Aims and objectives

This study aims at assessing the efficacy of a tailored message package for educating patients to reduce antibiotics use for symptomatic RTIs via a randomized controlled trial (RCT). The primary measure for assessment is reduction, in the intervention arm as compared with the control arm, in number of days in which antibiotics are used by patients with symptomatic RTIs. The secondary measures include differences between the two arms in:1) patients' knowledge about and attitude toward antibiotics;2) patients' quality of life and symptom severity and duration; 3)times of re-visits to clinics and antibiotics re-prescription for the same RTI episode; 4)times of re-occurrence of RTIs within six or twelve months after the intervention and related health service seeking and antibiotics consumption.

Intervention messages

The intervention consists of 12 short (less than 120 Chinese characters) messages to be sent in 12 consecutive days (once a day) to all the eligible patients in the intervention arm. Detailed content of the messages is given in Table 1.Each of these messages was based on the main drivers of excessive antibiotics as identified from our previous studies in rural Anhui Province and has specific aims. For example, the message, to be sent out on day 1, aims to build trust and assure patient not to worry about common RTI symptoms and most of which will start to relief within a few days and disappear within about one week. Similarly, the message on day 2 aims mainly to provide alternative ways for coping with RTI symptoms so as to divert his/her reliance on medications. While the message on day 3 tries tell the patient not or postpone uptake of the antibiotics prescribed his/her doctor.

Table 1 Messages to be send out to patients with symptomatic respiratory infections

No.	Content of message
Day 1	Dear [PatientName], many thanks for your trust and visit to our clinic for a [DiseaseDiagnosis]. What you were experiencing were mainly [PatientSymptom]. These are very common symptoms. They generally reach a peak within 1-3 days and then begin to relieve gradually. You needn't see any doctor again unless you do not get better within [NormalDuration]. From [DoctorName] with [ClinicName].
Day 2	Dear [PatientName], the best way to deal with most respiratory tract problems such as [DiseaseDiagnosis] is to improve your own body immunity and what you need to do are only the following. First, eat more protein-rich and digestible foods, such as fish soup and

	egg soup. Second, eat more fresh vegetables, fruits, garlic and ginger. Third, have more rest and drink more water. From [DoctorName] with [DoctorAffiliation].
Day 3	Dear [PatientName], most of the respiratory tract health problems such as [DiseaseDiagnosis] do not need antibiotics or anti-inflammation medicine, such as amoxicillin, cephalosporin, and others. The medications your doctor has prescribed for you are to be used only when there are clear indications. In other words, you need only to take fever pills when you have high fever; you need only to take antibiotics when your symptoms do not recover after one week. From [DoctorName] with [DoctorAffiliation].
Day 4	Dear [PatientName], [DiseaseDiagnosis] is easy to transmit to family members and friends. Please avoid contact with them, especially children and the elderly in the local community for 1-2 weeks. Please practice ventilating your living rooms, wearing masks when you go out or meet with people, avoiding eating out and going to crowded place. From [DoctorName] with [DoctorAffiliation].
Day 5	Dear [PatientName], most respiratory tract infections such as [DiseaseDiagnosis] are caused by virus. Generally, they are self-limiting without oral medicines or injections. Antibiotics or anti-inflammatory drugs do not work for viral infections, which can neither ease the severity of symptoms nor shorten the duration. Most importantly, antibiotics can cause antibiotic resistance and various other side effects. From [DoctorName] with [DoctorAffiliation].
Day 6	Dear [PatientName], taking antibiotics (such as amoxicillin and cephalosporin) will weaken your own body immunity, and will kill the good bacteria in your gut as well, or upset the balance of/in your stomach. The more antibiotics you take, the higher chance that you suffer from an antibiotic-resistant-infections. This infection is not only serious, but also difficult to treat and are easy to transmit to family members. From [DoctorName] with [DoctorAffiliation].
Day 7	Dear [PatientName], when you feel unwell with respiratory tract, you should not go to the retail pharmacies to buy antibiotics or anti-inflammatory drugs. China National Medicine Administration Bureau has banned pharmacies to sell anti-inflammation medicine/antibiotics to residents without a doctor's prescription. China National Health Commission advises not to have a drip or take anti-inflammation medicine/antibiotics for coughs, cold, sore throat or earache. From [DoctorName] with [DoctorAffiliation].
Day 8	Dear [PatientName], are you feeling any better from your [DiseaseDiagnosis]? If yes, you seem to be recovering as expected; If not, you should better see your doctor again. As antibiotics do almost no good for respiratory tract infections but have many side effects, we recommend you clearly tell your doctor that you don't want antibiotics whenever you consult a doctor in the future; or, if you are prescribed with antibiotics, ask your doctor whether the antibiotics can be avoided. From [DoctorName] with [DoctorAffiliation].
Day 9	Dear [PatientName], this illness suggests that you are prone to respiratory tract infections. Therefore, you need to strengthen your personal protection in the future. This include: eat more fresh vegetables and fruits; exercise more; wash hands more frequently; avoid crowded places when many people around you are having respiratory symptoms and wear a mask when you go out. From [DoctorName] with [DoctorAffiliation].
Day 10	Dear [PatientName], a certain proportion of respiratory tract infections are influenza. Influenza is highly contagious and easy to increase the extra risk of common health conditions like chronic respiratory tract diseases and cardiovascular and cerebrovascular diseases. Therefore, the State encourages residents to get influenza vaccination, especially for the elderly over 60 years old, patients with chronic diseases, children aged 6 months to 5 years and caregivers for infants under 6 months. From [DoctorName] with [DoctorAffiliation].
Day 11	Dear [PatientName], after recovery, if you have respiratory symptoms next time in the future, please do not hurry seeing a doctor, do not go to retail medicine shop to buy antibiotics without a prescription, and do not take leftover antibiotics. Please practice rest at home, drink more water and eat more protein-rich and digestible food and more fresh vegetables. Most respiratory infections are self-limiting and the symptoms start to relief within a few days. From [DoctorName] with [DoctorAffiliation].
Day 12	Dear [PatientName], this is the last message we plan to send you. We hope you will do as what the messages have suggested and avoid antibiotics use whenever possible. Antibiotics have no effect on most respiratory infections - they cannot relief the severity of symptoms or

shorten the disease duration. On the contrary, antibiotics are easy to cause drug resistance and various other side effects. Thank you for accepting and reading the all the messages and all the best wishes for you. From [DoctorName] with [DoctorAffiliation].

Message tailoring

The study uses a novel computerized method in tailoring the intervention to the need and context of individual patients.Each message is designed as a template inserted with substitution variables to be replaced with relevant values and/or text according to the actual conditions and contexts of the patient under concern. Taking the example of the message to be sent on day 1 (Table 1), it contains seven variables as specified as "[PatientName]", "[DiseaseDiagnosis]" etc. When sent to a patient, for example, named 'Li Si', who consulted doctor Zhang San at 'SanXiaoKou Community Health Center for sneezing, stuffy nose and sore throat and the doctor diagnosed the illness as common cold'. The message is changed into: *Dear Li Si, many thanks for your trust and visit to our clinic for a common cold. What you were experiencing were mainly* sneezing, *stuffy nose and sore throat. These are very common symptoms. They generally reach a peak within 1-3 days and then begin to relieve gradually. You needn't see any doctor again unless you do not get better within 14 days. From Dr Zhang San with SanXiaoKou Community Health Centre.*

The whole process of the message design, modification, translation (of substitution variables) and sending is facilitated by a user-friendly mini computer program. The program automatically extracts data about the patient's name, symptoms and diagnosis from the electronic medical record system routinely in use at all the participating clinics and then translates all the substitution variables into personalized texts or figures. So, implementation of the intervention incurs minimum additional workload for the participating doctors. What they need to do is mainly getting an informed consent from the patient or sending the messages and entering and check the patient's cell-phone number.Figure 1 illustrates how the mini program works. The upper part of the figure provides a name list of all the messages to be sent out to patients. The middle part shows an example message template and each doctor is allowed to modify the template for his/her own patients. While the lower part presents all the substitution variables capable of being automatically translated.

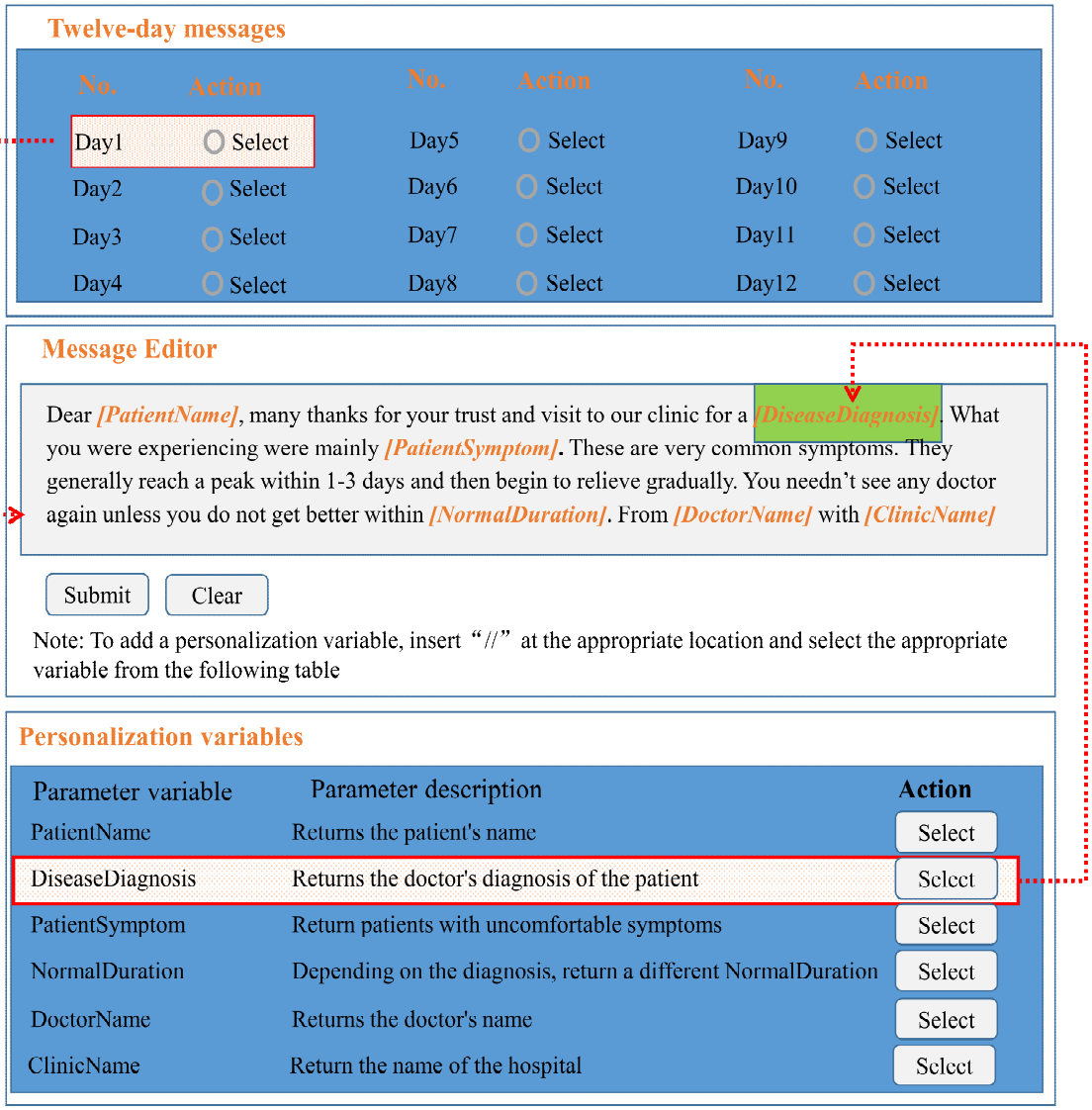

Fig.1example message generated from this template

Selection and randomization of study sites and participants

The RCT is implemented in Anhui, a in land province of China representing the majority of the population in the nation in terms of social, cultural and economic background.The study sites are township or community health centers in the province which are recruited through the following steps: 1) randomly selects 2 cities from 3 regions geographically dispersed across Anhui Province; 2) randomly selects 5 nonadjacent township/community health centers from each of the cities selected; 3) randomly assigns the health centers to the intervention or control group (at a 1:1 ratio); 4)recruits, consecutively,30 patients diagnosed with RTIs from each of the township/community health centers selected(Figure3). The trial randomization will be

conducted by an independent statistician from outside the project team and blinded to both data collectors and analyst.

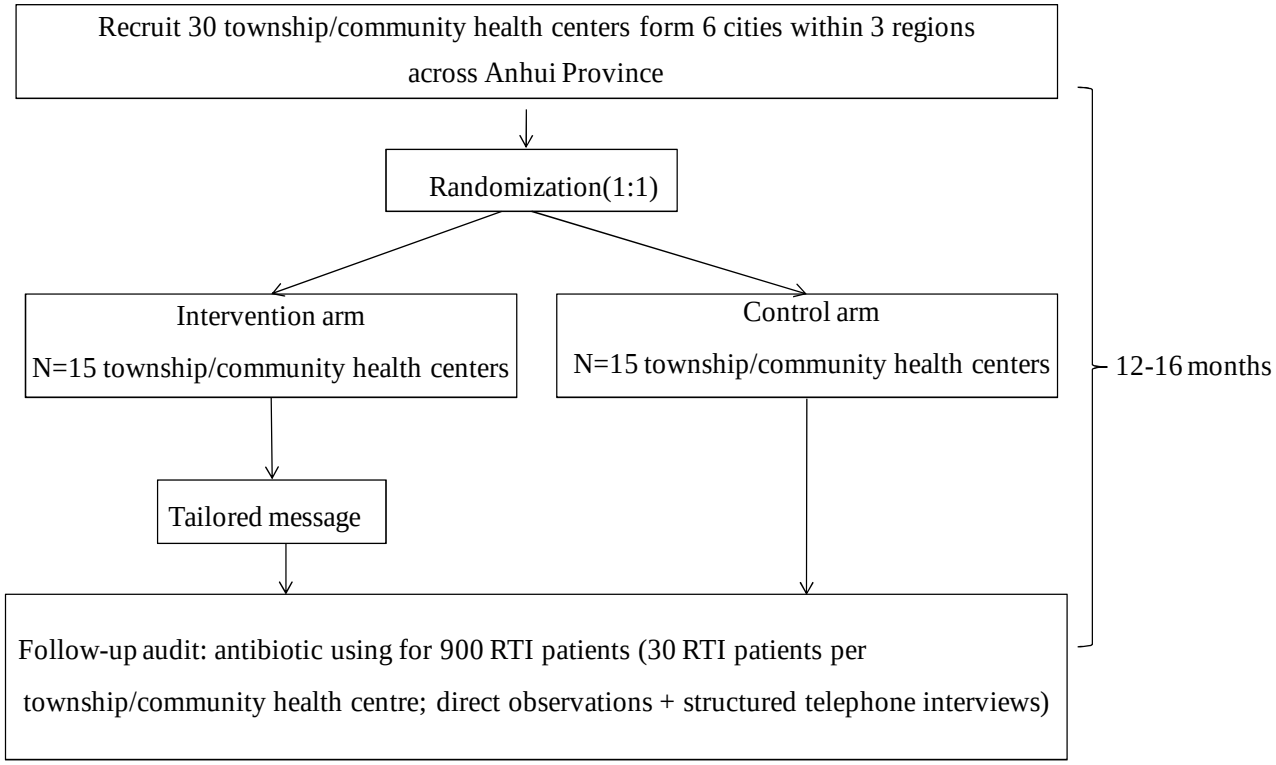

Fig 3 Trial flow chart

Patient participants

For each township/community health center as selected above, a researcher will undertake patient recruitment face-to-face on-site until 30 participants have been recruited.In other words, from the start date of the recruitment at the health center, all incoming patients with RTIs will be invited to participate. Inclusion criteria of patients who are: 1) 18 years or older and able to give consent to participate in the patient survey and/or follow-up interviews; 2) diagnosed with an RTIs in the recruitment consultation: blocked/runny nose, coughing with or without sputum, dry/sore throat, breathing problems, fever, ear inflammation (blocked ear, tinnitus, ear discharges, earache); 3)be able to read messages; 4）have a mobile phone that can receive messages.

Sample size calculation

The sample size of recruiting patients is calculated on base of the primary intervention assessment measures, i.e., changes in number of days of antibiotics using by the

patient. Our previous study recorded the number of days of antibiotics using by the patient was 4.35±2.06 for rural township health centers in Anhui province. There is no internationally agreed minimally important difference in the days of patients using antibiotic. However, we anticipate that a reduction of at least 15% in the days of antibiotic would represent a meaningful change at the population level. So, we assume that the intervention group is 20% lower than the control group.

Based on our previous study results, we suppose: 1) the days of antibiotics using by the patient reduction was about 0.87 days as compared between the intervention and control group; 2) standard deviation of the days of antibiotics using reduction was 2.06 days; 3) ICC value was 0.05. To detect a possible absolute difference of 0.87 days in the rates with 90% power, we will need 118 RTIs patients in each arm.Based on our previous study results the estimated ICC value was 0.05 and a design effect value would be 2.45. By allowing for a 20% attrition rate and for a 20% loss to follow-up rate, therefore we would aim to recruit at least 2.45*118*2*1.2*1.2=833 patients into the study and this translates into 30(833/30=28) patients per township/community health center.

Data collection

The study data will be collected through one baseline and five follow up telephone interviews. For any recruited patient, the baseline interview happens within 1-2 days of his/her visit to the health center; while the follow up interviews are scheduled at scheduled at 7, 14, 21,180 and 365 days after the baseline. The baseline and telephone interview will be performed by trained data collectors using a structured questionnaire adapted from our previous study.The main content of the questionnaire includes patient demographic characteristics (e.g., sex, age, education, residential area and medical insurance records), illness duration, symptoms,sickness severity, practitioner’s diagnosis & treatment, antibiotics or other medicines prescribed and name, dosage and quantity. Different measure data will be collected at different time points (see table 2).Patient days of patients using antibiotics for the whole RTI episode, illness severity and symptom will be recorded at time points of days 7,14 and 21; patients' knowledge about and attitude toward antibiotics,times of re-occurrence

of RTIs and related health service seeking and antibiotics consumption for the re-occurred infection will be solicited at day 180 and 365 after the consultation . Other healthcare use (clinic visits or consumption of other treatment) will be recorded at 14 and 21 days after the consultation In addition, patient quality of life will be measured using the EQ-5D-5L in the baseline interview and at 7, 180 and 365 days after consultation.

Table 2 List of the primary and secondary measures and when they will be collected at follow-up audit

item	Outcome measure	Initial consultation	patient telephone interview afterconsultation				
			7 days	14 days	21 days	180 days	365 days
Primary measure	Number of days of patients using antibiotics for the episode of RTI	√	√	√			
	Symptom duration and severity	√	√	√	√		
	Times of re-visits			√	√		
	Antibiotics re-prescription			√	√		
Secondary measures	Patients' knowledge about and attitude toward antibiotics					√	√
	Times of re-occurrence					√	√
	Health service seeking and antibiotics consumption for the re-occurred infection					√	√
	Patient quality of life (EQ-5D-5L)	√	√			√	√
	Patient attitude, beliefs andunderstanding of the message		√	√			

Data analysis

The data collected will be used to compare the differences between control and intervention group as a whole and subgroups in the intervention arm:Number of days of patients using antibiotics for the episode of RTI; the secondary measures including times of re-visits to clinics and antibiotics re-prescription for the same RTI ,quality of life, times of re-occurrence of RTIs and related health service seeking and antibiotics consumption for the re-occurred infection, scores of patients' knowledge about and attitude toward antibiotics. Estimation of statistical significance and confidence intervals will assume a type Ierror established in alpha=0.05, using the IBM SPSS

V25 statistics package. Missing data will be treated as missing at random and imputed using a chained-equations multiple imputation model.

Initial data analysis will consist of descriptive summaries intended to examine the patterns of the various measurements and check for normality of the continuous variables.And necessary transformations are explored and selected, if necessary, to induce approximate normality.Follow up analysis will use a similar modelling framework with distributions appropriate to the outcome, for example, linear modelling for continuous outcomes and Poisson/negative binomial for count out comes.