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Impact of mobile message reminders on tuberculosis treatment outcomes in Pakistan

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Impact of mobile message reminders on tuberculosis treatment outcomes in Pakistan

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Summary

Tuberculosis (TB) is the second leading cause of death from infectious disease globally. The treatment is long and results in side effects. Adherence to TB treatment regimens is essential for TB control, as failure to adhere can result in multi-drug-resistant TB. Mobile health offers the opportunity for remote delivery of health. We conducted a randomized controlled trial to gauge the impact of daily two-way SMS reminders on the treatment outcomes of people with drug-susceptible TB in Karachi, Pakistan.

We enrolled 2,207 people with drug-susceptible TB into the trial. Once enrolled, mobile phone-based randomization was used to allocate them to either the *Zindagi* SMS system or a control group that received the standard of care offered by the treating clinic.

The *Zindagi* SMS system was designed to increase adherence to TB treatment. The system is a two-way SMS reminder system in which patients were sent daily SMS messages and were asked to respond via SMS or a missed (unbilled) call to indicate that they had taken their medication. Patients who did not respond for seven days in a row were followed up over the phone. Over the study period, participants who were on the *Zindagi* SMS system throughout their treatment had a mean response rate of 29 per cent. Response rates started at 48 per cent in the first two weeks in the study and fell to 24 per cent (for participants in the eight month treatment regimen) or 20 per cent (for participants in the six-month treatment regimen). Eighty-five per cent of participants on the *Zindagi* SMS system responded to the system at least once.

The study found no difference in treatment success rate between the *Zindagi* SMS and control groups (83% vs. 83%, $p = 0.782$). When we adjusted the treatment outcomes to incorporate self-reported outcomes of participants that we interviewed who defaulted or transferred out of treatment, there was still no difference between the two groups (84% vs. 83%, $p = 0.871$). After controlling for the length of the regimen and the days in the study, self-reported adherence between both groups was similar ($p = 0.772$). There were also no differences between both groups in variables looking at physical and psychological health, after adjusting for the number of hypotheses tested. We also found no difference in treatment success for a variety of subgroups, after correcting for the number of subgroups being explored.

We conducted 31 in-depth interviews with participants. The interviews found that participants received support from family members and others in reminding them about their medication and providing motivation and support. The majority of participants on the *Zindagi* SMS system did not use the system as their primary mode of remembering to take their medication.

This study is the first large-scale, randomized controlled trial for SMS and TB globally and it found no impact. However, the fact that 85 per cent of participants responded to the system at least once indicates that there is still a potential for mobile health and TB. Policymakers and researchers could explore alternate mobile health interventions for people with TB such as combining SMS reminders with off-site clinical support, using SMS reminders to remind participants about clinic appointments, or combining SMS reminders with financial or other incentives to motivate participants to continue their treatment.

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Abbreviations and acronyms

ART	antiretroviral therapy
DOT	directly observed therapy
GP	general practitioner
GPRS	general packet radio service
HIV	human immunodeficiency virus
IRD	Interactive Research and Development (Pakistan)
MDR-TB	multi-drug-resistant tuberculosis
NGO	non-governmental organization
NTP	National Tuberculosis Control Program
PAP	pre-analysis plan
PKR	Pakistani rupee
SMS	short-message service
TB	tuberculosis
USD	United States of America dollar

1. Introduction

Tuberculosis (TB) is the second leading cause of death from infectious diseases globally. In 2013, 9 million people were infected with TB and 1.5 million died from the disease. The treatment of TB lasts six to eight months and can result in difficult side effects such as nausea, dizziness, skin rashes, pins and needles, and flu-like symptoms. Adherence to treatment regimens is essential for tuberculosis control. Failure to adhere to treatment can result in the patient continuing to transmit the disease and can lead to the development of multi-drug-resistant tuberculosis (MDR-TB). MDR-TB is more difficult to cure and requires a longer treatment regimen of up to two years, instead of six to eight months for drug-susceptible TB. Treatment costs for drug-susceptible TB are approximately USD20 per patient, whereas MDR-TB treatment can cost up to USD5,000 per patient.

The World Health Organization's recommended approach to promote adherence to TB medication is directly observed therapy (DOT). DOT requires health workers to watch each patient take their daily dose of medication. However, because of the human resource implications of having personnel visit patients each morning, DOT is often either relegated to family members with no verification that it was done, or is not done at all. In fact, in our current study, only 10 per cent of participants reported that their treating clinic had assigned them a treatment supporter, a family member or otherwise, to watch them take each dose of medication.

With the surge in mobile phone access globally over the past decade, mobile phone-based interventions have been explored in a wide variety of healthcare interventions, with mixed results (Free *et al*. 2013; Anglada-Martinez *et al*. 2014; Vervloet *et al*. 2012). Furthermore, there is a dearth of high-quality trials with adequate power, and most of the trials that have been conducted have been done so in high-income countries (Free *et al*. 2013; Anglada-Martinez *et al*. 2014; Vervloet *et al*. 2012).

The most rigorous trials for mobile health and long-term drug adherence have been conducted for adherence to antiretroviral therapy (ART) for people living with human immunodeficiency virus (HIV). Two early trials found an impact of short-message service (SMS)-based interventions on drug adherence to ART for people living with HIV (Lester *et al*. 2010; Pop-Eleches *et al*. 2011) and, based on these findings, a Cochrane systematic review was published, advocating their use (Horvath *et al*. 2012). However, more recent trials using motivational weekly SMS reminders in Cameroon and daily automated voice calls in India, found no impact of these interventions on drug adherence to ART (Mbuagbaw *et al*. 2012; Shet *et al*. 2014).

While there has been significant interest and small-scale pilot programs and studies looking at the potential for SMS reminders to promote TB treatment adherence, there is limited data on the efficacy of such interventions. To date, there has been no large-scale trial on SMS reminders for TB (Nglazi *et al*. 2013; Ahmed *et al*. 2012).

We conducted a randomized evaluation to gauge the impact of *Zindagi* SMS, a two-way SMS reminder system, on the treatment outcomes of people with drug-susceptible TB in Karachi, Pakistan.

2. The *Zindagi SMS* system

The *Zindagi* SMS system is a two-way, daily medication reminder system for patients with TB, developed by the informatics team at Interactive Research and Development (IRD) in Pakistan. Once a patient was enrolled onto the system, the system sent daily SMS reminders to patients, scheduled at the time that they specified during enrollment. The messages included a motivational message followed by a reminder to patients to respond to the system to indicate that they have taken their medication. For example, one reminder message said, *'Your health is in your hands. Take your medication and remember to respond by SMS or a missed call.'* The messages were in Urdu using the English script. Based on feedback from our initial one-month pilot of the system (Mohammed *et al*. 2012), TB was not explicitly mentioned in the messages in order to maintain patients' privacy because of the stigma surrounding the disease.

Patients were asked to respond to the system via an SMS message indicating the time that they took their medication or a missed call (i.e., calling the number and hanging up so that their call is registered but the caller is not charged). SMS responses were not verified for content. The missed call option was introduced September 2011, approximately six months into the evaluation. Participants were offered PKR60 (~USD0.60) per month to cover the costs of the messages. Initially, the patients were asked to pick up their reimbursements at the clinic where they were enrolled. In October 2013, the reimbursements were automated through patients' mobile phones.

Once the system received a response or a missed call, a confirmation message was sent back to the patient. If a response was not received for two hours, a second reminder was sent. If a response was not received for an additional two hours, a third and final reminder for the day was sent. Patients who did not respond for seven days were followed up with a phone call.

The two-way reminder system was designed not only to remind patients to take their medication, but to provide daily motivation to keep them invested in their treatment. Moreover, the request for a response was intended to keep patients actively engaged with the system, rather than passively receiving messages that they may ignore. Finally, in calling patients who were non-responsive for seven days in a row, the system enabled focused efforts on those patients who were not responding. The hypothesis was that this engagement would prevent forgetfulness and motivate patients to continue their treatment until it was complete.

3. Context

Pakistan had a population of 182.1 million in 2013. With an estimated prevalence of 670 TB cases per 100,000 population, Pakistan ranks fifth amongst TB high-burden countries globally (World Health Organization 2014). It accounts for 61 per cent of the TB burden in the countries in the Eastern Mediterranean Region (World Health Organization 2014). Pakistan also has the fourth highest burden of MDR-TB globally.

Pakistan had a TB treatment success rate of 91 per cent in 2012 (World Health Organization 2014). In the fiscal year 2012–2013, Pakistan had an annual cellular teledensity of 71.4 per cent (Pakistan Telecom Authority 2014).

Karachi is Pakistan's largest and most populous city with an estimated population of over 23 million (World Population Review 2014). This multi-ethnic coastal metropolis located on the Arabian Sea is the commercial capital of the country. We recruited participants at a variety of public and private TB clinics throughout the city.

TB treatment requires daily medication for six to eight months, taken first thing in the morning, on an empty stomach. TB medication in Pakistan is provided for free at public and private clinics throughout the country by Pakistan's National TB Control Program (NTP). In order to be eligible for free medication, clinics must report back case number and treatment outcomes to the NTP.

4. Timeline

The evaluation began in March 2011 and enrollment continued on a rolling basis until February 2014 when the required sample size was achieved. New clinics were added throughout the period. Once patients were enrolled, monthly midline surveys were conducted for the duration of their treatment and an endline survey was conducted once the treatment period was complete. Treatment outcomes were collected from the treating clinics as soon as they became available. Between May and June of 2012, the treatment regimen for TB patients in Pakistan was reduced from eight months to six months of treatment.

Qualitative interviews were also conducted between February 2014 and January 2015 on 32 purposively selected participants whose treatment was completed.

Table 1: Timeline of enrollments at various hospitals in Karachi

Event	Date
Enrollment began at the Indus Hospital	18 Mar 11
Enrollment began at general practitioner clinics	25 Mar 11
Enrollment began at the Sindh Government Hospital, New Karachi	01 Apr 11
Enrollment began at private labs	12 Mar 12
First patient enrolled in 6 month regimen	17 May 12
Enrollment began at Urban Health Center, Landhi	28 May 12
Enrollment began at the Jinnah Postgraduate Medical Centre (JPMC)	05 Jun 12
Last patient enrolled in 8 month regimen	20 Jun 12
Enrollment began at the Sindh Government Hospital, New Karachi	28 Jan 13
Enrollment began at the Civil Hospital	02 Mar 13
Enrollment began at Urban Health Center, New Karachi	06 Mar 13
Enrollment began at the Sindh Government Hospital, Liaquatabad	07 Mar 13
Enrollment began at Sindh Government Qatar Hospital	29 Mar 13
Enrollment began at Landhi Medical Complex	06 Apr 13
Enrollment began at the Sehatmand Zindagi labs	03 Oct 13
Qualitative data collection began	03 Feb 14
Endline surveys completed	01 Nov 14

5. Evaluation: design, methods, and implementation

The evaluation was an individual level, randomized control trial in which participants were enrolled through their treating TB clinics and randomly assigned to receive the *Zindagi* SMS reminders or the control group. The trial was registered at ClinicalTrials.gov, trial number NCT01690754.

5.1 Ethical review

The study was approved by the Institutional Review Boards at IRD in Karachi, Pakistan and at the Massachusetts Institute of Technology in Cambridge, MA, US.

5.2 Sample size calculation

The sample size was calculated using the outcome variable of treatment success. Treatment success is the key variable used to determine the success of a TB program. The sample size was calculated using a power of 80 per cent, a minimum detectable effect size of 5 percentage points, and the assumption of a change from 75 per cent treatment success in the control group to 80 per cent in the intervention group. This resulted in a desired sample size of 1,094 in each arm of the study, for a total of 2,188. We enrolled a total of 2,207 participants, with 1,110 randomized to the *Zindagi* SMS group and 1,097 to the control group.

5.3 Participant recruitment

Participants were recruited from one large private hospital, nine public TB clinics and a network of over 50 private general practitioner (GP) clinics and private labs. These locations were chosen to ensure the study covered the three main types of centers where TB patients are treated in Karachi. The large private hospital was the Indus Hospital, which has one of the largest TB clinics in Pakistan. The public TB clinics were dedicated TB clinics run under the purview of the NTP of Pakistan through the Provincial TB Program of Sindh. The GP clinics and private labs were those that are participating in programs conducted by the Indus Hospital and IRD to increase case detection for TB and thus were accessible to the researchers. Through these programs, these private providers are linked to the government's program through free medication for their patients, and their patient numbers and treatment outcomes are reported through IRD and the Indus Hospital to the NTP and Provincial TB Program of Sindh. While this is not a complete sample of clinics in Karachi, the range of clinic types (public, private and GP clinics) and variety of patient types, contributes to the study's external validity.

Participants were approached for enrollment through their treating clinics. For larger clinics, study representatives were based at the clinics and approached patients to seek their enrollment in the study. Those being treated at GP clinics or private labs were contacted on household visits or over the phone to ask them if they would be willing to participate. Once a participant was approached by study personnel, the study representatives screened them to ensure that they were eligible to participate. In order to be eligible, participants had to be newly diagnosed with smear or

bacteriologically positive pulmonary TB and to have been on treatment for less than two weeks at the time of enrollment. They had to be 15 years of age or older, report having access to a mobile phone and intend to live in Karachi for the duration of their treatment. In order to minimize spillover effects, patients who had another household member enrolled in the study were not eligible to participate.

Once a participant was determined to be eligible for participation in the study, the study representative would read them the oral consent form and ask them to consent. Of the 2,384 patients who were eligible, 417 (17 per cent) refused to participate.[1]

5.4 Randomization

Randomization was at the individual level. Once a participant had consented to participate, the study representative would fill out a basic information form on a mobile phone with key identifying information. They would then submit the data through general packet radio service (GPRS) and the participant would be assigned to either the intervention or the control group, using a randomly generated predetermined list of group assignment on the server. If the mobile phone-based system was not functioning or there were problems with GPRS, the study representative would call the research office. They would provide the same basic information to their supervisor who would then enter the data in Microsoft Excel and generate the group assignment for the participant using the randomization function.

Once a participant was assigned to the intervention group, the study representative explained the *Zindagi* SMS system to them and collected data on the phone number and time they wanted to receive the SMS messages. They were also given a brochure with information about the system, their reimbursements and the helpline that they could call. Each day, participants assigned to the intervention group were registered onto the *Zindagi* SMS system so that their reminders could begin. The randomization status of individual participants was not shared with their treating clinic.

Appendix A shows the balance check table between the intervention and control groups. The only statistically significant difference between the two groups is in tertiary schooling ($p = 0.038$) but, correcting for the number of variables being tested, this difference is no longer significant.

5.5 Data collection

Data collection was conducted using male and female surveyors who were trained by the research team on randomized evaluations, research ethics, data collection and the survey instruments.

[1] We are missing 9 per cent of our screening data so the screening and eligibility numbers have been proportionately increased.

When participants were enrolled, basic contact data was collected through an enrollment form which included sex, language, mobile phone ownership and contact information. All participants (in both treatment and comparison groups) were then followed up at their households, usually within one month of enrollment, for a more extensive baseline questionnaire that covers nine categories of information from the patient: (1) basic demographics; (2) household member characteristics; (3) mobility; (4) general health; (5) housing characteristics; (6) health-seeking behavior; (7) tuberculosis regimen and compliance; (8) mobile phone usage; and (9) assets and employment.

Once a month during months two through seven (for those participants on the eight-month treatment regimen) or months two through five (for those participants on the six-month treatment regimen), surveyors would attempt unannounced visits to all study participants' households to conduct a midline survey. The midline survey covered the areas of: (1) mobility; (2) general health; (3) health-seeking behavior; (4) tuberculosis regimen and compliance; (5) mobile phone usage; and (6) occupation. A potential threat associated with these visits could be that the visits themselves could have had an impact on the treatment behavior of participants. However, there is no reason to believe that this would be different between the *Zindagi* SMS and control groups.

Collection of sputum samples by the research team was also attempted for all study participants throughout their treatment. These sputum samples were independent of those collected by their treating clinic to determine their treatment outcomes. However, owing to the challenges of collecting sputum, there was a great deal of attrition for this variable.

Finally, following the completion of treatment, an endline survey was conducted. The endline survey collected information on: (1) mobility; (2) general health; (3) tuberculosis regimen and compliance; (4) medication reminders; (5) mobile phone usage; and (6) occupation.

We also surveyed participants who were reported as having defaulted or transferred out from treatment by their treating clinics. The survey asked questions about whether they had continued treatment after leaving their treating clinics and their reasons for leaving their treating clinic.

The enrollment forms were entered on mobile phones with paper forms as a backup in case of technical problems. All the remaining surveys were collected on paper forms. Paper forms were double entered to ensure accuracy.

We also conducted qualitative in-depth interviews with a subsample of our participants to understand their experiences during treatment. The interviews were conducted using a semi-structured guide that asked participants about: (1) their experiences in taking their medication; (2) the support systems they had to help them complete their treatment; and (3) the experience with the *Zindagi* SMS system for those randomized to receive the SMS messages. Participants for the qualitative interviews were selected using purposive sampling to ensure a diversity of sex,

treating clinic types, treatment outcomes and response rates (for participants in the *Zindagi* SMS group). Interviews were conducted until we achieved theoretical saturation. The interviews were conducted in Urdu, transcribed into Urdu in English script, and translated into English for analysis.

5.6 Outcome variables

The primary outcome for this trial was treatment success, using treatment outcomes recorded in clinic registers. Clinically reported treatment outcomes are the standard by which TB programs are assessed globally. However, the limitation with this outcome variable is that patients who default from treatment and those that are classified as having transferred out from their treating clinic are not followed up to see whether they continue their treatment elsewhere. There is no system linking the records of various clinics and, thus, it is difficult to verify whether a patient actually left their treatment or whether they sought and received care somewhere else. As a result, we also explore adjusted treatment outcomes, in which the clinically recorded treatment outcomes for those participants reported as having defaulted or transferred out of their treatment that we were able to interview were substituted with their self-reported outcomes. Similarly, in our adjusted outcomes we also substituted the outcome to 'died' for participants who we found during our study visits to have died before the completion of their treatment.

We also looked at self-reported adherence, in which all study participants were asked at midline visits whether they had taken their medication in the last 24 hours. While self-reported adherence can be misreported, there is no reason to believe that this would be done differently between the *Zindagi* SMS and the control group. Moreover, between February and April 2012, we conducted 159 IsoScreen tests in conjunction with some midlines on participants. The IsoScreen is a commercially available test that can detect the presence of isoniazid metabolites in urine to gauge whether drugs were taken within 24 to 30 hours before the urine sample was submitted. Isoniazid is a key drug in TB treatment. We compared the results of the IsoScreen results and the self-reported results on the 159 participants we tested to gauge the accuracy of self-reported adherence. While this was not a random sample and was conducted at a specific point in time, it can give us an indication of the reliability of self-reported adherence. We found that there was over-reporting of self-reported adherence; the IsoScreen test indicated that 17 per cent of those who said they had taken their drugs in the past 24 hours had not. However, these results were not statistically different between those randomized to the *Zindagi* SMS system and the control group. Thus, while self-reported adherence is an overestimate, there is no reason to believe that it is differently reported between our intervention and control groups.

Finally, we looked at variables at midline visits to assess the self-reported psychological and physical health of our participants. We asked questions using four-point Likert scales asking how much difficulty they had completing a range of physical tasks and how supported they felt during their treatment. We also used a picture of a ladder with six rungs, asking how likely they thought they were of being cured (with the highest rung being the most likely to be cured). We also used images

of five faces (taken from a pain scale) to ask participants how healthy they felt. Questions on the difficulty of completing tasks and how healthy participants felt were asked at every survey (baseline, midline, endline). The likelihood of being cured was asked at each survey except the endline survey. The question on how supported participants felt was asked only during the endline survey.

5.7 Analysis

We analyzed our data using an intention to treat analysis. If a participant was randomized to the *Zindagi* SMS group, they were included in that analysis, whether or not they actually received the SMS messages. As our main outcome of interest was clinically reported treatment outcomes, we had very low attrition of 10 participants (less than 1 per cent).

In the analysis of treatment outcomes, we used the χ^2 test for differences in proportions. We also used this same method of analysis for our adjusted outcomes based on self-reported outcomes of participants who we interviewed who had defaulted, transferred out, or whose family members said that they died during treatment.

We conducted our subgroup analysis in two ways. First, we conducted linear regressions on a variety of subgroups, using clinically recorded treatment success as the outcome. We then used the Westfall and Young free step-down resampling method for the family-wise error rate to adjust for the multiple subgroups being tested.

In accordance with our pre-analysis plan, we also explored subgroups for sex, vulnerability, high access to mobile phones and quality of care. While sex was composed of a single variable, the remainders were based on an index of variables. We had proposed an additional index of variables in our pre-analysis plan for participants who were likely to respond to the *Zindagi* SMS system, but were unable to find an index of variables that was a stronger predictor of response rates.

Vulnerability was composed of dummy variables for whether the participant was male, whether they had received any schooling, and the proportion of an index of 22 assets that they had in their household. Participants were considered vulnerable if they had a score of less than the median score of 1.545 on the vulnerability index.

Access to mobile phones was composed of dummy variables for whether participants owned a mobile phone, had at least one literate person in their household, and whether they said they knew how to send or receive SMS messages in a survey within their first month of enrollment. Participants were considered to have high access to mobile phones if they had a score on the mobile phone access index greater than the median score of 2.

Finally, quality of care was calculated on an index composed of: whether they were assigned a treatment supporter by their treating clinic; whether they had someone to remind them to take their medication in a survey within their first month of enrollment;

and the type of clinic they were being treated at, based on the treatment success rates for the various clinic types in the control group. A value of 0 was assigned for type of clinic if they were being treated at Indus, 0.5 if they were being treated at a public TB clinic, and 1 if they were being treated at a private GP clinic or lab. Participants were considered to have a high quality of care if they had a score on the quality of care index above the median score of 1. The subgroup analysis was conducted using a linear regression with an interaction term between group assignment and the subgroup variable.

In analyzing self-reported treatment adherence and the questions on physical and psychological health, we ran linear regression models on each of the outcome variables to see the difference between the *Zindagi* SMS group and the control group, after controlling for the days since enrollment and the regimen type.

Statistical analysis was conducting using STATA/IC version 12.0. A p-value of < 0.05 was considered to be statistically significant.

For the qualitative interviews, we conducted thematic analysis using open coding. The initial coding was conducted by two research assistants and then approved and finalized by the corresponding author.

6. Results

6.1 Participant characteristics

Between March 2011 and February 2014, we enrolled 2,207 participants into the study (Table 1).

Table 2: Demographic characteristics of participants

	SMS group (n = 1,110) n (%)	Control group (n = 1,097) n (%)	Total (n = 2,207) n (%)
Female	561 (51%)	518 (47%)	1,079
Age (mean and SD)*	33 (16)	33 (16)	
Urdu is mother tongue	549 (50%)	529 (48%)	1,078
Clinic type			
Indus Hospital	404 (36%)	385 (35%)	789
GP clinic or private lab	190 (17%)	193 (18%)	383
Public TB clinic	516 (46%)	519 (47%)	1,035
6-month treatment regimen	764 (69%)	777 (70%)	1,541
Own mobile phone	540 (49%)	565 (52%)	1,105
Schooling			
No school*	517 (49%)	475 (47%)	992
Primary (class 1–5)*	108 (10%)	115 (11%)	223
Secondary (class 6–10)*	325 (31%)	307 (30%)	632
Tertiary (above class 10)*	77 (7%)	101 (10%	178
Religious school*	15 (1%)	16 (2%)	31

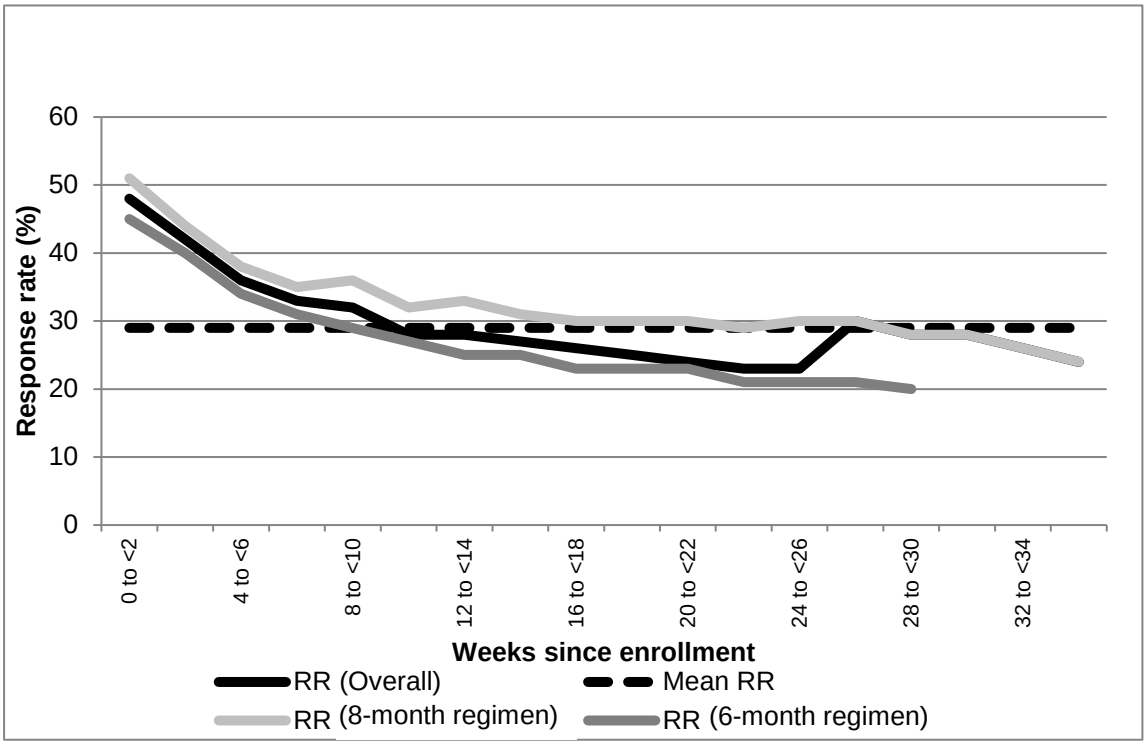
* There are 145 missing values for age; 146 missing values for no school and religious school; and 151 missing values for primary, secondary and tertiary. SD: standard deviation.

6.2 Fidelity of the intervention

For those enrolled onto the *Zindagi* SMS system, the system sent reminders or received responses for 174,284 patient days over the course of the study, excluding those sent or responses received after 180 days (six-month regimen) or 240 days (eight-month regimen). Assuming that each participant randomized to receive reminders should have received reminders for 180 days (six-month regimen) or 240 days (eight-month regimen), reminders should have been sent or received for a total of 220,560 patient days. Thus, the system sent or received reminders for 79 per cent of the patient days that it would have in a perfect implementation. The missed reminders were because of participants opting out of receiving reminders at enrollment (2 per cent); not enrolling in the system because they did not know their phone number at the time of enrollment and failed to contact the program to share their number subsequently (2 per cent); asking to leave the system or dying before the end of their treatment (3 per cent); or because of failures of the system to send out reminders due to system malfunctions, administrative errors or GPRS outages in the mobile network or within the city (14 per cent).

Of the 1,069 participants that were sent messages through the *Zindagi* SMS system, 912 (85 per cent) responded to the system at least once. Of the participants that were on the system for a minimum of 180 days (in the six-month regimen) or 240 days (in the eight-month regimen), the mean response rate during their treatment period was 29 per cent, ranging from 0 to 99 per cent. Response rates fell from 48 per cent in the first two weeks of treatment to 24 per cent (eight-month regimen) and 20 per cent (six-month regimen) in the last month of treatment (Figure 1).

Figure 1: Response rates over time in treatment



6.3 Primary outcome

There were no significant differences in clinically reported treatment outcomes between those that were in the *Zindagi* SMS group and the control group (Table 2). Because treatment outcomes are reported for over 99 per cent of participants there is very low attrition in this outcome.

Table 3: Clinically recorded treatment success between *Zindagi SMS* and control groups

	Zindagi SMS		**Control group**		
	n	**%**	**n**	**%**	**p-value**
Treatment success	917	83%	903	83%	0.782
Treatment complete	332	30%	325	30%	0.863
Cured	585	53%	578	53%	0.960
Default	108	10%	103	9%	0.775
Died	19	2%	19	2%	0.975
Treatment failure	27	2%	29	3%	0.758
Transfer out	33	3%	39	4%	0.446

As a robustness check, we followed up in detail with patients in the categories of default and transfer out, as these are patients with whom the clinic has lost touch. There is no statistical difference between treatment and control in the number of patients who defaulted or transferred out. We substituted the clinically recorded outcomes with those self-reported by the participants who defaulted and transferred out that we were able to interview after their treatment, or whose family members reported that the participant had died. Of the 283 participants that were reported as having defaulted or transferred out, we were able to interview 129 (46 per cent). An additional 49 participants (17 per cent) had died. Of the remaining participants, 23 (8 per cent) refused and we were unable to find an additional 82 (29 per cent) because they had moved or we were unable to find their homes. The self-reported outcomes were categorized using the criteria listed in Figure 2. There was no significant difference between treatment and control groups in our ability to interview those who had defaulted or transferred out.

Figure 2: Criteria for determining self-reported outcomes for participants

This figure describes the criteria for determining outcomes for participants who were reported as having defaulted or transferred out and had been interviewed after treatment, or those participants that were reported by their family members during study visits to have died.

Self-reported treatment outcome	Criteria
Completed	• Reported being on treatment at their treating clinic for 6 months or more (6-month regimen) or 8 months or more (8-month regimen) **and** • Said that they stopped treatment because their treatment was complete **and** • Knew their treatment was complete because their clinic doctor told them it was
Default	• Reported leaving treatment at their treating clinic after less than 6 months (6-month regimen) or 8 months (8-month regimen) after they were enrolled into the study and they did not restart treatment anywhere else **or** • Reported that their treatment at their treating clinic was incomplete when they left and they did not restart treatment anywhere else **or** • Sought treatment at another clinic after 2 months or more of leaving their treating clinic **or** • Continued treatment at a *hakim* or homeopath after leaving their treating clinic
Transferred out	• Started new treatment less than 2 months after leaving treating clinic **and** • Continued treatment at a GP clinic, private or non-governmental organization hospital, or a public clinic
Died	• Family reported during a study visit that they died less than 6 months (6-month regimen) or 8 months (8-month regimen) after they were enrolled into the study

When we adjusted the treatment outcomes to include the self-reported outcomes, the default rate reduced in both groups and there were still no significant differences in outcomes between the two groups (Table 3).

Table 4: Clinically recorded treatment outcomes substituted with self-reported outcomes

This table describes the recorded treatment outcomes that were substituted with self-reported outcomes from default and transfer out-patients interviewed at the end of their treatment, or those that were reported to have had died before their treatment was complete by their family members during study visits.

	***Zindagi* SMS**		**Control group**		
	n	**%**	**n**	**%**	**p-value**
Treatment success	923	84%	911	83%	0.871
Treatment complete	339	31%	333	30%	0.903
Cured	584	53%	578	53%	0.994
Default	74	7%	80	7%	0.572
Died	38	3%	29	3%	0.282
Treatment failure	26	2%	29	3%	0.655
Transfer out	43	4%	44	4%	0.875

There were 1,191 sputum samples collected for participants throughout the study, with 603 for those in the *Zindagi* SMS group and 588 for those in the control group. After controlling for the days in the study when the sample was taken, there was no statistically significant difference between both groups.

We are not concerned about the threat to the validity of our primary (or secondary) outcomes as a result of spillover effects from the treatment to control group. Patients were drawn from across Karachi, a city of over 23 million and the enrollment criteria ensured that there was no more than one patient in a household enrolled in a study.

6.4 Subgroup analysis

In our first method of subgroup analysis, there was a statistically significant difference only in the treatment outcomes of the *Zindagi* SMS group versus the control group in the subgroup of participants that were recruited through GP clinics or private labs. However, when the
p-values were adjusted using the Westfall and Young free step-down resampling method for the family-wise error rate to adjust for multiple subgroups being tested, this was no longer significant (Table 4).

Table 5: Subgroup analysis using treatment success as the outcome

Subgroups	*Zindagi* SMS group n	*Zindagi* SMS group %	Control group n	Control group %	*Zindagi* SMS coefficient	Naïve p-value	FWER-adjusted p-value
Sex							
Male	438	80%	468	81%	–0.012	0.618	0.999
Female	479	86%	435	84%	0.019	0.394	0.974
Quality of care							
Indus Hospital	317	79%	301	78%	0.005	0.872	1
GP clinic or private lab	180	95%	167	87%	0.082	0.006*	0.069
Public TB clinic	420	82%	435	84%	–0.023	0.331	0.954
Assigned a treatment supporter	89	87%	84	79%	0.080	0.124	0.698
Not assigned a treatment supporter	793	84%	768	84%	–0.004	0.815	1
Reminded to take medication (within one month after enrollment)	355	82%	324	83%	–0.011	0.689	1
Not reminded to take medication (within one month after enrollment)	436	87%	446	84%	0.022	0.318	0.953
Access to a mobile phone							
Own mobile phone	450	84%	474	84%	0.022	0.806	1
Don’t own mobile phone	467	82%	429	81%	0.023	0.502	0.994
No schooling	416	81%	381	80%	0.004	0.875	1
Any schooling	461	88%	469	87%	0.006	0.758	1
At least one literate person in the household	753	85%	744	84%	0.008	0.629	0.999
No literate people in the household	129	80%	108	81%	–0.016	0.736	1
Can send SMS (within first month of enrollment)	263	88%	232	87%	0.014	0.624	0.999
Cannot send SMS (within first month of enrollment)	528	83%	538	82%	0.001	0.958	1

*p < 0.05; FWER: family-wise error rate.

Our second method of examining subgroups through indices also found no significant difference in treatment success rates between the *Zindagi* SMS group and the control group within any of the subgroups (Table 5).

Table 6: Subgroup analysis using subgroup indices with treatment success as the outcome variable (p-values in parenthesis)

	Subgroups			
	Male	**Vulnerable**	**High mobile access**	**Good quality of care**
	Coef (p-value)	**Coef (p-value)**	**Coef (p-value)**	**Coef (p-value)**
Zindagi	0.019	0.020	0.003	0.018
	(0.420)	(0.402)	(0.874)	(0.407)
Subgroup	–0.029	–0.035	0.043	0.003
	(0.206)	(0.132)	(0.160)	(0.901)
Interaction	–0.030	–0.029	0.021	–.0.028
(subgroup**zindagi*)	(0.346)	(0.379)	(0.631)	(0.428)
n	2,197	2,038	1,858	1,857

6.5 Secondary outcomes

There were no significant differences in secondary outcomes between the *Zindagi* SMS group and the control group, after adjusting for days since enrollment and regimen type. Initially, the variable with ease of completing tasks showed a statistically significant difference between those in the *Zindagi* SMS and control groups. However, once we adjusted our p-values using the Westfall and Young free step-down resampling method for the family-wise error rate for the number of secondary hypotheses being tested, this was no longer statistically significant (Table 6).

Table 7: Secondary outcome variables

	Took medication in the last 24 hours[1]	**Perceptions on likelihood of being cured[1] (6 = very likely, 1 = not likely)**	**How healthy they felt[1] (5 = very healthy, 1 = very unhealthy)**	**Ease of completing tasks[1] (4 = no difficulty, 1 = lot of difficulty)**	**How much support was received[1] (4 = lot of support, 1 = no support)**
Zindagi	0.002	–0.008	–0.012	–0.017	0.020
Naïve p-value	0.772	0.473	0.423	0.036*	0.521
FWER adjusted p-value	0.89	0.89	0.89	0.162	0.89
N (surveys)	11,301	9,560	11,324	11,235	1,658
N (patients)	2,091	2,068	2,091	2,088	1,658

*p < 0.05; FWER: family-wise error rate.

[1]Controlling for the length of the regimen, days in the study, and days in the study squared.

6.6 Qualitative data

We interviewed a total of 32 participants. Due to a failure with our recording equipment during one interview, 31 interviews were included in the analysis. Participants were interviewed using purposive sampling to ensure diversity in characteristics. Participants were purposively sampled using sex, group assignment, clinic types, response rates on the IR (interactive reminder) system, and treatment outcomes. We interviewed a total of 19 males and 12 female participants. Twenty-one participants were from the *Zindagi* SMS group and 10 from the control group. Seven participants had the treatment outcome of treatment success, five had defaulted, two transferred out and six failed treatment. Sixteen participants were being treated at the Indus Hospital, 11 at a public TB clinic, and four at GP clinics. Of the participants on the IR system, two had never responded, three had a response rate of greater than zero but less than 10 per cent, seven had a response rate from 11 to 50 per cent, and eight had response rates above 50 per cent. One of the participants randomized to the IR system did not receive messages due to an administrative failure in registering him onto the system. See Table 7 for qualitative participant characteristics.

Table 8: Qualitative study participant characteristics

	Frequency (n = 31)
Female	12
Age (mean)	32.3
Urdu is mother tongue	12
Clinic type	
Indus Hospital	15
GP clinic or private lab	5
Public TB clinic	11
6-month treatment regimen	26
Own mobile phone	19
Schooling	
No school	13
Primary (class 1–5)	7
Secondary (class 6–10)	7
High school (above class 10)	3
Religious school	1

During the interviews, we explored three key areas related to the evaluation with participants: their experiences with taking their medication, support systems that they had during their treatment, and their experiences with the *Zindagi* SMS system, for those who were enrolled on it.

6.7 Experience taking the medication

During our interviews, we explored participants' experiences with taking their medication. Participants said that they remembered to take their medication in a variety of ways. Several participants said that they remembered to take their

medication as a part of their daily routine when they woke up or right after their morning prayers. Most participants said that they were very regular with their medication and rarely forgot. A female participant said, '*I was so consumed by my illness that I would always remember to take the medicine.*' The majority of participants said that they had family members who would remind them to take their medication, whether they remembered on their own or not. Some family members would bring the medication to the participant each day so that they could take it. Two participants said that they set alarms to help them remember their medication. One of those participants also used to receive the *Zindagi* SMS reminders, which would come before the alarm and would assist him in taking his medication.

Two participants indicated that they would forget to take their medication at times. One participant said, '*Sometimes when I went to weddings I used to forget taking my tablet along with me. I had to come back from so far just to eat my tablets.'* One participant said that if he ever missed a dose, he would take double the dosage the next day.

The majority of participants said that they were very regular with their medication. Some had gaps of a day or two during their treatment, but were regular for the most part. Two participants said that they missed a dose once and told their clinic doctor who scolded them, emphasizing the importance of taking each dose of the medication. As a result, they never missed doses again. One participant said that he missed 14 days in the middle of his treatment, as he had to have eye surgery.

Three participants who were reported as default by their treating clinics said that they left their treatment before it was complete. One participant said that she left her treatment because of financial problems, as both her brothers were unemployed. While the TB medication at her treating clinic was free, the medication supplements such as vitamins and supportive foods were costly. Two participants said that they left their treatment because of their busy schedule once they were feeling better. One male participant said, *'[I stopped my treatment because of] my carelessness. They told me that I have to have the treatment but I was so busy with my work. When I started to feel better I left [the treatment].*'

A common theme that emerged in participants' experiences in taking their medication was the side effects and difficulties that participants experienced with their medication. Side effects included body aches, general weakness and fatigue, itching, and nausea and vomiting. Other participants said that the large size of the pill made it difficult to swallow. However, the majority of participants said that, despite these side effects and difficulties, they continued to take their medication. For example, a female participant said, '*It was very hard to take the medicine. It would hurt and I used to feel even sicker after taking it. But I had to take it. [The doctors] told me that if I want to get rid of the disease then I have to get my treatment properly*.' Some participants said that they experienced no side effects or difficulties with the medication.

6.8 Support systems

Participants had a variety of support systems during their treatment. The most common form of support was from family members. Family members would provide a great deal of support such as reminding participants to take their medication, motivating them to continue their treatment, providing encouragement and hope, and taking care of the participant and their physical and nutritional needs. A few participants said that they found support in religion, two participants said that they got support from their clinic doctor, and one said he got support from the SMS messages that he received. One participant felt that he did not receive adequate support from his family.

6.9 Experiences with the *Zindagi* SMS system

Of the participants on the *Zindagi* SMS system, some participants appreciated the system because they said that it was a helpful reminder. However, the majority said that they would remember to take their medication themselves and the SMS reminders were just reinforcement for them. Some participants said that, while they usually remembered to take their medication on their own, the messages reminded them a few times when they forgot to take their medication, particularly at the start of the treatment. One participant said that the SMS reminders helped him take his medication in a timely manner. He said, '*The regular SMS reminded me to take the medicine because when I was at work it helped me remember to take the medicine. I was never late because of this.*'

Others said that the messages reminded family members who owned the mobile phone to check up on them to ensure that they had taken their medication. Finally, some participants said that, while the messages were not helpful to them given that they remembered to take their medication, perhaps the system would be useful to other people.

Another theme that emerged was that some participants reported that they felt supported by the system. Participants said that they enjoyed receiving the message and appreciated that they were being asked after. While this was mostly true for participants who were literate or had a literate family member who could read the messages to them, a male participant who could not read the actual messages said, *'I cannot read but it really makes me happy that I get messages. It really makes me happy that at least someone is asking about me.'* Some participants appreciated the messages because they were motivational and reminded them about the importance of taking their medication. One participant said, '*[The messages] made us realize that we are not supposed to miss our doses. If you miss a dose you will have to begin all over again. The SMS reminded us not to miss our doses.*'

Some participants said that the reminders were not helpful because they would remember to take their medication regardless. A few participants said that they were not helpful as they were unable to read them. One participant said that she never received the reminders, despite the system logging daily reminders for her.

One participant said that she disliked the daily reminders and would have preferred to receive them more infrequently, especially when she received repeated reminders because she was unable to respond due to a lack of credit on her mobile phone. She said, '*We knew that we had to take medicines every day. Sometimes I did not have balance. The messages kept coming and I couldn't reply to it with a missed call. This is what bothered me.*'

Participants would respond to the messages in a variety of ways. Some would read the messages and respond themselves. For others, a family member would read the messages and respond. Most family members shared the messages with the participant, either by reading the message aloud, letting them know that the message came, or asking them whether they took their medication. Some family members would just respond to the system themselves, without telling the participant. One participant who owned his own mobile phone would show messages to people to ask what they were about, as he could not read them. One participant was not aware that the messages were arriving. She said that she never received reminders. However, she had a response rate of 38 per cent, which seems to indicate that a family member was responding on her behalf, without telling her.

Participants shared a variety of reasons for not responding to the system. These included being non-literate, being busy, not having enough credit on their mobile phone, or that their mobile phone was not working.

7. Discussion

In this first large-scale randomized control trial for SMS reminders and TB, we found no significant impact of the SMS medication reminders on treatment outcomes, self-reported medication adherence, or a set of physical and psychological variables. There were also no statistically significant impacts of the reminder system on treatment success rates within a variety of subgroups, after adjusting for the multiple subgroups being tested.

To our knowledge, this trial has the largest sample size of any trial on SMS reminders and medication adherence. With an attrition rate of less than 1 per cent on treatment outcomes, our primary outcome variable, this trial is very robust. Finally, with representation of participants seeking treatment from public clinics, a large private hospital, and private GP clinics and labs, this trial has representation of a variety of patient populations in Pakistan, contributing to its external validity.

A limitation of our trial was that we lacked an objective medication adherence measure. Our measure of adherence was self-reported adherence, which, as the IsoScreen tests indicated, is an overestimated measure. It is therefore possible that there was a potential difference in adherence between the *Zindagi* SMS and control groups that was not picked up through the self-reported adherence measure. However, while it was a non-random subsample, our IsoScreen tests indicated that misreporting was similar in both the *Zindagi* SMS and control groups.

Another potential limitation of our trial is that our primary outcome variable relied on clinically recorded treatment outcomes by treating clinics. These outcomes could be

incorrectly stated by clinics to meet the expected success rates encouraged by the NTP of Pakistan. However, given that the clinics were blind to allocation, there is no reason to believe that this was done differently between the *Zindagi* SMS and control groups. Moreover, from our sub study, in which patients who had been reported as having transferred out or defaulted were followed up, the differences in self-reported outcomes by these patients were similar in our intervention and control groups.

Finally, another potential limitation of our trial is that it took place in Pakistan, where the government reported a very high treatment success rate (see Appendix B for definitions of treatment outcomes) of 91 per cent in 2012 (World Health Organization 2014). Thus, the results could perhaps differ in contexts with lower success rates and this could be a potential direction for future work.

While there are no other large-scale, randomized trials on mobile phone-based interventions and medication adherence for TB to our knowledge, we compared our results with the literature on HIV and SMS. Our results are similar to those found by Mbuagbaw *et al*. (2012), who found no impact of weekly motivational SMS reminders on adherence to ART in Cameroon. Similarly, Shet *et al*. (2014) found no impact of an automated interactive telephone reminder system on adherence to ART in India, a socioeconomic context that is similar to Pakistan. While Lester *et al*. (2010) and Pop-Eleches *et al*. (2011) found a positive impact of their SMS interventions on drug adherence to ART treatment, there are reasons that can explain the divergence in results. For example, the Lester *et al*. trial was not merely an SMS reminder system, but a support system which enabled participants to get off-site follow-up and support by a clinician if they indicated that they had a problem or they did not respond to the SMS. This additional support could explain the differences in results from our trial. The Pop-Eleches *et al*. trial was merely an SMS reminder system. However, the trial explored weekly reminders, rather than daily reminders. In addition, Shet *et al*. hypothesize that the positive result could be because the trial tested multiple hypotheses (with variations on long, short, daily and weekly reminders, at various points in time), without correcting for the number of hypotheses being tested. With only one hypothesis with a significant result (weekly SMS reminders), with a p-value of 0.03, they hypothesize that if this was corrected for the number of hypotheses being tested, the result would no longer be statistically significant (Shet *et al*. 2014). Finally, it is important to note that the contexts of HIV and TB vary, particularly given that ART is a lifelong treatment, whereas TB treatment is time-bound for six to eight months.

Our study results indicate that simple SMS reminders, albeit two-way reminders with phone calls for non-responsive participants, did not have an impact on treatment outcomes for patients with drug-susceptible TB. This could be because the SMS reminders, which were intended to combat forgetfulness and provide support, did not address the underlying factors that contribute to patients leaving their treatment. Moreover, our qualitative data showed that the majority of participants on the *Zindagi* SMS system had other primary methods of remembering their medication, either through their daily routine or through the support of family members.

However, the fact that 85 per cent of those on the *Zindagi* SMS system responded to the system at least once indicates there is potential for SMS-based interventions in this patient population. Despite low literacy rates amongst our patient population, the response rate indicates that, using family support, this population has the potential to send and receive SMS messages. However, the qualitative work suggested that low literacy, being busy, lack of mobile phone credit, and the mobile phone not working were reasons given for low response rates. The relatively low response rate of 29 per cent over the treatment period that fell over the course of treatment suggests that participants may have tired of daily medication reminders. Perhaps messages with longer intervals at random points would be more effective.

Future studies could focus on other interventions related to SMS. One potential intervention would be to combine SMS reminders with off-site support as the Lester *et al*. (2010) trial did for HIV patients in Kenya. SMS reminders could also be used to remind patients of clinic appointments, as various forms of reminders (telephone calls, home visits, letters) for clinic appointments have been found to be beneficial in studies with TB patients (Liu *et al*. 2014).

Finally, it may be beneficial to couple SMS reminders with financial or other incentives to motivate patients to stay on course with their treatment. The three default participants in our qualitative study said that they left their medication for financial reasons or because they became consumed by their professional obligations. Financial incentives could potentially counteract these barriers and increase adherence. Our current study was initially intended to have an arm with incentives for medication adherence but the technology to link SMS reminders with adherence had manufacturing challenges.

To conclude, as the first large-scale, randomized control trial for SMS reminders for medication adherence for patients with TB, the study found no impact.

Appendix A: Balance check table

		Control proportion	IR proportion	p-value
Overall characteristics				
	Males	0.53	0.49	0.119
	Mean age	32.6	32.7	0.821
	Ever married	0.59	0.58	0.583
	Urdu is mother tongue	0.5	0.48	0.262
Education				
	No schooling	0.47	0.49	0.232
	Religious school	0.02	0.01	0.791
	Primary (Class 1 to 5)	0.11	0.1	0.477
	Secondary (Class 6 to 10)	0.3	0.31	0.653
	Tertiary (more than Class 10)	0.1	0.07	0.038
Economic characteristics				
	Participant is a household head	0.28	0.25	0.179
	Participant is a financial head	0.22	0.22	0.853
	Household size (mean)	7.1	7.2	0.491
	Live in house owned by household	0.53	0.54	0.869
	Own some land	0.59	0.61	0.34
	Asset index (mean)	0.53	0.53	0.965
	Ever worked for pay	0.57	0.58	0.714
Mobile phone access and familiarity				
	Mobile phone ownership	0.52	0.49	0.18
	Had sent or received SMS	0.3	0.32	0.379
Clinic type				
	Indus Hospital	0.35	0.36	0.524
	GP clinic or lab	0.18	0.17	0.768
	Government clinic	0.47	0.46	0.698
	Less than 30 minutes travel time to clinic	0.41	0.41	0.717
	Assigned a treatment supporter by clinic	0.1	0.1	0.593
Health				
	Have other illnesses	0.15	0.14	0.364
	Ever smoked cigarettes, *beedi*, or a water pipe	0.2	0.2	0.978
	Days unwell before TB diagnosis (mean)	100.4	103.7	0.599

Appendix B: Definitions of treatment outcomes

Cure: A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.

Treatment failure: A patient whose sputum smear or culture is positive at five months or later during treatment. Also included in this definition are patients found to harbor a multi-drug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive.

Died: A patient who dies for any reason during the course of treatment.

Default: A patient whose treatment was interrupted for two consecutive months or more.

Transfer out: A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.

Treatment success: A sum of cured and completed treatment.

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