with follow-up visits to dispense medication, check for side effects and emphasise continued adherence.

3.8.1 Enrolment procedures: intervention and control districts/counties

Participants will be screened and offered enrolment into the study, if eligible, at the time they are determined eligible to start tuberculosis treatment. Figure 1 describes the screening and enrolment flow.

At enrolment, following informed consent, participants will complete a questionnaire covering

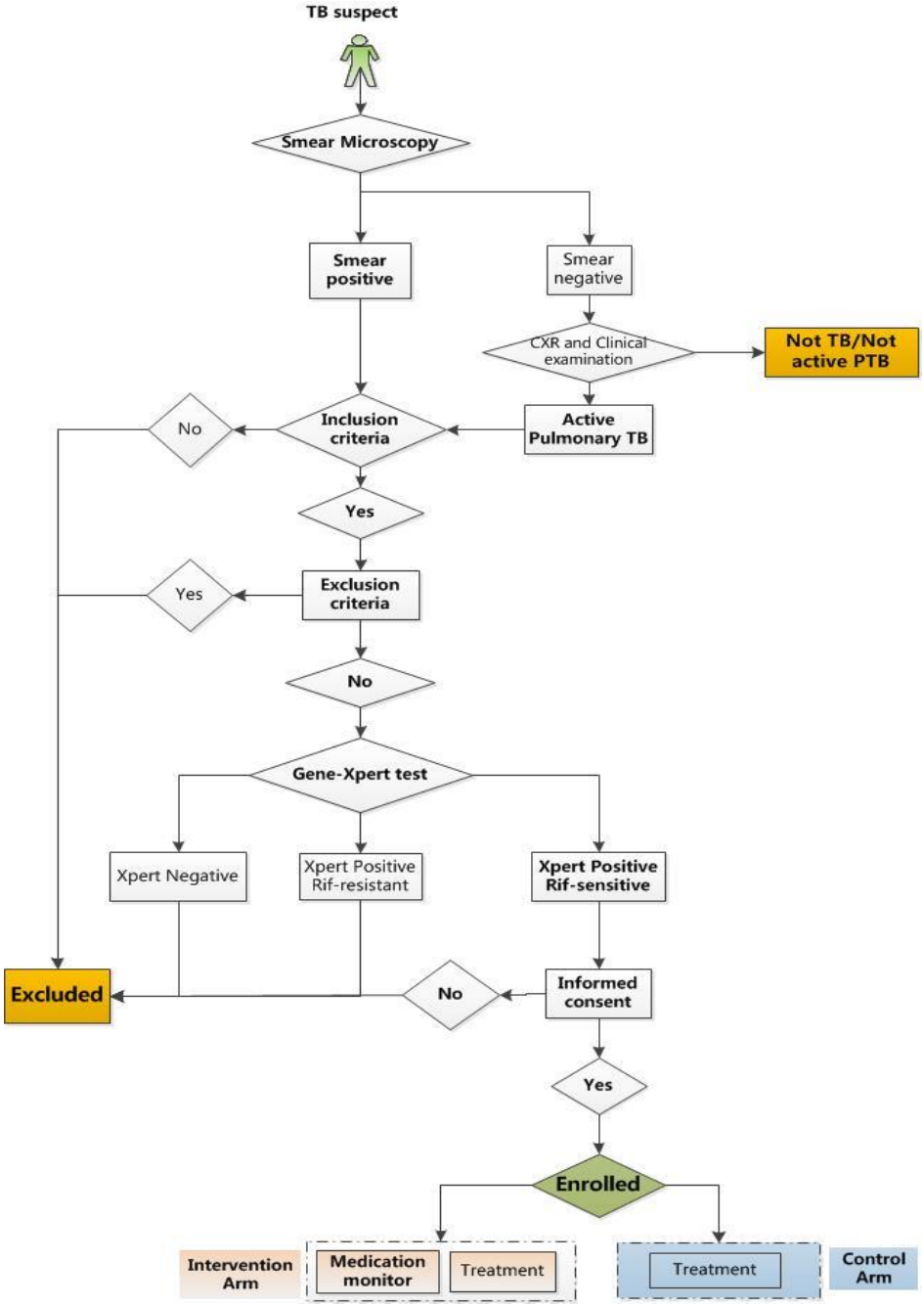
- Locator information
- Socio-demographic information

- Height and weight (for BMI)
- Routine supervision of treatment (control patients only)

Participants in both intervention and control districts/counties will also be asked to give a sputum specimen for microscopy and Gene Xpert. Ideally the results of these diagnostic tests will be known on the same day in which case if the participant satisfies the inclusion criteria he/she will be offered enrolment into the study. If sputum results are not available on the same day participants who satisfy the inclusion criteria other than the Gene Xpert criterion will be offered enrolment into the study and if subsequently found not to satisfy the Gene Xpert criterion will then be withdrawn from the study (see section 3.6.1).

Participants are given a medication monitor box and 30 days of medication, which they will be asked to keep in the medication monitor box. The box records the date and time of each opening. A follow-up visit at the TB dispensary/hospital is set for 30 days time.

Figure 1: Screening and enrolment flow



3.8.2 During treatment procedures: intervention and control districts/counties

Participants will return to the TB dispensary/hospital for each of five monthly follow-up visits (months 1-6).

Patients in the intervention arm will be required to bring their medication monitor box to each monthly follow-up visit, at which the doctor or designee will connect it to the computer and download the data. Information will be collected on travel, inpatient visits, side effects and any problems with the box. In the control arm data from the box will be downloaded once, at the end of treatment or earlier if patient stops using the medication monitor before the end of treatment; the doctor will not be able to access these adherence data. In either arm, if applicable, the doctor or designee will assist the patient to fix any problems with the box and if necessary to replace it.

If a patient is found to be Gene Xpert negative or Gene Xpert positive and rifampicin resistant on the sputum collected at enrolment, then they are withdrawn by day 30 (first follow-up visit), as described in section 3.6.1.

Sputum will be collected at month 2 for an exploratory endpoint of two-month smear conversion.

Sputum will be collected for culture (using Lowenstein-Jensen) and smear at the end of treatment to enhance the definitions of treatment "cure" and "failure".

The medication monitor data will cease to be collected in the following situations:

(i) Patients who have been excluded from the study (see section 3.6.1) or patient-initiated withdrawal (see section 3.6.2);
(ii) Patients who die during the course of treatment
(iii) Patients who are lost to follow-up during treatment
(iv) Patients who are defined as failing treatment
(v) Patients who have stopped taking FDC or stopped using the medication monitor for any other reason.

3.8.3 Post treatment procedures: intervention and control districts/counties

Following the end of treatment, the treatment outcome, as recorded by the National TB Control programme, will be abstracted.

Patients defined as cured or completed treatment will be followed up after the end of treatment.

Patients will be seen at the TB hospital/dispensary at two further follow-up visits, 12 and 18 months after start of treatment, for a chest x-ray and to collect a sputum specimen for culture in order to measure recurrence. Patients will also be asked if they have re-started TB treatment, and if so data information from the TB register and TB diagnosis will be abstracted. The hospital/dispensary doctor, nurse or other staff member will help facilitate patient attendance at these post-treatment follow-up visits.

In addition these patients will be telephoned at months 9 and 15 after the start of treatment and asked about TB symptoms and whether they have re-started TB treatment. Patients with TB symptoms will be advised to attend a health care clinic. If a patient has restarted TB treatment information from the TB register and TB diagnosis will be abstracted.

If a patients who have moved to another county/district, they will be asked to return to the original TB hospital/dispensary for their follow-up visit. If this is not feasible, an attempt will be made by the local TB control programme in the new country to collect a sputum specimen for culture and chest x-ray.

A small incentive will be given to patients for attending the 12 and 18 month follow-up visits to compensate for travel costs and for their time.

Study procedures are summarised in Table 3.

Table 3: summary of study procedures for intervention and control arms

	Screening & Enrolment	Month 1	Month 2	Month 3	Month 4	Month 5	6 months [or end of treatment]	9 months[1]	12 months[1]	15 months[1]	18 months[1]
Screening for eligibility including sputum for GeneXpert	√										
Informed consent	√										
Locator information	√		[√]				[√]		[√]		
Baseline questionnaire	√										
Sputum for smear	√		√			√	√				
Sputum for culture							√		√		√
Chest x-ray examination							√		√		√
Patient record review (end of treatment outcome)							√				
End of treatment questionnaire							√				
9 & 15 month phone interview[1]								√		√	
12 & 18 month questionnaire[1]									√		√
Intervention arm only:											
Measurement of whether intensive management/ DOT initiated		√	√	√	√	√					
Adherence data – downloaded from MM		√	√	√	√	√	√				
Control arm only:											
Control arm: measurement DOT/family supervision	√		√				√				
Adherence data – downloaded from MM							√*				

[√] update if changed. MM medication monitor; * earlier if patient stops using the medication monitor before the end of treatment; [1]from start of treatment

3.9 Ascertainment of outcomes

All participants will provide sputum at baseline, 2, 6 (or end of treatment), 12 and 18 months after the start of treatment and interviewed at 6, 12 and 18 months after the start of treatment to determine primary and secondary outcomes (see section 3.6 and Table 3). In addition data from the TB record will be abstracted to define treatment loss to follow-up and other TB treatment outcomes. Post end of treatment, participants will be actively traced, if necessary, using locator information obtained at enrolment and at follow-up if appropriate.

The treatment outcomes will be determined as binary outcomes, according to the following table, such that having at least one "yes" will be recorded as poor outcomes and at least one "no" without any "yes" will be recorded as good outcome.

Electronic data from the medication monitor box will be used to define adherence outcomes.

Table 4: Ascertainment of primary and secondary outcomes

	Primary outcome	Secondary outcomes	
	Poor outcome	Poor treatment outcome	Lost to follow-up
NTP outcome:			
Cured	N/A	No	No
Completed treatment	N/A	No	No
Failed treatment	Yes	Yes	No
Lost to follow-up	Yes	Yes	Yes
Death	Yes	Yes	N/A
Side effect	Yes	Yes	Yes
Changed to MDR treatment	Yes	Yes	No
Positive culture results:			
Six months (end of treatment)	Yes	Yes	N/A
12 months	Yes	N/A	N/A
18 months	Yes	N/A	N/A
Negative culture at 18 months and:			
Cured	No	N/A	N/A
Completed treatment	No	N/A	N/A
CXR results satisfying case definition for TB:			
12 month visit	Yes	N/A	N/A
18 month visit	Yes	N/A	N/A
Self-reported started TB treatment:			
12 month visit	Yes	N/A	N/A
18 month visit	Yes	N/A	N/A

Death or lost to follow-up post six months	N/A	N/A	N/A

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3.10 Pilot study and run-in period

A pilot study will be conducted in four counties/districts before the start of the enrolment into the trial. The purpose of the pilot study is to field test: the medication monitors and associated software; recruitment process; the monthly adherence feedback given to patients by the managing Doctor; case report forms. The pilot study will be conducted in four counties/districts reflecting a mix of intervention and control counties/districts and different TB services (designated hospital and TB dispensary), and with the aim of enrolling around 100 patients. TB patients satisfying the inclusion criteria for the main trial will be offered enrolment into the pilot study following informed consent, and will be followed up for three months. See appendix for the pilot study patient information sheets and informed consent forms.

Following the pilot study all 24 counties/districts will have a 3-month run-in period. This period will be used to help staff familiarise themselves with the recruitment and follow-up processes and ensure all monitoring processes are being implemented. TB patients recruited during this period will be followed up the end of treatment but not contribute to the trial outcomes.

4 Economic analyses

The economic evaluation will compare the cost-effectiveness of the medical monitor (intervention arm) to the standard of care (as defined by the control arm practice within the study) within a partial 'extended economic' evaluation framework. The methods used will adhere to the Bill & Melinda Gates Foundation reference case standards.

The **population** being studied is the trial population. However, if the intervention has a positive outcomes, the economic evaluation will include a modelled analysis to allow for the generalisation of the results to other areas in China, informing policy through the assessment of affordability and cost-effectiveness more broadly. The **intervention** being studied is the medical monitor, against the **comparator** of the 'standard of care' in the control arm. In addition, the intervention will be compared against different combinations of observation approaches, to explore cost-effectiveness for other populations.

The **outcomes**, are as below and include: cost measurements to assist in the assessment of affordability; cost-effectiveness outcomes; and equity outcomes.

- Mean cost per patient treatment month for each arm
- Mean cost for each arm, and incremental cost of the intervention compared to control arm per patient completing treatment
- Mean cost for each arm, and incremental cost of the intervention compared to control arm per death and DALY averted
- Mean number for each arm, and incremental number of the intervention compared to the control of cases of catastrophic cost

Cost-effectiveness measures will only include the health benefits for a population of TB patients starting treatment, and will exclude indirect health benefits to others, through reductions in TB transmission. These indirect health benefits could be added in at a later stage, working together with

others who have been supporting TB control in China using transmission modelling; depending on the study results.

The study will be conducted from a **societal perspective** and include both patient and provider incurred costs. The **time frame** of the study is the lifetime of the study cohort (those on TB treatment) and therefore the downstream costs of continuing to treat relapse cases after the study period will be included.

The economic evaluation will require the collection of primary cost data of both patient and provide costs, given the current scarcity of secondary cost data from China. As to not interfere with the overall study data collection, primary cost data collection will be conducted as a stand-alone 'costing study', which will be submitted for separate ethics approval at a later data. This study will be designed in the first year of the trial, once local health economics partners have been identified. The economic evaluation will however use the primary data collected on patient events (visits, drugs and tests received) and outcomes, as detailed below and above, from the main trial data collection instruments.

The analysis will be carried out in two stages. First, **a within trial analysis** will be conducted comparing cost-effectiveness within the trial population and period, using statistical methods to estimate the probability that the intervention is cost-effective. This analysis will also examine the numbers of cases of catastrophic costs averted by the intervention. The second stage will use a **decision analytical model** to extend these results over time to include downstream costs (such as the further treatment of relapses). This second analysis will also be used to estimate budget impact over a five year period, and to model and explore the transferability of results to other populations. If the trial is unsuccessful in terms of primary outcomes only the first stage of the analysis will be carried out. The study will used standard methods to analyse both the within trial and modelling results. Results will be presented using cost-effectiveness planes, and cost-effectiveness acceptability curves. These show the probability that the intervention will be cost-effective. Basic and probabilistic sensitivity analyses will be conducted to interrogate uncertainty. Trade-offs between equity (who benefits and poverty cases averted) and efficiency (cost-effectiveness) will be examined. The study implementation will be carried out encouraging participation and involvement of decision makers, in order to ensure that the study results are presented and interpreted in way that is optimal in terms of decision support. Results will be reported adhering to the CHEERS guidelines (27).

5. Data management

5.1 Data management responsibilities

The data management responsibilities are as follows:

- Oversee and coordinate the management of data;
- Oversee data quality control, including running data queries;
- Ensure the availability of databases to capture data from participant interview and case note abstraction from medical records at the end of treatment;
- Ensure the safekeeping of data and access control;
- Ensure proper data management documentation is maintained;
- Manage data reporting processes;
- Manage integration of data from different sources;

- Ensure processes are in place for backup and data recovery.

5.2 Application and database

The database and the capturing application will be developed using appropriate software. Scheduled backups will be done on a monthly basis. A password will be required to gain access to the database. When data sets are generated for data analysis, personal identifiers will be removed.

5.3 Quality control

Data will be validated on entry, using range and consistency checks. Logical data checks will also be performed on the data. Incomplete and incorrect data queries will be sent back to sites electronically for error resolution. Study records (consent forms, CRFs, screening logs) will be kept in a secure location accessible only to authorised study staff. All records will be archived in a secure storage facility for at least ten years after the completion of the study.

6. Statistical considerations

6.1 Sample size estimation

Recently published data from TB treatment trials and our own TB adherence trial in China have helped inform sample size calculations for this trial. Recently completed phase III TB treatment trials, conducted under clinical trial conditions, found the percentage with poor outcome at the end of treatment of 8.5%-11.2%, and by 18 months from enrolment ranging from 13.2%-15.7%, in the control arm. Note these data are collected under clinical drug trial conditions and in a pragmatic setting poor outcomes likely to be higher.

Data from our first adherence trial in China found a combined poor outcome at the end of treatment or 9.2%. This was in the absence of culture to define treatment success and so it is reasonable to expect a higher poor outcome when using culture to define end of treatment outcomes.

Table 4a: Summary of data from the first TB adherence trial in China (26) and a observational study conducted in China in 1991, reported by Cao et al. (28).

During treatment:	Estimate	Data source
Default / loss to follow-up	9.20%	phase I CRT, control arm, excluding patients with side effects & transferred out
Treatment failure	0.20%	as above; likely to be higher with culture confirmation
Death	0.50%	as above

Recurrence:	Estimate	Data source
6 months from end of treatment	1.00%	Cao, 1991 - recurrence measured over 6, 12 & 24m from end of treatment using smear microscopy (restricted to new patients)
12 months from end of treatment	2.00%	as above

Table 4b Summary of data from control arms of recent phase III TB treatment trials: modified intent to treat population

	Oflotub (8)	ReMox (7)	Rifaquin (9)
Poor outcome at end of treatment*	8.5% (67/785)	9.9% (55/555)	11.2% (21/188)
Poor outcome at 18m from randomisation**	13.2% (98/744)	15.7% (87/555)	14.4% (27/188)

* includes treatment failure, death, loss to follow-up

** includes poor outcome at the end of treatment and recurrence in a 12 month period after the end of treatment

For the primary outcome we have therefore assumed the percentage with poor outcome 18 months from enrolment in the control arm is 18%.

Assuming 12 clusters per arm, 125 patients per cluster, 5% individuals whose outcome at 18 months cannot be ascertained, composite poor outcome estimated to be 18% in the control arm and taking account of the clustered design, using a coefficient of variation of 0.3, there will be 97% and 85% power to assess 50% and 40% reduction in poor outcome, respectively.
If k=0.25 then assuming 12 clusters per arm, 125 patients per cluster and composite poor outcome estimated to be 18% in the control arm there is 92% and 82% power to assess 40% and 35% reduction in poor outcome, respectively.
We will allow some clusters to over or under-recruit as long as the overall harmonic mean is 125. The maximum number of TB patients enrolled per cluster will be around 150.

6.2 Statistical analysis

All outcomes will be measured in a subset of patients satisfying the modified intent-to-treat population, defined as patients consenting to the study and excludes patients withdrawn from the study as described in section 3.6.1.

Analyses will use methods appropriate for the clustered randomised trial design, giving each cluster equal weight. Quantitative outcomes will be summarised as the mean for each cluster and the difference of means for intervention vs. standard of care arm. For binary outcomes or rate outcomes the overall risk (rate) for each cluster will be calculated, and the ratio for intervention vs. standard of care arm. The standard error for each effect measure will take into account stratified randomisation. An adjusted analysis will be conducted to help reduce variability across clusters with respect to primary and secondary outcomes and, after visual inspection, if imbalance across study arm of patient or district/county level factors is observed.

Subgroup analyses will be conducted for the primary outcome and may include urban/rural, gender, literacy levels, migrant/non-migrant and type of health care provider.

A detailed analysis plan will be finalised prior to the end of data collection.

7. Protection of human participants

This study will be conducted in accordance with requirements of the funders and approving ethics committees.

7.1 Regulatory approvals

Approval will be sought from the Research Ethics Committees of the Chinese Center for Disease Control and Prevention, China and the London School of Hygiene & Tropical Medicine, UK.

7.2 Risks and benefits for participants

Participants in both intervention and control arms will receive around 200RMB (in total) if they attend for study review visits at 12 and 18 months after enrolment, as compensation for their time and travel expenses.

In addition, all patients will benefit from a free Gene Xpert test at enrolment, allowing quick diagnosis of drug resistance to Rifampicin, as well as free cultures at the end of treatment, 12 and 18 months.

7.3 Consent

District/county participation
Participation of district/county will be by the consent of local health bureaus via the Center for Disease Control and Prevention.

Individual participation
Informed consent will be sought from potential participants using information sheets available in Chinese Mandarin. Written informed consent will be sought, using standard consent forms.

7.4 Confidentiality

All study records will be managed in a secure and confidential fashion. All records will be stored at the participating TB clinics and offices at provincial level in locked filing cabinets and access to the records will be restricted to specified study team members. Case report forms will be identified using the participant's study number only, with locator information stored separately.

7.5 Study discontinuation

The study may be discontinued at any time by the funder. No interim analysis is planned.

8. Trial governance and management

8.1 Trial steering committee

The trial steering committee will oversee the trial and monitor its progress. The Trial Steering Committee will advise the Chief Investigator (CI) and trial investigator team.
Membership of the trial steering committee includes Dr Daniel Chin, Dr Wang Lixia, Dr Wang Xiexiu, Dr Bruce Thomas and Dr Katherine Fielding.

8.2 Trial investigator team

The Trial Investigator team will be responsible for the trial design, leading the implementation, data analysis and publication. Membership will include:
Dr Liu Xiaoqiu, Zhang Hui, Jiang Shiwen, Li Xinxu, Huang Fei, Xu Caihong, Li Xue and Gao Yongxin
Dr Katherine Fielding, Dr James Lewis, Dr Anna Vassall

8.3Trial implementation team

Led by Dr Liu Xiaoqiu, the Trial implementation team will be responsible for site training; study monitoring; and day to day implementation of the trial.

9. Logistics

9.1 Timeline

	Y1 (2016)				Y2 (2017)				Y3 (2018)				Y4 (2019)			
	q1	q2	q3	q4	q1	q2	q3	q4	q1	q2	q3	q4	q1	q2	q3	q4
Preparation																
Pilot study																
Run-in phase																
Main study recruitment																
Follow up																
Analysis/write-up																

10. Dissemination plan and publication policy

The research findings will be presented first to national stakeholders, and disseminated to stakeholders. The results will be written up as one or more articles for submission to a suitable scientific journal.

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Appendix 1: Participant information sheets and consent forms

Main study:

1. Participant information sheet: intervention districts/counties
2. Participant consent form: intervention districts/counties
3. Participant information sheet: control districts/counties
4. Participant consent form: intervention districts/counties

Pilot study:

1. Participant information sheet: intervention districts/counties
2. Participant consent form: intervention districts/counties
3. Participant information sheet: control districts/counties
4. Participant consent form: intervention districts/counties

Run-in phase for main study:

1. Participant information sheet: intervention districts/counties
2. Participant consent form: intervention districts/counties
3. Participant information sheet: control districts/counties
4. Participant consent form: intervention districts/counties

Appendix 2: Case report forms and data collection tools

Appendix 3: Description of treatment supporter in the control arm

Patients will choose one of the following methods of treatment adherence supervision in consultation with their doctor at the start of treatment:

(1) Medical staff's supervision
Village doctors will be responsible for keeping the "Notebook for TB Patients' Treatment Management". They shall see observe the patient taking each dose in person in the village clinic or at the patient's home on the day when the patient needs to take medicine. They will keep a record of the drug-taking situation into the "TB Patients' Medicine -taking Record Card" in the "Notebook for TB Patients' Treatment Management".

(2) Family members' supervision
Village doctors are required to meet patients and their supervisors for three times to ask about the supervisors' basic information, including name, telephone number, etc. and then submit such information to doctors at the Center for Disease Control and Prevention at the county level. They also need to train supervisors and make them keep the "Notebook for TB Patients' Treatment Management".
Supervisors are required to see patients taking each dose in person, and to keep a record of the drug-taking situation into the "TB Patients' Drug-taking Record Card" in the "Notebook for TB Patients' Treatment Management".
Village doctors shall visit every patient once every two weeks to determine the medicine-taking situation and the use of the electronic medication monitor and monitor the adverse reaction, which will be recorded into the "Log Sheet of Visits to TB Patients" in the "Notebook for TB Patients' Treatment Management" with village doctors' signature.

(3) Self-administration
Patients who receive self-administrative treatment shall keep the "Notebook for TB Patients' Treatment Management", take drugs punctually and keep a record of the drug-taking situation on the record card.
Village doctors shall visit such patients once two weeks to get the picture of the medicine-taking situation and the use of electronic medication monitor and monitor adverse reaction, which will be recorded onto the "Log Sheet of Visits to TB Patients" in the "Notebook for TB Patients' Treatment Management" with village doctors' signature.