EVALUATION OF A TEXT MESSAGING INTERVENTION FOR PATIENTS WITH TUBERCULOSIS IN ARGENTINA

by

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ABSTRACT

Treatment adherence remains a major challenge in tuberculosis (TB) control. Mobile phone text messaging is a promising tool to support TB treatment adherence. The purpose of this study was to develop a text messaging intervention to promote TB treatment adherence, assess feasibility and acceptability, and to explore initial efficacy. A collaborative team of clinicians, administrators and patients in treatment developed the intervention. Content analysis, based on the Information-Motivation-Behavioral Skills (IMB) model, guided educational message selection. To identify considerations for a larger trial a socio-technical evaluation model adapted from Conford, and Barber and associates was applied.

The intervention was implemented as a mixed-method, randomized controlled pilot-study at a public pulmonary-specialized hospital in Argentina. Patients newly diagnosed with TB who were18 or older, without drug resistance or HIV, and had access to a mobile phone were recruited. Participants were randomized to usual care plus either medication calendar (n=19) or text messaging intervention (n=18) for the first 2 months of treatment. Data were obtained through interviews, field notes, self-reported adherence, sputum microscopy, and treatment outcomes.

Most potential participants had access to mobile phones and knew how to send a text, supporting feasibility of the intervention. The majority of the participants (60%) indicated not being adequately informed about disease or treatment. Participants

identified themes of feeling *cared for*, *responsible for their treatment* and valued the option to ask questions and receive quick answers. Texting group participants reported adherence 77% of the days (*SD* 23.5, range 22-100), whereas only 53% in the control group returned calendars. Sputum conversion and treatment outcomes were similar in both groups. Considerations for conducting a larger trial included reducing cost, improving the automated features, and strengthening capacity to return patients to treatment.

A collaborative approach and application of the IMB model to guide development was supported. Overall the texting intervention was well accepted and feasible, daily reporting was superior, and adherence was monitored in real time. Although there was not clear evidence that the texting intervention was more efficacious, feasibility and acceptability results suggest that there is value in assessing this interactive intervention in a larger-scale study.

This dissertation is dedicated to the patients who contracted TB, and who shared their plight, challenges and stories of being diagnosed and undergoing treatment.

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LIST OF ABBREVIATIONS

DOTS	Direct Observation of Treatment Short Course: 5 Part TB Control Approach
DOT	Directly Observed Therapy
ISTC	International Standards for Tuberculosis Care
MDG	Millennium Development Goals
MDR-TB	Multidrug-resistant TB
SAT	Self-administered Treatment
SMS	Short Message Service
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively Drug-resistant TB

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CHAPTER 1

INTRODUCTION

Statement of Problem

Tuberculosis (TB) is a major global public health problem, particularly in low- and middle- income countries (Das & Horton, 2010). Although the rate of increase in new cases is slowing, the number of cases globally continues to increase due to population growth (World Health Organization, 2006). In 2010, experts indicated that there was more TB than at any other time in history (Das & Horton, 2010). According to the World Health Organization (WHO) Global Tuberculosis Report the global incidence rates began to fall after 2010, but the absolute number of incident cases has fallen more slowly (World Health Organization, 2012b). For various reasons TB has resurged as an enormous global health problem, most notably due to TB accompanying the HIV/AIDS epidemic, multidrug-resistance and extensively drug-resistant TB (Corbett et al., 2003). Globally TB is identified as the seventh leading cause of death (World Health Organization, 2008a) and the third most common infectious disease causing death worldwide, following HIV/AIDS and diarrheal diseases (World Health Organization, 2004). There were an estimated 8.7 million new TB cases identified, 14.1 million active cases, and 1.4 million deaths attributed to TB in 2011 (World Health Organization, 2012b). Furthermore, there is a large potential reservoir for TB. Up to one third of the

world population, or about 2 billion people, have the latent form of the disease, which can develop into the active form (World Health Organization, 2013).

Concerted efforts to control TB have been established. In 2000 the Millennium Development Goals (MDG) were drawn up by 189 world leaders in order to address the needs of the world's poorest people and target some of the major global health problems (Millennium Campaign, 2008). The MDG number 6C aims to halt and reverse the incidence of TB by 2015 (Millennium Campaign, 2008). In addition to endorsing the MDG to halt and reverse the incidence of TB two additional targets were established by the World Health Organization's (WHO) Stop TB Partnership with global governmental and nongovernmental organizations (World Health Organization, 2009b). The two additional targets were to decrease by one-half the TB prevalence and death rates by 2015 compared with 1990 levels and to eliminate TB as a public health problem by 2050 (World Health Organization, 2009b). Eliminating TB as a public health problem would require a global incidence of less than one case per 1 million per year of active TB cases (World Health Organization, 2009b).

Poor treatment success is a barrier to progress for TB control and is not improving. The WHO target TB success rate is 85% of cases (World Health Organization, 2003). Treatment success is defined as either bacteriological confirmation two times during the course of treatment or treatment completion (World Health Assembly, 1991). One strategy aimed to help control the TB epidemic is the WHO internationally recommended Direct Observation of Treatment, Short course (DOTS) (World Health Organization, 1999). The DOTS strategy has five key components, which include securing political commitment, strengthening detection and diagnosis, ensuring drug availability,

monitoring outcomes and directly observed treatment (DOT) for at least the first 2 months of treatment (World Health Organization, 1999, 2002). The DOT component has been recommended to assure drug adherence and requires that a trained healthcare worker or treatment supporter observes medication ingestion daily (World Health Organization, 2003).

Although progress has been made using the DOT strategy, its effectiveness has also been questioned (Figueiredo et al., 2009; Frieden & Sbarbaro, 2007; Khan, Walley, Witter, Shah, & Javeed, 2005; Macq, Theobald, Dick, & Dembele, 2003; Volmink & Garner, 2007; Volmink, Matchaba, & Garner, 2000). Furthermore, the DOT component continues to be challenging for patients and healthcare services in many communities globally (Hill et al., 2005; Khan, Walley, Witter, Imran, & Safdar, 2002; Sanchez & Bertolozzi, 2009). Case management using the DOT intervention is expensive, requires added commitment of human resources, and can be burdensome to patients required to travel daily to a clinic to take medication (Hill et al., 2005; Khan et al., 2002; Sanchez & Bertolozzi, 2009). Even when treatment is provided free of charge by public health services, there are still direct and indirect costs to the patient in travel to healthcare services, as well as lost wages to attend a clinic (Figueiredo et al., 2009).

There are still many countries in which the TB rates are either stagnant or decreasing more slowly than should be expected even with the DOTS strategy in place (Tuberculosis Coalition for Technical Assistance, 2009). As an example, the National TB Program in Argentina acknowledges that overall treatment success has varied little and there has been no significant improvement over the past 10 years despite DOTS coverage reported as being available countrywide since 2002 (Instituto Nacional de Enfermidades

Respiratorias E. Coni, 2010, 2011). Poor improvement in TB control is considered to possibly be due to incomplete application of effective control measures (Tuberculosis Coalition for Technical Assistance, 2009).

TB in Argentina

In Argentina, from 2008 to 2010, the average treatment success rate was 46% for sputum smear positive cases (confirmed pulmonary TB diagnosis) (World Health Organization, 2012a). Countrywide, in 2011, the incidence rate was 26/100,000 (World Health Organization, 2012a); however the distribution of TB cases between regions varied greatly, from 0-200 cases/100,000 (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2011). In addition, from 2002-2007, Argentina was found to have the third highest prevalence of multidrug resistant TB (MDR-TB) of the 10 countries in the WHO American region, 2.2% and 15.4%, among new and previously treated TB cases, respectively (World Health Organization, 2008b). MDR-TB is considered a critical situation in Argentina where only one main infectious disease reference hospital had regularly available second-line drugs (Palmero et al., 2004).

Of the sputum smear-positive cases reported in 2007, only 54% were documented to have received DOT (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2010). When further evaluated by province, the Province of Buenos Aires reported 20% of the cases being treated by DOT (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2010). Among those who received DOT treatment, success was 13% higher and default rates 55% lower than self-administration of treatment (success rate: DOT 78%, SAT 69%; default rates: DOT 11%, SAT 20%) (Instituto Nacional de Enfermidades

Respiratorias E. Coni, 2010). Similar findings were found in one health region analysis of 2003 reports (Chirico, Kuriger, Etchevarria, Casamajor, & Morcillo, 2007).

Argentina suffered a tremendous socioeconomic crisis in 1990-2002, which left nearly 60% of the country's population below the poverty line and resulted in a historically high rate of unemployment at 21.5% in 2002 (Zeballos, 2003). Possible health effects attributed to the crisis, specific to TB, included higher rates of complications and death, increased resistance and spread of resistant strains, and unfavorable short- and long- term epidemiological scenarios (Zeballos, 2003). Prior to the economic crisis, Argentina was considered a successful reference for many Latin American countries and the world. Aside from the residual effect of the economic crisis in Argentina, cause for low treatment success rates is not well understood.

Significance of Problem

TB is in most cases curable using a combination of drugs introduced in the 1950s and 1980s. However, there remain challenges to completing the 6- month treatment course successfully for people with drug-susceptible TB (Enarson & Billo, 2007). Patient adherence to treatment is recognized as the cornerstone to treatment success and nonadherence to TB treatment is a major obstacle to TB control. Consequences of low treatment success rates include poor patient outcomes, such as prolonged infectivity, increase in risk of relapse after treatment, generation and propagation of drug resistance, treatment failure, and increased mortality (Maartens & Wilkinson, 2007; Mitchison, 1998). Low treatment success also poses a serious health risk for communities.

Potential barriers to adherence to TB treatment include limited family or healthcare system support of patients with TB, impact on patient's work time and ability to work,

lack of knowledge regarding disease and treatment, and issues of stigma (Gebremariam, Bjune, & Frich, 2010; Iribarren, Rubinstein, Discacciati, & Pearce, 2011; S. A. Munro et al., 2007). Stigma from TB diagnosis and daily clinic attendance for treatment have been recognized as barriers for TB patients and have been found to impact TB case detection and treatment adherence (Cramm, Finkenflugel, Moller, & Nieboer, 2010; Gebremariam et al., 2010).

Nurses play a major role in TB control and are often the frontline healthcare worker around the world to facilitate diagnosis and to initiate and monitor treatment (Carlevaro, 2009). Nursing interventions in TB control can include establishing programs, proposing policy, conducting research, and providing direct patient care and education (Oblitas et al., 2010). Although nurses often undertake the bulk of TB control work, much of their involvement is invisible due to a lack of publications by nurses working in the field, accompanied by a lack of direct reference to their work in policies and strategic plans (International Council of Nurses (ICN), 2010). Commonly nurses are overburdened with multiple tasks and strengthening nurses' capacity in TB control measures is needed (International Council of Nurses (ICN), 2010). The need for strengthening nursing capacity is supported, especially where the only treatment option is self-administration.

One way to strengthen nurses' capacity is to utilize the technology at hand, such as mobile phones and data management software, to help to efficiently monitor patients through treatment. Regular supervision and support promote greater opportunities for education, resolution of barriers, and quick detection of nonadherence and monitoring of reactions or worsening symptoms (World Health Organization, 2009a). To improve adherence, recommended measures include heightening TB patients' involvement in their

own care and improving communication between patients and their healthcare team (Barclay, 2009; Kaplan, 2006). A proposed method to improve adherence is through mobile phone text messaging, using Short Message Service (SMS) (Barclay, 2009; Kaplan, 2006). However, there are few published reports of actual use of text messaging to promote TB treatment adherence (Mohammed et al., 2012).

Preliminary Work

Factors associated with the low success rates in Argentina were not well understood. In response, a qualitative study was conducted to identify treatment strategies employed and to explore barriers and facilitators to successful TB treatment from the perspective of patients, healthcare teams, and directors at local, regional, and national levels (Iribarren et al., 2011). Modeled on recommendations for descriptive, exploratory, qualitative research (Sandelowski, 2000, 2010), investigators used semistructured, in-depth individual and group interviews with a purposive sampling of 5 out of the 13 districts within the high TB burden Health Region V, based on historic treatment success rates and case burden. Participants (N=42) included key TB personnel (physicians, nurses, social workers, and other TB treatment staff); TB program local, regional, and national directors; and patients and family members. Interviews with the regional director and staff and with the national TB director were also conducted. In addition, researchers participated in a day long regional TB workshop to understand overall system function.

Investigators found that treatment strategies varied and were negotiated in order to maintain patients in treatment. Healthcare personnel and district and regional directors reported strategies of *daily* DOT, *during the week* DOT that was used when healthcare centers were closed on weekends, a *negotiated* or *personalized* number of DOT days in

attempt to maintain patient in treatment, and self-administration of treatment (SAT), which was primarily at hospital based clinics. Patient records, treatment documentation, and case reporting were kept by paper-based records. According to the Regional and National directors, most active TB cases elect to continue treatment supervision at hospital-based clinics rather than local healthcare centers or possibly the patients were not referred to local healthcare centers to complete TB treatment.

Participants recognized TB treatment as complex and multifactorial. A wide range of factors (*N*=37) classified as barriers and facilitators to TB treatment success were identified by participants. Factors were classified into three main categories: personal (patient and healthcare personnel), social, and system or organizational factors (Iribarren et al., 2011). Examples of *personal* factors identified include lack of TB understanding at individual and community level, fear related to TB, discrimination or stigmatization and interpretation of *feeling better* means cured. *Social* factors included support from family and friends, continuity of healthcare personnel, co-morbid conditions (e.g., alcohol or drug addiction, HIV/AIDS), and lack of trust in healthcare centers by patients and hospital personnel. Examples of *system* or *organizational* factors included lack of availability of services (e.g., DOT not being offered at hospital-based clinics); lack of accessibility (e.g., not open 24 hr, provision of DOT without appointment or wait); and high concentration of cases being treated at the hospital level. Examples of patient-centered care and creative strategies to overcome barriers were identified (e.g., provision of DOT without appointment and through separate door, training night security guard to provide DOT). Main themes identified were *commitment*, *continuity* and *collaboration*.

Findings included barriers that potentially contribute to the overall persistent low rates of treatment success in Argentina. Some of the barriers identified by patients were overcome by communication and relationships established with healthcare personnel. DOT was described as a broader package of support in which healthcare personnel characteristics, provision of food, or other provider-patient interactions play a vital role. Findings have implication for practice and research, including collaboration with health systems of neighboring countries.

Specific findings in that research served as the foundation for the proposed research study: (1) SAT was the primary treatment strategy offered at hospital based clinics where the vast majority of patients received treatment; (2) patients lack TB understanding; and (3) the majority of the identified barriers were classified as system level. Thus, the proposed research to improve TB care outcomes is based on a logical determination to maximize a ubiquitous and cost-effective technology to improve health system care, monitoring, and patient engagement in their care, in low-income, low-recourse settings.

Study Purpose

This dissertation research was comprised of two phases. The purpose of the first phase was to develop, in collaboration with a TB-specialized healthcare team and patients, an SMS-based intervention to promote TB treatment adherence. The purpose of the second phase was to implement and assess the feasibility and acceptability of the SMS intervention, explore its initial efficacy, and to identify feasibility issues to be considered for conducting a larger trial.

Specific Aims

Phase 1 (Intervention Development)

The aim of the first phase was to describe the development of a collaborative, theory-guided short message service (SMS)-based intervention to promote tuberculosis (TB) treatment adherence.

Phase 2 (Pilot Study)

The aims of the second phase exploratory pilot study were as follows:

Aim 1

Evaluate the structure, process, and feasibility of conducting a trial with an SMS intervention in Argentina (e.g., the number of eligible participants, number consenting, number completing, log of issues, barriers, glitches and key informant interviews with providers and TB program director).

Aim 2

Examine the initial efficacy of the intervention comparing usual care and a medication calendar, to usual care plus a patient-mediated, mobile phone text messaging-based intervention on outcomes of: (a) adherence rates (e.g., patterns of adherence, percent of days reporting adherence); (b) sputum-smear conversion rates; and (c) final treatment outcomes were added as an additional outcome.

Aim 3

Evaluate perceptions of intervention acceptance, acceptability, and feasibility (including intervention cost), and how to optimize the intervention from the perspective of the patients and TB-specialized healthcare team.

Theoretical Framework

Two theoretical frameworks were used in this research during development and evaluation. The Information-Motivation-Behavioral Skills (IMB) was used to facilitate educational message selection during intervention development (Fisher, Fisher, Amico, & Harman, 2006; Munro, Lewin, Swart, & Volmink, 2007), and the socio-technical framework was used to evaluate the intervention during implementation (Barber, Cornford, & Klecun, 2007).

The IMB model was used in this research to develop a coding scheme and to select the educational messages that were used in the intervention. The IMB model suggests that to initiate and maintain a desired behavior, such as medication adherence, adherence-related information and motivation must be provided, along with appropriate tools and strategies to maintain the behavior (Fisher et al., 2006). Adherence-related information should target information gaps and focus on delivering accurate information regarding disease, its treatment and transmission, and medication side effects or drug interactions (Fisher et al., 2006; S. Munro et al., 2007). To strengthen motivation and to change or maintain adherence related behavior, social support needs to be provided and beliefs and attitudes towards adherence must be acknowledged. The IMB model was initially developed to promote HIV prevention interventions in inner-city minority settings (Fisher & Fisher, 1992; Fisher, Fisher, Bryan, & Misovich, 2002) and was then adapted to

promote antiretroviral treatment adherence (Amico, Toro-Alfonso, & Fisher, 2005; Fisher et al., 2006). TB researchers have suggested that the IMB model could be helpful to promote adherence to TB treatment as well (Fisher et al., 2006; S. Munro et al., 2007).

The socio-technical framework was used to evaluate the intervention during implementation and help identify issues to consider in conducting a larger trial using the text-messaging based intervention (Barber et al., 2007). Examining a technical intervention while in use can provide an opportunity to understand and respond to user and provider needs and improve the intervention (Harrison, Koppel, & Bar-Lev, 2007). The socio-technical approach helps guide researchers to conduct an in-depth formative evaluation and achieve improvements in system design and implementation by considering technological innovation as a social process (Berg, Aarts, & van der Lei, 2003). Evaluation is an important step in system development and can help define the intervention's ability to meet overall organizational goals, in this case TB control measures. Evaluation includes recognizing complaints, challenges, and shifts in relationships or user acceptability. Insufficient evaluation can lead to unintended consequences of intervention implementation, and may undermine quality and safety, leading to implementation failure (Berg et al., 2003; Harrison et al., 2007).

The socio-technical framework for evaluating an intervention is a way to organize formative evaluations (Barber et al., 2007). According to the socio-technical approach, the investigator must look beyond the technical aspects of system function, and take into account the human perspective and organizational context (Cornford, Doukidis, & Forster, 1994). The socio-technical framework can be structured like a matrix. The structure, process, and outcomes are observed through system function (technical),

human, and organizational lenses. S*tructure* is the components that make up the system, *process,* is how those components interact, and *outcome* is the result of the interaction of structures and processes (Barber et al., 2007; Cornford et al., 1994). The framework was used to guide the analysis and outputs of phase 2. Table 1.1 describes how the socio-technical framework is reflected by particular aspects of this study. Examples of structural aspects related to system function were the technical details of hardware and software setup, requirements regarding the data and how they were organized, and the content of the text messages sent during the intervention. Technical/system process elements were related to the software's information processing (e.g., FrontlineSMS software functions). The expected outcome (deliverable) of the development phase, from the technical perspective, was that the FrontlineSMS software was up and running, and that the expected functionality of the software (such as sending and receiving text messages, and the ability to store and retrieve the data) was tested through actual use.

From the human and organizational (social) perspective, structural development aspects included the work conditions and staff patterns, and skill level and intervention training needed at the research site (e.g., computer skills, experience with text messaging). At the organizational level, structural aspects included estimating the cost of the intervention and organizational support for management and equipment needs. Process elements in the social perspective focused on communication interactions during the intervention (e.g., changes in workflow and negotiation of who monitored the system, protocol management). Development *outcomes* from the social perspective included the text message implementation protocol, an operational outline established in collaboration

Table 1.1. Theoretical/Conceptual and Evaluation Framework

	Technical	**Social**	
	System Function	**Human Perspective**	**Organizational Context**
Structure	Technical detail: computer- based intervention details • User requirements • Hardware, software setup	Adapting work conditions to intervention • Skill level and training needed • Work conditions	Sustainability: costs, management and equipment needs • Cost • Sustainability requirements • Organizational / technical support
Process	Information processing • What intervention captures • How organized • Software function	Participation / social interaction • Team's participation • Process of sending, receiving, responding to text messages	Altered practice / service delivery • Aspects of intervention (how fits into program) • Changes in workflow and monitoring
Outcome	Technical performance: efficiency, reliability • Hardware/software issues • System reliability • Applicability	Quality of service and individual outcomes • Perceptions of quality • Changes in workflow/load • Text message relevance	Global effect • Lessons learned • Process of implementing • Considerations for larger trial

Note. Adapted from Conford et al. (1994) and Barber et al. (2007)

with the local TB team (organizational context), and training of key personnel to use the software (human perspective).

Phase 2, the pilot research study, was comprised of three aims encompassing overall clinical efficacy and global effect of the intervention (aim 1); and lessons learned, optimization and sustainability of the intervention, and potential application to other settings (aim 3). Evaluation of the intervention implementation *structure and process*, aim 2, informed the evaluation for the future delivery of the intervention.

The research aims did not map exclusively to one cell within of the socio-technical framework matrix. Aim 1 was principally situated within the *outcome* at the organizational context, reporting on overall sample outcomes. Aim 2 evaluated structure and process across the system functions and human perspective. Along with the quantitative data, a matrix with principal findings reported outcomes from the system function, human perspective, and organizational context. Aim 3 focused on the organizational perspective of *sustainability* and considers the balance between the system/technical aspects and human perspective in determining ways to optimize the structure and processes of the intervention for long-term use. See Table 1.2. for mapping of research aims to the framework.

Rationale

The proposed study was conducted in an outpatient clinic within a public pulmonary specialized hospital within a high TB burden health region in Argentina. The rationale for conducting the proposed research in the selected hospital was threefold: (1) the investigator had an established collaborative relationship with a regional TB director and a research institute through a 1-year mentored research experience as a Fogarty International Clinical Research Scholar; (2) the hospital was in a high TB burden health region; and (3) the current standard of treatment delivery at the selected hospital was self-administration of treatment.

The rationale for the proposed intervention was based on the trialing and successful preliminary findings of text-messaging based interventions proposed for antiretroviral therapy adherence (De Costa et al., 2010; Lester et al., 2009) and the transition on the part of WHO's international recommendations to provided patient-centered support

Table 1.2. Mapping of Research Aims to Framework and Potential Findings

	System Function	**Human Perspective**	**Organizational Context**
Outcome	Relevant, applicable, reliable	Quality of service, individual outcome	Global effect; lessons learned
Aims	2 and 3	2 and 3	1 and 3
Types of findings	• Hardware/software issues • Appropriateness • Issues of system • Perceptions • Text message relevance	• Perceptions of quality • Outcomes for individuals (i.e., adaption by staff) • Changes in workflow, workload • Experiences	• Population outcomes • Efficacy of intervention • Process involved in implementing • Balance tech/human perspective • If intervention is continued
Analysis from	Study log Interviews	Study log Interviews	Quantitative data Interviews

to promote medication adherence rather than strictly DOT (Tuberculosis Coalition for Technical Assistance, 2009). Furthermore, the rapid adoption of mobile phones has led researchers to suggest that mobile phone-based interventions may be a viable medium to improve TB treatment outcomes (Barclay, 2009).

Ideally an effective vaccine or new effective drugs requiring a shorter treatment course will be developed. In the meantime, we need to focus efforts on improving treatment success with current treatment regimens in order to reach the STOP TB goal of decreasing by 50% the TB incidence by 2015 and eliminating TB as a public threat by 2050 (World Health Organization, 2009b). Thus, the proposed research to promote TB treatment adherence was based on a logical determination to maximize a ubiquitous and potentially cost-effective technology (mobile phone) to deliver an appropriate, usable, and efficient intervention to monitor and engage patients with their own TB care, in low-income, low-resource settings.

Overview of Dissertation

This dissertation is organized into seven chapters, three of which have been prepared as manuscripts (Chapters 4, 5 and 6) with distinct formatting according to the requirements of each journal. This chapter provides an overview of the problem of TB both globally and specifically in Argentina, the specific aims of the study and the theoretical frameworks applied. Chapter 1 also highlights the preliminary work that led to the collaborative relationships and the groundwork from which this dissertation ensued. Chapter 2 provides the literature review on TB pathology and treatment, strategies in use for assuring adherence, and applications of mobile phones in the health sector and then specifically in TB management. Chapter 3 is an overview of the study design and methods used in this research study. Within Chapters 4, 5, and 6 further detail of methods used for each phase of this study are provided. Chapter 4 details the collaborative development process of phase one to finalize the text messaging based intervention. Chapter 5 provides the findings of the randomized controlled pilot study. Chapter 6 describes the socio-technical evaluation of the intervention to identify considerations for conducting a study using the text messaging based intervention on a larger scale. Chapter 7 summarizes and synthesizes the findings from both phases, highlights limitations encountered, and makes recommendations for research and practice.

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CHAPTER 2

REVIEW OF THE LITERATURE

Introduction

The literature review was conducted using multiple databases and strategies. Electronic databases searched included PubMed, the Cochrane Library, Google Scholar, and Latin American and Caribbean health sciences (LILAC). CINAHL has been used in the past, but previously has not yielded much outside of PubMed. Mesh terms and keywords used for searches included tuberculosis, mobile phone, text-messaging, drug adherence, DOT, treatment completion, and socio-technical approach. Website and online resources, such as the World Health Organization and the Centers for Disease Control and Prevention, were searched for up-to-date protocols, TB related statistics, and publications. The Global Health Direct Online is an online platform of communities developed by the Global Health Delivery Project (http://www.ghdonline.org). The Global Health Direct Online platform was used to post queries and request resources in global TB treatment and management from a global network of healthcare providers and researchers. In addition, the online FrontlineSMS forum was used to post questions during the implementation phase to troubleshoot issues (FrontlineSMS, 2011). Reference lists of published articles and relevant reviews were checked for additional references. Authors of relevant papers were contacted regarding any further published or

unpublished work. For example, articles and information were obtained through email correspondence with the developers and directors of FrontlineSMS, the computer-based text messaging system that was used in this study. Table 2.1 highlights the general categories and subcategories outlined to guide the review of literature.

TB History, Pathogenesis, and Treatment

History of TB

TB is an ancient disease that has accompanied humankind for millennia. Fossil records from 5000 BC show prehistoric humans with evidence of TB (Nebraska Department of Health & Human Services, 2007). The disease was first formally described by Hippocrates around 460BC and has been known by many names, including consumption, white plague, and wasting disease. In 1882 Robert Koch identified the bacterium *Mycobacterium tuberculosis* as the cause of the disease (Centers for Disease Control and Prevention, 2010). The sanitariums used to isolate and treat TB patients prior to antibiotics were mostly closed by the mid-1970s (Centers for Disease Control and Prevention, 2010).

Table 2.1. Literature Review Topics and Subtopics

Category	Subcategory
TB	History, Pathogenesis and Treatment
Treatment Strategies	DOT Debate
Medication Adherence	Outcomes of Nonadherence Barriers to Adherence Theoretical Approaches to Adherence
Mobile Phone Potential	Mobile Phones in Healthcare Settings Mobile Phones in TB Management
Summary of Literature Knowledge Gap Filled by This Study	

Pathogenesis

TB, most commonly caused by the bacteria *Mycobacterium tuberculosis,* typically affects the lungs (pulmonary TB), but can affect other parts of the body (extrapulmonary TB) (Centers for Disease Control and Prevention, 2010). Symptoms can include cough, fever, and weight loss (Centers for Disease Control and Prevention, 2010). Like the common cold, pulmonary TB is a communicable disease and spreads from person to person via droplet nuclei carrying the bacteria through the air by cough, sneeze or spit (Centers for Disease Control and Prevention, 2010). Sputum-smear positive pulmonary TB cases are highly infectious and have the potential to infect 10 to15 people per year if left untreated (World Health Organization, 2007). It is estimated that every second a person is newly infected with TB somewhere in the world (World Health Organization, 2007). Most infections result in the latent form of TB, which can remain dormant for life. One in 10 cases transition into active TB disease (World Health Organization, 1999). If left untreated TB has a 50% mortality rate (World Health Organization, 2007).

Active TB occurs when the immune system is weakened by various emotional or physical triggers (World Health Organization, 1999). Most notably, HIV infection is recognized as an important risk factor for activating latent TB and also increases the risk of rapid progression of the disease once infected (Corbett et al., 2003). Other predisposing conditions that increase transition, from latent disease to active, include diabetes, substance abuse, immunosuppressive therapy, and organ transplant (Centers for Disease Control and Prevention, 2010).

Treatment

First line TB medication was discovered in the 1940s and 50s and has been used since that time (Centers for Disease Control and Prevention, 2010). In the Direct Observation of Treatment, Short course (DOTS) strategy, the "S" represents short-course treatment. Short course treatment refers to a treatment regimen that lasts 6 to 8 months and uses a combination of anti-TB medications compared to a long-course regimen, which lasts 12-18 months (World Health Organization, 1999).

Standardized treatment regimens are based on whether the patient is classified as a new case or a previously treated case. The WHO recommends that first time TB diagnosed patients receive a 6-month treatment regimen consisting of a 2- month *intensive* phase with four drugs daily (rifampicin, isoniazid, pyrazinamide, and ethambutol), followed by a 4- month *continuation* phase with two drugs (isoniazid and rifampin) daily or intermittently (three times a week) (World Health Organization, 2006). Suspected or confirmed tuberculosis caused by drug-resistant organisms should be treated with appropriate second line drugs for at least 18-24 months past confirmed sputum culture conversion (Tuberculosis Coalition for Technical Assistance, 2009). Therapy is less effective and more costly for MDR-TB.

Pulmonary TB treatment response should be monitored by conducting follow-up sputum microscopy after completing the intensive phase. If positive after the intensive treatment phase, the patient should be retested after receiving 3 months of treatment. If positive after 3 months of treatment, drug susceptibility testing and cultures need to be conducted (Tuberculosis Coalition for Technical Assistance, 2009). The American Thoracic Society, CDC, and Infectious Diseases Society of America (2003) recommends

basing treatment completion on the number of doses taken. For example, for the 6-month daily (7 days/week) regimen, dosages must include at least 182 doses of rifampicin and isoniazid and 56 doses of pyrazinamide. If doses are not delivered within 6 months it is recommended that treatment continue until doses are received (MMWR Recommendations and Reports, 2003). If there is an interruption in treatment of 14 days or more during the initial phase it is recommended that treatment be restarted from the beginning (MMWR Recommendations and Reports, 2003).

Treatment Strategies

The International Standards for Tuberculosis Care (ISTC), standards 7 through 13, outline appropriate treatment regimens, measures to assure treatment adherence, standards to address poor adherence when it occurs, and appropriate monitoring of response to therapy (Tuberculosis Coalition for Technical Assistance, 2009). The key component of a public health response to TB is to protect and care for the individual and community, fulfilling the role of preventing ongoing transmission and the development of resistant strains (Tuberculosis Coalition for Technical Assistance, 2009).

A current objective of TB treatment strategies is for patients to take on an active role as partners with healthcare team members (World Health Organization, 2009a). To contribute to personal as well as community health, patients can share information with healthcare providers and pass on their expertise gained during treatment with others in the community (World Health Organization, 2009a). Regular supervision and support promotes greater opportunities for education, resolution of barriers and quick detection of nonadherence and monitoring of reactions or worsening symptoms (World Health Organization, 2009a).

The ISTC indicate that supervision and support should be individualized and should draw on the full range of recommended interventions and available support services, including patient counseling and education (Tuberculosis Coalition for Technical Assistance, 2009). A central element of the patient centered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs. These measures should be "tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider" (Tuberculosis Coalition for Technical Assistance, 2009, p.12). Suggested treatment strategies include DOT, use of treatment supporters, or appropriate incentives to assure treatment adherence (Tuberculosis Coalition for Technical Assistance, 2009).

DOT Debate

The idea of DOT emerged in the 1950s and was the central strategy to assure treatment adherence and to cure TB (Bayer & Wilkinson, 1995; Kelly Morris, 1997). However, the efficacy of DOT has been the subject of extensive debate (Macq, Theobald, Dick, & Dembele, 2003; Pope & Chaisson, 2003; Volmink & Garner, 2007).

A Cochrane Systematic Review conducted by Volmink and Garner (2006) aimed to evaluate the effectiveness of DOT. In the 10 randomized controlled trials included in the review (approximately 4000 participants), Volmink and Garner (2006) found no statistically significant difference when comparing DOT and self-administration in respect to the number of people cured (RR 1.02, 95% CI 0.86 to 1.21) or the number of people who completed treatment (RR 1.06, 95% CI 1.00 to 1.13). Stratifying treatment outcomes by location, DOT at home or at a clinic, resulted in a small improvement using home-based DOT (1.10, 95% CI 1.02 to 1.18) (Volmink & Garner, 2007). When

comparing DOT observed by healthcare workers, family members, or therapy provided without supervision, Khan and colleagues (2002) demonstrated no statistically significant differences in the cure rate for the different arms. The researchers found that DOT with healthcare workers was the least cost-effective approach, and therapy provided without supervision was the most cost effective (Khan et al., 2002). Similarly, Walley and colleagues (2001) evaluated healthcare worker observed, family observed, and therapy provided without supervision and found similar cure rates (64%, 55%, and 62%) and completion rates (67%, 62%, and 65%) across groups, respectively. Of note, the research described above conducted by Khan and colleagues (2002) and Walley and colleagues (2001) was included as then unpublished data in the Cochrane review (Volmink & Garner, 2007).

However, some researchers have contested the validity of the studies used in the Cochrane review (Pope & Chaisson, 2003). Pope and Chaisson (2003) proposed that there was a failure of analysis to account for additional study interventions that could have affected treatment completion, such as financial accessibility, patient choice of treatment observer, or time to take observed dose at clinic (Pope & Chaisson, 2003). In addition, Pope and Chaisson (2003) argue that the DOT intervention was operationalized differently in each of the three main randomized studies that were evaluated in the Cochrane review. Nonetheless, the Cochrane review clearly noted that DOT programs may be attributable to simultaneous inputs rather than direct observation specifically, and the studies included clearly matched the inclusion criteria of the review (Volmink & Garner, 2006).

Macq and colleagues (2003) conducted a study to understand the varying perspectives and implementation practices of DOT internationally. They conducted open-ended, qualitative interviews with professionals (*N*=19) from 17 countries in Africa, Asia, Europe, and Latin and North America who were attending an international TB conference. The investigators identified a wide array of treatment model options being applied, including substantial variations of WHO-recommended DOT. In addition, the researchers found a shift in the DOT provider from professionals to lay community people and a shift in DOT application from initially rigid to more locally tailored patient-specific approaches to make treatment more accessible to patients. Macq and colleagues (2003) concluded that work was needed to establish better case-holding, improve cure rates and identify equitable treatment delivery approaches. In addition, they suggested that context specific approaches needed to be explored and evaluated based on patient and provider perspectives (Macq et al., 2003). No Argentine representative was included in the sample; thus the Argentina provider experience was not represented.

Medication Adherence

Medication adherence is recognized as a complex and dynamic phenomenon within various contexts (e.g., personal, social, economic, or political) (Munro, Lewin, Swart, & Volmink, 2007; S. A. Munro et al., 2007). Many health behavior change theories exist, as well as theories focused on medication adherence. Theories can help guide behavior change interventions by promoting the understanding of a health-related behavior, directing research, guiding the interpretation of outcomes or by helping to translate and transfer an intervention from one setting or health issue to another (S. Munro et al., 2007; Ruppar, 2010). Progress in adherence research has been slow and has resulted in overall

disappointing effects over the last 30 years (van Dulmen et al., 2007). Unlike chronic disease, nonadherence to an infectious disease, such as TB, can lead to public health risks including prolonged infectivity and drug resistance (Maartens & Wilkinson, 2007; Mitchison, 1998). Adherence to long -term medication is defined as a medication regimen of 3 months or greater (S. Munro et al., 2007). This section aims to evaluate theories related to drug adherence, specifically in TB or long- term medication adherence.

In regard to terminology, the word *compliance* is now considered to be more closely associated with blame or judgment, while the currently used term *adherence* is thought to better capture the complex concept (World Health Organization, 2003). Initially the problem of compliance was considered a *patient* problem and only later were issues related to the provider and now the whole system considered in regard to treatment of long- term or chronic conditions (World Health Organization, 2003). Behavior change, involving learning, adapting and maintaining behavior are necessary to adhere to long-term medication regimens and may include strategies such as providing awards, reminders or promoting social support (World Health Organization, 2003). However, few studies have evaluated long-term adherence, making it difficult to indicate what kinds of interventions are capable of fostering long-term adherence improvements (van Dulmen et al., 2007). Furthermore, theory based research that reflects the complexity of TB has essentially been missing in studies on adherence and TB (Sumartojo, 1993).

Leventhal and Cameron (1987) identified five major theoretical approaches to adherence issues: biomedical; behavioral; communication; rational decision (also referred to as cognitive); and self-regulative systems. Each of the perspectives may have one or more theories that apply their approach. Table 2.2 illustrates the theoretical perspectives,

Table 2.2. Summary of Theoretical Approaches to Adherence

Approach	Theories	Behavior Assumptions	Behavior Changed by:	Interventions Examples
Biomedical	Biomedical (often lacks explicit theoretical explanations)	• Patient passive recipient of HC providers • Health/disease has biomedical cause (e.g., bacterial, virus) • Nonadherence caused by patient characteristics	• Targeting patient factors • Technical solutions	• Prescribe medications • Technical innovations (e.g., new devices to administer or monitor) • Biochemical measures to assess adherence • Implication of dosage and packaging
Behavioral	Operant, Social, Behavioral Learning	• Skills can be taught to manage illness	• Stimuli/cue • Rewards reinforce • Antecedent/consequence	• Reminders • Incentives • Reinforcement • Feedback
Communication		• Improved communication will improve behavior (e.g., adherence)	• Clear and comprehensible communication skills • Timing of instruction	• Persuasive communication • Patient education • Improve patient-provider interaction
Cognitive	Health Belief Model Social-cognitive Theory of Reasoned Action Protection motivation	• Determined by perceived health threats / benefits • Expectation of future events and outcomes • Individuals will choose action to most positive outcome	• Intent to improve ability to manage disease • Motivation determined by perceived social, group, norms and consequences regarding behavior acceptability and beliefs	• Education • Cost/benefit analysis as motivating factor • Weigh benefit and barriers

Table 2.2 continued

Approach	Theories	Behavior Assumptions	Behavior Changed by:	Interventions Examples
Self-Regulatory	Self-Regulation Theory	• People motivated to avoid and treat illness threats and actively solve problems • Aim to reach a state of internal equilibrium • Personality, beliefs and social and cultural context help inform how a health threat is represented and coping strategies selected	• Influenced by subjective experiences and emotions, perceptions of current status and goal • Plan to reach goal • Appraisal of progress helps differentiate between compliance for prevention and for cure • Illness representation mediated between health threat and action taken	• Theories do not provide specific guidance related to the design of interventions
Education (considered cognitive didactic approach)	May contain components of ≥ one theory (e.g., communication, cognitive, and self-regulatory)	• Teaching can be provided in different ways (e.g., individual, group, audio-visual, phone)	• Tailor to needs and situation • Transfer information and knowledge about disease and its management • *Why* adherence needed emphasized to influence attitudes and motivations	• Quality patient and provider relationship • Provider empathy, friendliness, interest and concern • Change dysfunctional ideas and perceptions • Aim is self-management
Stage	Trans-theoretical Model	• There are 5 discrete stages and processes of change	• Perceive advantages and disadvantages of behavior	• Intervene at specific stages of change

Adapted from Munro et al. (2007), van Dulmen et al. (2007), and the World Health Organization (2003)

examples of theories under each perspective, assumptions, factors that influence behavior changes according to each perspective, and examples of interventions. The table has been adapted from a systematic review of health behavior theories, a review of reviews pertaining to patient adherence to medication, and from the WHO report on adherence to long- term medications (S. Munro et al., 2007; van Dulmen et al., 2007; World Health Organization, 2003).

The systematic review by Munro and colleagues (2007) summarized and examined the usefulness of 11 health behavior theories in developing interventions to promote long-term adherence, specifically in TB and HIV/AIDS treatment. Although the aim of the study was to conduct a meta-analysis to assess effectiveness of theory based interventions, Munro and colleagues (2007) cite difficulties due to: (a) various methodological problems; (b) questions whether theories developed in, for example the US or UK are transferable to other social contexts; and (c) challenges to comparing theories across health categories. Munro and colleagues (2007) concluded that there was no clear or conclusive evidence yet for the support of any of the evaluated adherence behavior theories. For example, reviews on health care behavior interventions using the communication perspective showed limited and mixed results on effects such as adherence (S. Munro et al., 2007). Ultimately for TB or HIV/AIDS adherence research Munro and colleagues (2007) suggested identifying common variables in the theories to help provide guidance to the most important variables and to attempt to integrate theories along with considering dimensions, outside of the individual patient control, such as organizational and structural factors (S. Munro et al., 2007).

In a review of reviews to identify theories for effective interventions to improve patient adherence to medication treatment, van Dulmen and colleagues (2007) found that comprehensive interventions that combined cognitive, behavioral, and affective components were more effective than single focus interventions (e.g., purely educational being least successful). However, a Cochrane review on medication adherence interventions with a follow-up period of at least 6 months concluded that: (a) less than half of the interventions resulted in improved adherence; (b) interventions that were effective were complex and labor-intensive; and (c) large improvements in adherence and treatment outcomes were not seen with even the most effective interventions (Haynes et al., 2005). To foster theory development for effective interventions, such as technical solutions, that are not associated with a specific theory, van Dulman and colleagues (2007) recommended collaborating with and drawing from other fields and perspectives (e.g., ergonomics, human engineering, and technical sciences). Secondly, van Dulmen and colleagues (2007) point out that there are effective behavioral interventions, such as incentives and reminders, that may be specifically worthwhile for nonadherent patients who forget to take their medication. Finally, it remains inconclusive which theory (behavioral, biomedical, or educational) or effective components are more or less effective in improving adherence due to a lack of studies that specifically contrast theories and their components (van Dulmen et al., 2007).

Although theory-driven system change strategies based on health behavior theories are recommended, each of the theories has notable weaknesses (Ruppar, 2010). In addition, individual theories are seldom used alone for intervention development, specifically the biomedical, behavioral, or communication theories (S. Munro et al.,

2007). For example, developing good provider-patient interactions, as guided by the communication theory, is necessary and has been shown to improve patient satisfaction, yet in itself it is not sufficient to elicit adherence behavior change (World Health Organization, 2003). Although the self-regulation perspective and theory recognizes that an individual's representation in health and choice for coping strategy is informed by their personality, social and cultural surroundings, the theory offers little to guide the design of interventions, such as ways to promote adherence (World Health Organization, 2003). Criticisms of the stage theory or transtheoretical model include not providing information on how or why people change or succeed, assigning arbitrary time periods, and for applying discrete stages into which actions cannot easily be separated (S. Munro et al., 2007). The cognitive approaches fail to address patients' behavior coping skills (World Health Organization, 2003). Given the complexity of medication adherence and the multitude of theories available with no one theory providing clear or measurable differences, there remains the need for further testing of interventions that are theory driven (S. Munro et al., 2007; van Dulmen et al., 2007; World Health Organization, 2003).

Mobile Phone Potential

The mobile phone is cited as the most rapidly adopted technology on the planet (ITU, 2009). In 2009, there were an estimated 4.6 billion mobile phone subscribers (ITU, 2009). In 2013, that figure has grown to 6.8 billion, which is almost as many mobile phones subscribers as people on earth (ITU, 2013). As services have become more affordable the penetration of mobile phone use has increased (ITU, 2013).

The continuous growth in mobile phone use has also been seen in Argentina. In 2010, with an estimated population of 40.9 million (Instituto Nacional de Estadistica y censos (INDEC), 2001), there were 50.4 million mobile phones in service, in contrast to 9.2 million land lines, and 5.8 billion SMS text messages sent monthly (Instituto Nacional de Estadistica y censos (INDEC), 2010). In 2013, the number of mobile phones in service increased to 59.6 million and the number of SMS text messages to 11.3 billion (Instituto Nacional de Estadistica y censos (INDEC), 2013).

Kumar and colleagues (2013) outline a myriad of potential mobile health (mHealth) based interventions, such as sensors embedded within a mobile phone, rapid diagnostic tools, and means to monitor and provide remote healthcare services. SMS text messaging, specifically, also holds potential to improve clinical management and treatment adherence by increasing communication, promoting patients as partners and decreasing stigma associated with daily clinic attendance to receive TB treatment (Kaplan, 2006). However, it is uncertain whether the platform of SMS- based technology, specifically interventions with the purpose of supporting or altering a health outcome, can replace the face-to-face contact with healthcare team members provided by DOT (Barclay, 2009; Kaplan, 2006). The success of healthcare delivery using mobile devices is stated to be dependent upon collaborative transdisciplinary research efforts among computing, engineering, and medical researchers (Kumar et al., 2013).

In healthcare, the use of text messaging to improve health outcomes is a growing area of investigation. Studies applying text messaging intervention span from promoting outpatient appointment attendance (Downer, Meara, & Da Costa, 2005; Downer, Meara, Da Costa, & Sethuraman, 2006; Kruse, Hansen, & Olesen, 2009), managing chronic

diseases such as asthma, diabetes and weight management (Hanauer, Wentzell, Laffel, & Laffel, 2009; Hung et al., 2007; Vidrine, Arduino, & Gritz, 2006) to conducting smoking cessation programs (Vidrine et al., 2006) and infectious disease contact follow-up (Cochrane, Lowbridge, Maywood, & Conaty, 2009). These studies demonstrated that text messaging is a feasible, acceptable, and effective intervention tool for the multiple applications.

Mobile Phone Use for Medication Adherence

Few studies have evaluated medication adherence using mobile phone mediated interventions. Puccio et al. (2006) piloted a daily mobile phone voice call reminder to improve antiretroviral medication adherence with eight adolescents. Investigators in this 12-week pilot study concluded that the reminders were practical and acceptable to participants, but after termination of reminders the improvements in viral suppression worsened for all but two patients (Puccio et al., 2006). A text messaging based study sending two messages per week to provide information on hypertension and to remind patients (N=67) to take their medication concluded no significant difference in rate of medication compliance, based on blood pressure measured at established intervals and pill count, between control and intervention group (Marquez Contreras et al., 2004).

Kaplan and colleagues (2006) conducted a review to evaluate the efficacy of mobile phone use for healthcare interventions in developing countries. The researchers found almost no published literature using mobile phones for interventions to influence clinical outcomes, evidence of effectiveness, or cost effectiveness for infectious disease treatment or chronic conditions (Kaplan, 2006). Only recently have mobile phone based interventions been suggested or studied as a potentially effective tool to help combat

infectious diseases, particularly HIV/AIDS (Lester & Karanja, 2008; R. Lester et al., 2009; K. Morris, 2009; Ybarra & Bull, 2007). The two trials, which were underway during the development of this current dissertation study, aimed to evaluate mobile phone use in drug adherence for treatment of HIV in Kenya and South India (De Costa et al., 2010; R. Lester et al., 2009). To date two randomized controlled trials (RCTs) have been published (R. T. Lester et al., 2010; Pop-Eleches et al., 2011). In Kenya, Lester et al. (2010) sent a weekly text message to patients (n=273) with one word in the local language which meant "How are you?" asking the participants to respond within 48 hr comparing self-reported adherence to patients in a control group (n=265). Also in Kenya, Pop-Eleches et al. (2011) randomized 431 patients to one of four groups where they received short reminders to take medication or long reminders to take medication along with a motivational message either daily or weekly. Those who were randomized to the control group received a mobile phone, but no text messaging intervention. Both of the published RCTs demonstrated improved antiretroviral therapy (ART) adherence using SMS support (R. T. Lester et al., 2010; Pop-Eleches et al., 2011). In addition, Horvath et al. (2012) conducted a Cochrane review which included two RCTs (the two just mentioned), and concluded that there is high quality evidence that text-messages enhanced adherence to ART compared to standard care. In the Cochrane review authors indicated that there are three RCTs in progress.

Mobile Phone Use for TB Management

In Nigeria mobile phones are being hailed as a promising solution to the growing TB crisis (Appiah, 2013). Researchers have trained TB supervisors to use a mobile phone based checklist to monitor patients and collect data during supportive supervision visits

(Appiah, 2013). Improvements in quality of care have been identified, such as cure rate (62% to 79%) and initiation of preventative treatment for HIV-TB coinfections (33% to 100%) over a 1- year period. A rapid diagnostic test to identify drug resistance with GenXpert is also being tested. In contrast to paper charting and tracking, researchers note that the mobile phone based checklist is improving data accuracy and reducing time for data to be received by TB officers, allowing for quick responses to problems (Appiah, 2013). However, researchers also caution that care must be taken because patients can still be lost in the wireless networks and not everyone will quickly or easily adopt the mobile phone expansion (Appiah, 2013).

In Malawi, Mahmud and colleagues (2010) implemented a first of its kind text message-based intervention to bridge the communication gap between patients and healthcare providers. The investigators introduced a communication network between community health workers and physicians using FrontlineSMS open-source SMS software. The intervention consisted of supplying community health workers and home-based nurses with mobile phones and hospital staff with a laptop equipped with FrontlineSMS software and training them to use and manage SMS messages. The text messages were analyzed for category of message, amount of usage, and efficiency of outcomes (cost, worker time saved/lost, and patients enrolled in the TB treatment program). The network usage was assessed after 6 months, with the majority of SMS messages sent by healthcare workers reporting on adherence for TB and antiretroviral treatment and symptom reporting. Mahmud and colleagues (2010) also assessed piloting cost, worker time/gained, and lost and patient enrollment in TB programs. Reported cost savings by a home based care nurse and TB coordinator was $1000 and $2000, with 500

and 648 hours of time saved, respectively. The TB coordinator was able to double the patient load from 100 to 200 cases due to the time saved. The cost of nearly 3000 SMS messages over the 6- month period amounted to approximately $250, with an estimated hospital net savings of nearly $3000 and overall estimated 2,048 worker hours saved (Mahmud et al., 2010).

Other mobile phone based TB interventions have focused on providing Mobile Direct Observation of Treatment (MDOT) or video (V-DOT) (DeMaio, Schwartz, Cooley, & Tice, 2001; Hoffman et al., 2010; Wade, Karnon, Eliott, & Hiller, 2012). In the US DeMaio et al. (2001) assessed TB treatment adherence with six patients using two-way video phones, at a cost of $200USD each. The researchers found similar adherence outcomes as standard DOT. In another proof-of-concept pilot study, Hoffman and colleagues (2010) provided video-capable mobile phones to 13 TB patients in Nairobi, Kenya. The intervention included sending a daily video of the patient taking the TB medication by a treatment supporter with the video-capable phones, and receiving on average one video and four SMS health messages per week. Nurses reviewed the videos and participants completed three questionnaires at intake, 15 days and after 1 month to rate technology, receptivity and preferences. The participants in this study preferred health testimonials over health messaging videos, and reminders were valued. In Australia, Wade et al. (2012) conducted a retrospective cohort study (N=128) comparing M-DOT with in-home DOT by a healthcare provider. The researchers found fewer missed observations using M-DOT than with the traditional DOT and cost-effectiveness was documented. In all of these studies the video capable mobile phones were provided to the participants and almost all participants and healthcare professionals found the

model feasible, acceptable or a viable alternative to clinic or community health worker DOT (DeMaio et al., 2001; Hoffman et al., 2010; Wade et al., 2012). However, challenges using the video monitoring were also reported. Hoffman and colleagues (2010) indicated that they experienced slow system access, sporadic availability of treatment supporters to take video-recording, and recognition of the cost and current lack of video-enabled mobile phones in Kenya's general population. Authors recommended further studies evaluating MDOT's impact on medication adherence and cost effectiveness compared to other technologies and if it can be applied to other diseases.

In another mobile phone application Kunawarak et al. (2011) conducted a randomized control study with patients (N=98) with MDR and non-MDR TB in Thailand. The intervention group received daily reminder calls by an officer in a TB center to the patient's mobile phones and the control group received DOT by a family member. The researchers found a higher completion success rates in both intervention groups using daily mobile phone call reminder (p<0.001) than in the control group who received DOT by a family member, a significantly higher sputum conversion rate in patients with MDR (p<0.001), but a nonsignificant difference in sputum conversion between groups of the non-MDR patients (Kunawararak et al., 2011).

Few studies have specifically employed the text messaging feature of mobiles phones. Prior to conducting this dissertation study only one unpublished report was found using SMS messages as daily reminders for patients to take TB medication (Bridges.org, 2005). The study was conducted by a company, *On Cue* in Cape Town, South Africa (Bridges.org, 2005). The report indicated that the technology was functionally efficient and convenient for the patient, but due to project management

issues the intervention was not maintained and no peer-reviewed publication has been produced from the project conducted in 2003 (Bridges.org, 2005; Green, 2003). The company is now known as SIMpill and is selling its product commercially. More recently, Mohammed and colleagues (2012) applied the text messaging feature of the mobile phone in a nonrandomized study with 30 participants in India. The intervention included sending daily text message reminders to participants and asking them to respond with texting-in the time they took their medication. The intervention was for 1 month and participants on average had already been in treatment for 3 months. Overall the patients responded that they took their medication 57% of the time (Mohammed et al., 2012).

Summary of Literature

Mankind's longstanding history with TB, the mode of pathogenesis and the long treatment course illustrate some of the challenges faced in TB control efforts. TB is and will remain a major global public health problem until new treatment options or an effective vaccination is discovered and implemented on a global scale. In the meantime, the role of public health entities is to protect communities by caring for individuals with TB and limiting ongoing transmission and further development of drug resistant strains of the microorganism.

A current objective in TB management is to promote patients as partners (World Health Organization, 2009a) while individualizing and tailoring interventions to meet patient needs (Tuberculosis Coalition for Technical Assistance, 2009). Medication adherence is recognized as paramount to treatment success. Some of the highlighted barriers to TB treatment adherence, such as limited support, impact on work, lack of

knowledge regarding disease and treatment, and issues related to stigma (Cramm, Finkenflugel, Moller, & Nieboer, 2010; Iribarren, Rubinstein, Discacciati, & Pearce, 2011; S. A. Munro et al., 2007), may be circumvented using the mobile phone as a medium of interaction. While DOT might be an ideal treatment strategy for assuring treatment adherence (World Health Organization, 2009b), DOT efficacy has been questioned and its challenges to apply have limited its application in many settings (Macq et al., 2003; Pope & Chaisson, 2003; Volmink & Garner, 2007).

The mobile phone is currently an impressive global resource with the potential to improve health outcomes, especially in developing countries where access to healthcare services may be limited. With the rapidly expanding wave of wireless access and the growing body of mHealth intervention literature, there remains the need for rigorous testing and evaluation (Kaplan, 2006). Multiple studies using the mobile phone have shown acceptability and feasibility of the technology. Text messaging, specifically, holds promise to improve TB outcomes, but is yet uncertain (Barclay, 2009). Testing of concrete health outcomes, such as TB sputum clearance rates, has also been recommended (Mahmud et al., 2010).

Knowledge Gap Filled by This Study

No RCTs have been published reporting on text-messaging based interventions to promote TB treatment adherence. Moreover, SMS- based interventions have mostly focused on sending reminders or education messages (Chen, Fang, Chen, & Dai, 2008; Cochrane et al., 2009; Downer et al., 2006), but there are no published reports of trials of patient-initiated messaging intervention intended to promote the patient as a partner. In addition, theory driven interventions are recommended (S. Munro et al., 2007). Although

a video-mediated DOT program is appealing, video enabled mobile phones are currently more expensive and less accessible in many parts of the world. Given the gap in understanding of the feasibility or efficacy of mobile phone interventions in TB management and the reality that self-administration of therapy is the only treatment option for many, other patient-centered treatment strategies need to be developed and evaluated (Frieden & Sbarbaro, 2007)

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CHAPTER 3

METHODS

Research Design and Procedure

The proposed dissertation research was comprised of two phases. The first phase resulted in the final development of the text messaging based intervention in collaboration with the TB team in Argentina (see Chapter 4). The second phase was a mixed methods exploratory pilot study examining the feasibility, acceptability and initial efficacy of the intervention (see Chapter 5 and identifying issues to be considered for conducting a larger trial (see Chapter 6).

Phase 1

The collaborative research team was provided with the overall study objective and design and asked to participate in the final development of the intervention and protocol to guide intervention implementation. Collaborative efforts aimed to promote staff interest and 'buy in'. Educational text messages and reminders were developed and assessed for content validity, cultural and social appropriateness by the research team who were experts in TB and local Argentinean healthcare personnel. Educational text messages included recommendations from patients currently in treatment, advice from physicians and nurses, and from multiple sources using the IMB model. The team

established an algorithm to address and respond to text messaging issues or other potential situations. The algorithm included, for example, steps on how to respond to the situation when a notification was not received. Best methods to recruit patients at treatment initiation and roles of staff members were determined as a group. As part of the socio-technical approach the structure, process, and outcome were evaluated from a system, human, and organizational perspective.

Phase 2

The intervention was implemented as a mixed methods exploratory pilot study. Mixed methods research integrates traditional quantitative and qualitative research paradigms into a combined design, maximizing the strengths of both research paradigms (Creswell & Plano Clark, 2007; Tashakkori & Teddlie, 2003). Mixed method designs represent a pragmatic approach to obtaining valuable answers to questions best answered by multiple methodological frameworks (Johnson & Onwuegbuzie, 2004). Traditional quantitative research focuses on deduction, confirmation, and hypothesis testing using statistical analysis, whereas qualitative research approaches the topic through exploration, induction, and hypothesis generation (Creswell & Plano Clark, 2007). The combined design helped maximize the strengths of each paradigm and provide a rich understanding of the intervention process and outcomes.

All eligible participants received standard of care and were randomly assigned to a control arm, in which participants also instructed to complete a medication administration calendar or to the intervention arm, in which they received the text messaging intervention. See Figure 3.1, Phase 2 initial flow diagram, for the original protocol,

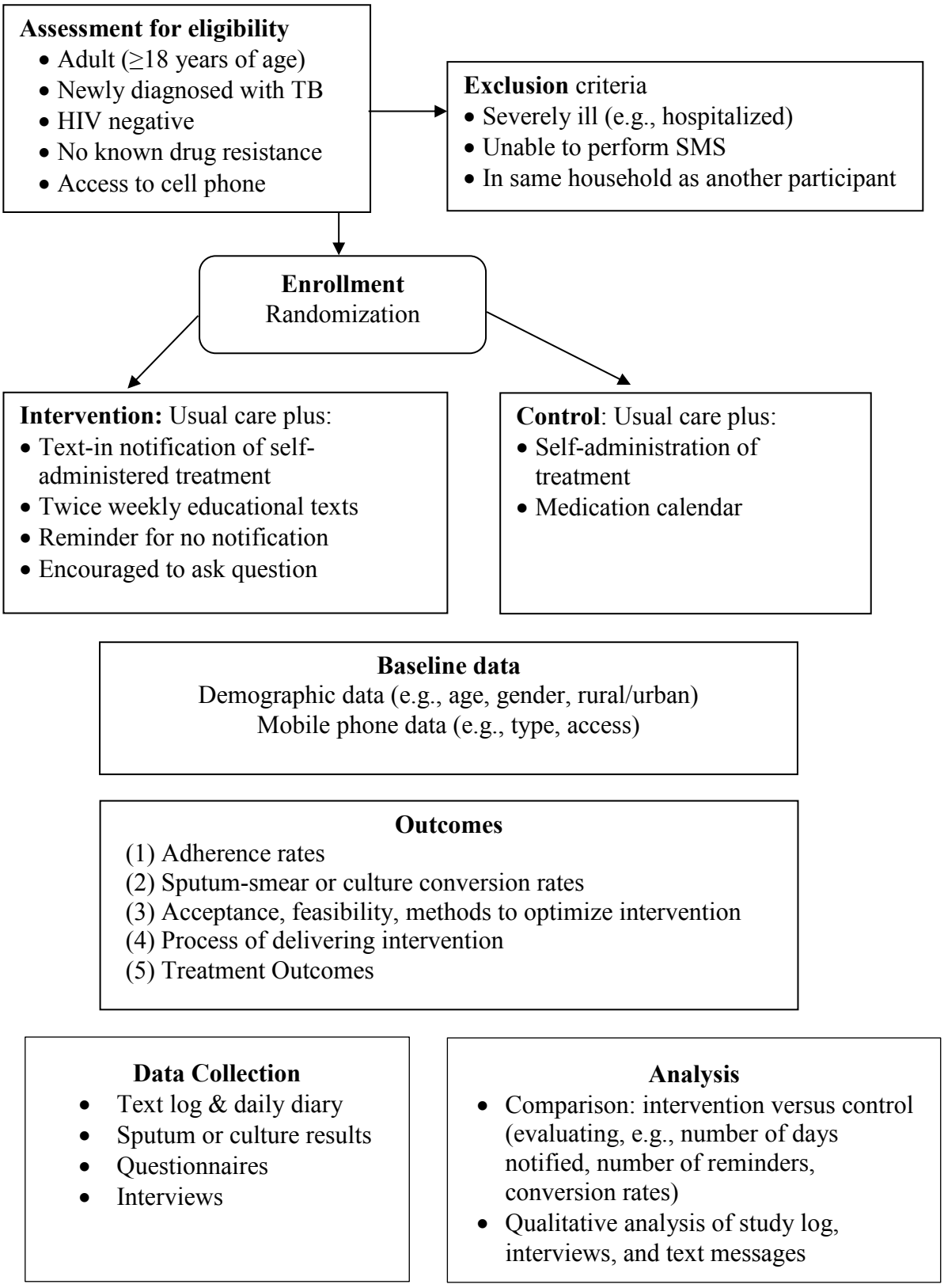

Figure 3.1. Phase 2 initial flow diagram

which reflects the amended inclusion criteria, completed intervention, and added treatment outcome variable. See Chapter 5 for the final Participant Flow Diagram.

Intervention

The intervention required patient participation and aimed to support communication between healthcare personnel and the patients to promote the patient as a partner. The intervention group was asked to 'text-in' daily after self-administration of medication. Educational text messages were sent twice weekly (e.g., regarding importance to continue treatment even if feeling better) and patients were encouraged to ask questions. A confirmation text message was sent to participants indicating the notification was received by staff. FrontlineSMS software was used to store and manage the text messages (FrontlineSMS, 2011). Participants were informed that the intervention was being provided within clinic hours and that an emergency must be directed through standard routes.

Control

The control group received the standard of care and was asked to return a medication calendar at the end of each month. Participants in the control group were not instructed to 'text in' nor did they receive educational text messages. Usual care included follow-up visits scheduled by primary care provider, medication allocated for a 1- month period, and treatment by self-administration. An analysis of concordance between self-report measures (interview, diary, or questionnaire) and non-self-report measures (electronic measures, drug levels, pill count, clinical opinion) found a medium to high concordance for diary measures and a questionnaire of medication adherence (Garber, Nau, Erickson,

Aikens, & Lawrence, 2004). A medication calendar was selected to enable daily comparison across control and intervention groups. In contrast, questionnaires ask about missed doses during a defined time period or medication use behaviors (Garber et al., 2004).

Process Measures

Acceptance and Feasibility of Intervention

Acceptance and feasibility of the intervention was assessed by interviews (see Appendix F Interview guide), and by examining the text messages received over the course of the intervention. Interviews included questions on technical feasibility, receptivity to text messaging intervention, patient preferences and receptivity to receiving health messages on mobile phone. Cost of intervention is a component of feasibility and was estimated by averaging the number of text messages sent per participant over the course of the study assessed during interview. Interviews lasted 15 to 60 minutes and were audio-recorded and transcribed verbatim (Lincoln & Guba, 1985) in the language of origin by a local, native Spanish speaker.

Exploratory Outcome Measures

Medication Adherence Rates

TB medication adherence rate was used as an intermediate variable to compare daily 'text-in' log (intervention) and daily medication diary (control). There is no empirical rationale for what percentage of medication missed constitutes nonadherence in TB management; therefore an empirical method of monitoring quantity and timing of medication taken is necessary to define adherence (World Health Organization, 2003).

Adherence data were analyzed in a number of ways. The rate of adherence was defined as the number of nonholiday or weekend days notified in the 60 days / 60 - the number of holiday or weekend days. The percent of notifications that were received without a reminder was defined as number of notifications without a reminder / total number of notifications. The calendars were assessed for the total number of nonholiday or weekend days notified.

Sputum-Smear Conversion Rates

Sputum specimens were ordered by the patients' physicians. Sputum smear conversion is a measure of adherence using the end-result of treatment as an indicator of success (World Health Organization, 2003). The WHO recommends sputum smear testing after completing the first 2 months of treatment (World Health Organization, 2009). Sputum smear or culture conversion was measured as conversion rate from positive at treatment initiation to negative at the end of the intensive treatment phase. The probability of detecting acid-fast TB bacilli in sputum microscopy is directly related to the concentration of bacilli in the sputum (Tuberculosis Coalition for Technical Assistance, 2009). Sputum smear results are likely to be positive when there are at least 10,000 organisms per milliliter of sputum, and at concentrations below 1,000 organisms per milliliter there is less than 10% chance of not observing acid-fast bacilli (Tuberculosis Coalition for Technical Assistance, 2009). For every 1000 sputum smear positive patients at the start of treatment, 183 (less than 20%) and 83 (8%) at 2 and 3 months, respectively, are expected to remain smear-positive when medication is taken as directed (World Health Organization, 2009). If patients were determined to have TB

drug resistance, by testing culture sensitivity, they would have been removed from the study protocol, because of required change in medication regimen (types and duration).

Treatment Outcomes

The treatment outcomes are classified as confirmed cure, treatment completion, abandoned treatment (leaving treatment for at minimum 2 months), or death. Treatment success rate was defined as the percent of patients who either completed treatment (without bacteriological confirmation) or were confirmed cured (negative sputum smear or culture in last month of treatment and on at least one previous occasion) (World Health Organization, 2009).

IRB Review

The study was the Institutional Review Boards of the University of Utah, Salt Lake City and the foreign IRB; *el Instituto Universitario del Hospital Italiano* of Buenos Aires, Argentina. The ethics committee at the Hospital Cetrangolo provided written approval of the study. The hospital did not have its own IRB.

Setting

The province of Buenos Aires concentrates 45% of the reported TB cases of the country (5,565/12,278 in 2004), of which 78% of the cases are in the areas surrounding the capital city (Chirico, Kuriger, Etchevarria, Casamajor, & Morcillo, 2007). Region V, north of the capital city, reports about a third of those cases detected in the province (1,571/5,565 in 2004) with an incidence rate of 49.2/100,000 (Chirico et al., 2007). (See Figure 3.2.) Individuals were recruited from the outpatient pulmonary clinic within the

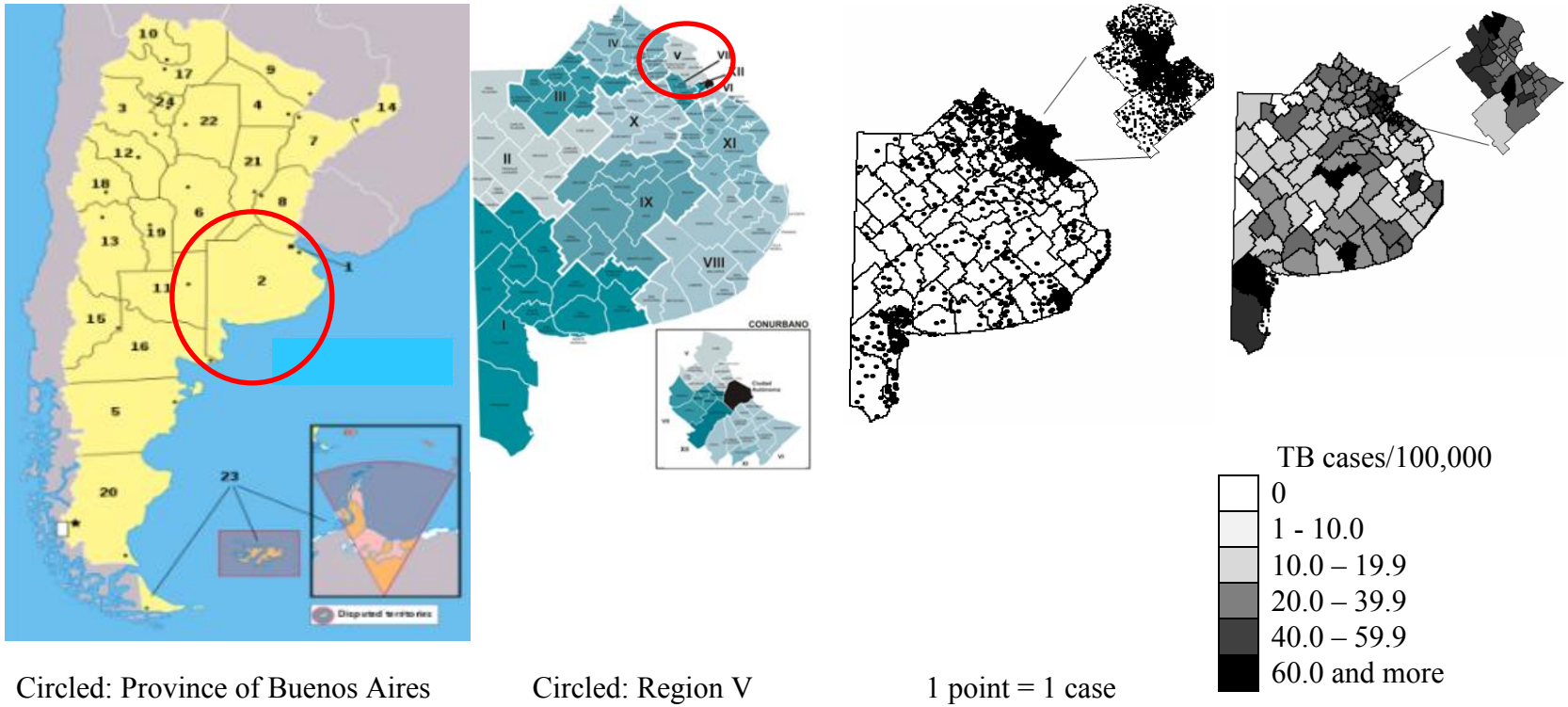

Figure 3.2. Maps of provinces, health regions, TB case burden and concentration, 2006
Adapted from Ministario de Salud (2008) & National Institute of Respiratory Illnesses (INER) (2007)
*Province of Buenos Aires

public hospital, Hospital Cetrangolo, located in Region V in the province of Buenos Aires, Argentina. The hospital serves both urban and suburban communities.

Participant Selection Criteria

Newly diagnosed TB patients who met the following inclusion criteria were recruited: ≥18 years of age, no known TB drug resistance, HIV negative (per self-report or medical record), initiating TB treatment for the first time, electing to continue treatment and follow-up at hospital, own or have personal access to a mobile phone, and able to operate mobile phone to communicate using text-messaging. *Excluded* were patients who were severely ill (e.g., requiring hospitalization) or resided in the same household with another study participant.Participants were adult men and women of all racial and ethnic backgrounds who met inclusion criteria.

An IRB addendum was made to the eligibility criteria after trial commencement to include patients receiving treatment who had previously completed or had abandoned treatment or had other forms of TB. This change was made because there were patients (*n*=15) being excluded for these reasons and the research team felt they might benefit from the intervention. Four patients were recruited who had or may have had extra-pulmonary TB and at least 2 had been treated previously.

Sample Size and Rationale

A convenience sample of 38 participants was recruited into the study. The recruitment goal of 40 adults (20 per group) was calculated based on Schoenfeld's statistical considerations for pilot studies (Schoenfeld, 1980). The sample size was based on the comparison between the proportion of patients who successfully complete

treatment compared to the WHO recommended rate of 85% (World Health Assembly, 1991). The treatment success for self-administration reported in local reports was about 67% (Chirico et al., 2007; Instituto Nacional de Enfermidades Respiratorias E. Coni, 2010). However, treatment success rates reported by the WHO were much lower, for example 48% in 2010 (World Health Organization, 2011). The more conservative higher rate was used to calculate the sample size. Applying Schoenfeld's recommendations to identify if intervention warrants further testing, a sample of 17 per group was needed to detect a response rate of 85%, compared to a 65% response rate (Schoenfeld, 1980). Therefore, the recommended cut off (clinical signal) that indicates further testing in a larger trial was 71% treatment success in the intervention group (Schoenfeld, 1980). Sample size was set at 20 per group to account for a 15% attrition rate. For a Chi-square analysis 5 cases per cell are required; with 40 cases the estimated cell sizes was 10 in a 2 X 2 design (Tabachnick & Fidell, 2006).

Sampling Procedure

Patients meeting inclusion criteria were continuously recruited as they were diagnosed and started treatment. During the recruitment period there were 122 patients diagnosed with TB (see Chapter 4 for Participant Flow Diagram). Prior to initiation of the study it was agreed upon by the dissertation committee that a sample size of 10-15/group was acceptable. The PI extended the recruitment period and time at the research site in order to continue recruitment. Recruitment was stopped at 37 participants after extended period at research site ended.

A minimum of 5 interviews was predetermined, but 12 interviews were conducted. For interview sampling procedures all participants in the intervention group were asked

to participate in an interview. Attempt was made to interview participants who had a low rate of notification. None of the participants abandoned treatment during the intervention period. See Chapter 5 for further detail on patients' notification rates.

Recruitment and Randomization

Recruitment and screening of potential participants was conducted by the clinic nurses and the PI. The recruitment and screening occurred in the nurses' office within the outpatient pulmonary clinic on a daily basis as patients came in to the hospital to receive test results and to start treatment. The clinic nurses identified eligible participants and introduced the study. The PI reviewed the study purpose and the consent form and obtained signed informed consent. The discussion and consent was provided in Spanish and the patients were given a copy of the signed consent form.

A computer-generated random allocation sequence was created to randomly assign consenting participants to either the intervention or the control groups. Block randomization of 10 was used to ensure balanced representation in the control and the intervention arm. Sequentially numbered and sealed opaque envelopes with the random assignment enclosed were used for treatment allocation concealment. Sixty envelopes were produced to account for attrition and allow for continued recruitment in the case of patients electing to drop out of study or no longer meeting inclusion criteria. Because of the nature of the intervention blinding of the group allocation could not be conducted. Research team members knew group allocation and if patients knew one another they potentially could share their group allocation. However, physicians were not made aware of the group allocation of their patient unless the patient informed them.

Retention

Participants received compensation for participating in the study in the form of prepaid phone credit (40 Argentinean pesos, about 12USD each month) or when phone credit was not usable (e.g., phone plan) equivalent cash compensation upon submitting a grocery receipt. Those who were assigned to the intervention group received an additional amount of about $10USD per month to cover the cost of texting-in daily. For time spent during an interview participants were given an additional about $10 USD.

Data Collection Methods

The pilot study was conducted during the participants' first 2- month intensive TB treatment phase. Participants: (a) reported medication adherence by one of two methods, diary (control group) or SMS (intervention group); (b) completed a questionnaires at baseline; (c) provided sputum samples at the end of their second month of treatment if ordered by their physician; and (d) were invited to participate in in-depth interviews (intervention group) at the end of the 2 months. (See Table 3.1.)

Data Collection Tools

Questionnaire

Demographic data and data regarding mobile phone use were collected at the time of recruitment using a brief questionnaire (see Appendix A). The questionnaire was conducted at the time of recruitment and questions were asked by PI or research team member. The questionnaire was adapted by the Argentinean research team (see Chapter 4 for details).

Table 3.1. Data Collection Methods and Analysis

Variable	Collection Method	Timing	Measure	Type of Data	Analysis
Feasibility, Acceptability (perceptions, cost)	▪ Interview ▪ PI log ▪ Text log	▪ End of 2 months ▪ Ongoing	▪ Audio-recorded, verbatim ▪ How intervention used ▪ Totals in Argentinean Pesos/USD	Q Q C	Content Descriptive
Medication Adherence Rates	▪ Text log ▪ Diary	▪ Daily ▪ Submit monthly	▪ Self-reported adherence ▪ Notifications received with/without a reminder	C C	T-test T-test
Sputum or Culture Conversion	▪ Lab analysis	▪ Baseline ▪ End of 2 months	▪ Conversion % (smear + to -)	D	Chi-squared test
Treatment Outcome	▪ Regional database	▪ End of treatment	▪ Cure, completion, abandoned, relapse, death	Categ	Chi-squared test

Note. C=continuous variable, D=dichotomous variable, Categ=categorical, Q=qualitative

Computer-Based Software System

FrontlineSMS (http:www.frontlinesms.com/) is a free, open-source computer based software that enables a computer to be used as a central hub from which text messages can be sent, received, and organized. FrontlineSMS software can be used with a laptop and phone with SIM card or with an internet mobile phone credit plan. This software system was used as the platform to receive, monitor, and send text messages. Any phone contact or extra effort to contact patients was noted in an excel file and in a research log maintained to document process issues.

Medication Calendar

Monthly medication calendars were created and given to the control group participants as they entered the study. Participants were given only the months they needed. A demonstration of how to document medication administration on the calendar was provided by the PI or research staff. Participants were asked to submit the diary to

the RNs or to the research team in the Regional TB office when they picked up their monthly supply of medication. There was no follow-up or notation of why they did not submit. Patients would come in once per month and if the RN did not realize that patient was enrolled in the study, he/she did not query the patient.

Digital Audio Recording Device

Interviews were audio-recorded using the audio recording software on the study computer. See Appendix F for interview questions guide.

Sputum / Culture Microscopy

When ordered by the patient's physician sputum samples were collected at end of the 2-month intensive treatment phase. Sputum microscopy testing was performed and tested per standard hospital and laboratory protocol.

Treatment Outcomes

Treatment outcomes were collected by reviewing the patient's medical record or reports in the regional TB program records. Treatment outcomes could include: cure, completion, abandonment, treatment failure, death from disease or transferred out. Treatment success rate was defined as the percent of patients who either completed treatment (without bacteriological confirmation) or were confirmed cured (negative sputum smear or culture in last month of treatment and on at least one previous occasion) (World Health Organization, 2009b).

Plan for Data Management and Analysis

The following describes how data were managed and analyzed in both research phases. Four software programs were used for data management or analysis. FrontlineSMS - Version 1.6.16.3 (FrontlineSMS, 2011) was used to manage the text messaging intervention. The software used to build databases for secure, on-line data entry and management was RedCap Software - Version 5.0.9 (Harris et al., 2009). Six databases were built to enter data from eligibility screening, the baseline questionnaire, the text messages, structured interview questions, and calendars and to track phone credit. When entering text message data into the RedCap database built for the text messages, the messages, which included questions, symptom or side effect reporting, comments, or other issues, were entered as text for further analysis. From the RedCap databases the data were exported to IBM SPSS Statistics – Version 20 (Chicago, IL) to conduct analyzes. Tests of chi-square were used for dichotomous and categorical variables and the independent T-test for continuous outcome variables (see Table 3.1). The transcribed data from the interviews and text massages that were entered into the RedCap text message database were uploaded to ATLAS.ti – Version 6 (GmbH, Berlin, 2009) to augment qualitative analysis.

Phase 1

The PI documented the process of intervention and protocol/ algorithm development in a daily study log. The educational text messages were assessed for content validity and cultural and social appropriateness by research team members who were TB experts and local Argentineans: the Regional TB director/pulmonologist, Regional TB social worker, and TB-specialized nurses. The text messaging FrontlineSMS software was

tested by sending text messages to and from the study mobile phone and other research team members' mobile phones. The detailed process of intervention development can be found in Chapter 4.

Phase 2

Feasibility, acceptability, and exploration of initial efficacy and issues to consider for conducting a larger scale study was assessed during the implementation phase (see Chapters 5 and 6).

Feasibility

A detailed log of patients screened for recruitment was maintained to track eligibility, reasons for ineligibility, or reasons for refusals. A study log and field notes were also maintained to document issues, barriers, glitches, informal meeting notes, informal protocol discussion, and key informant interviews with providers and TB program director. The feasibility issues for conducting the study were assessed by examining recruitment log for, e.g., number of patients without access to mobile phones and the number of patients unable to use text messaging function. The baseline questionnaire data were assessed for: time to arrive to clinic, type of mobile phone access (e.g., personal or shared, mobile phone plan), and baseline TB understanding. Baseline TB understanding was assessed by asking an open-ended question 'what do you know about TB?' The baseline questionnaire was conducted after the patients had seen his or her treating physician and were picking up medication before returning home to start their TB treatment.

Acceptability

Issues of acceptability were assessed by analyzing the interviews and evaluating the text messages. Acceptability considered the patient perceptions of the intervention, how to optimize the intervention, and how the intervention was used (e.g., types of messages sent/received, average number of questions, average number of reminders sent per patient, average number of side effects reported). Three interviews were conducted via text-messaging for patient convenience, using the structured questions only. The audio-recorded interviews (n=9) were transcribed verbatim in the language of origin by a local, native Spanish speaker (Lincoln & Guba, 1985). The transcripts were analyzed in Spanish by the bilingual PI and verified by a bilingual committee member. Content analysis was used to code (in vivo, open, selective) (Krippendorff, 2004; Strauss & Corbin, 1998) and identify themes (Denzin & Lincoln, 2000). Selective coding was used to identify content reflecting acceptance, feasibility issues, and technical problems. In vivo coding was used to select quotes reflecting these themes. These data were used to contextualize findings and improve the intervention.

The FrontlineSMS data can be exported to an excel file. However, the data could not be assessed for all outcomes of interest. Therefore, to assess how the intervention was used a database was developed in the program RedCap (Harris et al., 2009) and the SMS data were coded for sender, day (e.g., weekday or holiday weekend), number of messages per day, and type of message (e.g., notification, question, or reminder) and entered into the database.

Initial Efficacy

To evaluate the initial efficacy of the intervention, outcomes of *self-reported adherence*, *sputum smear or culture conversion*, and *treatment success* were analyzed. Baseline demographic characteristics (e.g., age, gender, education) were compared across groups for equivalency. Self-reported adherence was measured by reviewing data collected in FrontlineSMS for the intervention group and the medication administration calendars for the control group. Sputum-smear or culture conversion was considered converting from positive to negative from treatment initiation to after completing 2 months of treatment and treatment outcomes were compared.

Considerations for Conducting a Larger Scale Study

Considerations for conducting a larger trial using the text messaging intervention, such as technical issues, were assessed by analyzing the daily study log. The data analysis was guided by the socio-technical approach, adapted from Cornford, Doukidis, and Forster (1994) and Barber, Cornford, and Klecun (2007). Intervention *structure*, *process,* and *outcome* processes were evaluated at the *system*, *human,* and *organizational* levels. This analysis was conducted from the healthcare team perspective, but included issues of technical feasibility identified in the text messages received from participants. The data were analyzed for example for issues regarding the software features, how the intervention was integrated into the workplace, and organizational limitations. The cost of the intervention was calculated by identifying the cost per text message according to the websites of all the mobile phone service providers and identifying the average number of text messages sent by the patient and the healthcare team staff. In Argentina

the cost of the text message is only incurred by the sender, the received text message is free of charge. See Chapter 6 for further detail.

Summary of Analysis

Quantitative and qualitative data were combined to assess lessons learned and potential application to other settings (Johnson & Onwuegbuzie, 2004). Analysis of the global effect of the intervention was guided by the socio-technical approach (Berg, Aarts, & van der Lei, 2003; Cornford et al., 1994). To improve the intervention patient and healthcare team member input and issues of burden, barriers, or any glitches were considered.

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CHAPTER 4

COLLABORATIVE RESEARCH TO DEVELOP A TEXT-MESSAGING INTERVENTION

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Abstract

Objective

To describe development of a collaborative, theory-guided text messaging-based intervention to promote tuberculosis (TB) treatment adherence.

Methods

A collaborative team of researchers, clinicians, administrators, and patients in treatment participated in the development. Field notes were maintained to document the team process. Content analysis based on the Information-Motivation-Behavioral Skills (IMB) model was used to facilitate educational message selection. Searches were conducted in the World Wide Web (WWW) and PubMed in 2011-December and other sources were used to crosscheck and augment message selection.

Results

The development steps included: a) establishing intervention components; b) developing educational messages; c) adapting and formatting text messages; and d) determining protocol steps. We selected 16 educational messages to be delivered as part of the intervention by assessing patient recommendations and reviewing a large set of coded educational material. Final development was achieved in 3 months.

Conclusion

A collaborative approach and application of a theory to guide the intervention design and development is supported and considerations for developing a text message-based intervention are provided. Although a collaborative approach was more time consuming,

it resulted in a more responsive, culturally appropriate, and comprehensive intervention. Further empirical evidence is needed for applying the IBM model for adherence-promotion for TB efforts.

Introduction

The mobile phone, specifically the short message service (SMS) or text messaging feature, has gained increasing recognition as a potentially powerful tool to deliver an array of healthcare interventions (Cole-Lewis & Kershaw, 2010; Fjeldsoe, Marshall, & Miller, 2009). Examples include improving appointment attendance (Downer, Meara, Da Costa, & Sethuraman, 2006; Kruse, Hansen, & Olesen, 2009), chronic disease (e.g., diabetes, asthma) management (Hanauer, Wentzell, Laffel, & Laffel, 2009; Hung et al., 2007) and smoking cessation programs (Vidrine, Arduino, & Gritz, 2006). In tuberculosis (TB) management, SMS has been suggested as a promising method to improve treatment adherence (Barclay, 2009), yet there has been little research conducted (Mohammed et al., 2012). Some of the attractive features of SMS include: it is commonly used; it is more economical than a phone call; it can be sent, stored, answered, and retrieved at the user's convenience; and the service is now accessible to nearly all people on earth (ITU, 2013). However, few studies have reported on the process of text messaging intervention development or the application of theory to guide development (Owens et al., 2010).

Those who have described development of text messaging interventions have focused on evaluating content or establishing the intervention. For example, Gold, Lim, Hellard, Hocking, and Keogh (2010) conducted focus groups with young people to evaluate content of pre-established text messages for sexual health promotion to assess

acceptability and potential impact of messages. The researchers described considerations for message style, language, and length of text, but not how content was developed. Owens et al. (2010) reported involving service users and clinicians in the development of a text messaging-based intervention to reduce self-harm by conducting participatory workshops and searching for a theoretical basis for the emergent intervention. The research that has been conducted using SMS to promote TB treatment adherence was by Mohammed and colleagues (2012), who sent daily reminders to participants (N=30) in a nonrandomized study in India. Participants were asked to text-in the time they took their medication and responded to reminders 57% of the time over a 1-month intervention period (Mohammed et al., 2012). SMS reminders or messages have also been used to promote HIV/AIDS treatment adherence in large randomized control trials (Lester et al., 2010; Pop-Eleches et al., 2011) with a Cochrane review concluding that there was high quality evidence that text-messages enhanced adherence to antiretroviral therapy (ART) compared to standard care (Horvath, Azman, Kennedy, & Rutherford, 2012). Nonetheless, these reports do not describe the process of message development.

The Information-Motivation-Behavioral Skills (IMB) Theory provides a model to promote adherence to treatment (Fisher, Fisher, Amico, & Harman, 2006; Munro, Lewin, Swart, & Volmink, 2007). The IMB Theory was initially developed to promote HIV prevention interventions in inner-city minority settings (Fisher & Fisher, 1992; Fisher, Fisher, Bryan, & Misovich, 2002) and was then adapted to promote ART treatment adherence (Amico, Toro-Alfonso, & Fisher, 2005; Fisher et al., 2006). The model supports the hypothesis that to initiate and maintain a desired behavior, such as medication adherence, adherence-related information and motivation must be provided,

along with appropriate tools and strategies to maintain the behavior (Fisher et al., 2006). Further, adherence-related information should target information gaps and focus on delivering accurate information regarding disease, its treatment and transmission, and medication side effects or drug interactions (Fisher et al., 2006; Munro et al., 2007). Motivation can be strengthened by focusing on beliefs and attitudes towards adherence and by providing social support or social norms for engaging in behavior change.

Given the increase use of mobile phone-based interventions there is a need to describe how interventions are developed, how educational message content is selected, and how theory can be applied to develop SMS messages. The purpose of this paper is to detail the techniques and methods used to develop a SMS-based intervention in collaboration with a multidisciplinary research team and patients in Argentina. Information provided will assist future development of similar SMS interventions which are often not well described in the literature.

Methods

Study Design

This developmental work was the first phase of an interventional pilot study (1F31NR012614-01A1) evaluating the feasibility, acceptability, and initial efficacy of the text messaging-based intervention to promote TB medication adherence for patients receiving treatment by self-administration. The goal was to finalize the intervention in a collaborative process involving the multidisciplinary team and patients. The development steps included finalizing intervention components; developing educational messages and adapting them to Spanish language and SMS format; and determining protocol steps for implementation. The research team reviewed the overall study

objectives and participated in final development of the intervention through virtual and in-person meetings. The PI maintained a daily study log and field notes of interactions with the research team and patients (e.g., meetings, informal protocol discussions) to document the process of intervention development.

Collaborating Team

Collaborative relationships were initially established during a study the PI helped conduct while participating as an NIH/Fogarty Clinical Research Scholar at the Institute of Clinical Effectiveness and Health Care Policy in Buenos Aires (IECS), Argentina (July 2008 to June 2009). All team members participated in varying aspects of the intervention development. The multidisciplinary team consisted of: a regional TB director/pulmonologist, the lead regional TB social worker, a regional TB technician, two TB-specialized clinical nurses, and the hospital TB program director/pulmonologist. The regional TB director was involved from the beginning of initial drafting of the research proposal. The regional director, lead social worker, nurses, and regional TB staff member were the lead intervention development team. The clinic nurses also identified patients who were in active treatment and who might be interested in participating in message content development. These patients were asked what type of information/education they would have liked to have known or received during the first phase of treatment, what concerns or doubts they had regarding treatment, and what they would recommend to help others complete treatment.

Setting

In Argentina, the TB treatment success rate remains well below the World Health Organization (WHO) TB key target of 85%, averaging 46% from 2008-2010 (World Health Organization, 2012) and about half of the TB patients receive treatment by self-administration (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2010). This study was performed in the outpatient clinic at a public pulmonary specialized reference hospital within Health Region V in the province of Buenos Aires, Argentina. Region V serves a large geographic region with a population of 3.5 million and accounts for one quarter of the TB cases within the province (Chirico, Kuriger, Etchevarria, Casamajor, & Morcillo, 2007).

Educational Text Content Development

In addition to input from patients in treatment and the research team, the PI conducted online literature searches to identify potential TB educational material. The searches were conducted without a date limit in the World Wide Web (WWW) and PubMed in December, 2011, using search terms *tuberculosis* and *patient education*. Searches were also conducted for HIV/AIDS patient education to identify IMB-based language that could be adapted to TB patient education. Potential relevant content included educational material (e.g., fliers, pamphlets) written for patients as the target audience, accessible on-line, free of charge, and included information for active TB (could also include information on disease background and transmission). Excluded were materials not pertinent for patients with active TB (e.g., how it is diagnosed, treatment for latent TB infection), and graphics and photos because they may be more challenging to use in text messages or may not be received by all phones. Links were followed within

multiple sites (e.g., WHO, Centers for Disease Control and Prevention, specific institutes or university centers, state public health departments) to obtain patient educational material. Searches were conducted until no new material was found. Because the aim was to produce text messages in the Spanish language, when available Spanish versions of the educational material were collected to facilitate the translation process.

The on-line literature searches produced 12 TB and 8 HIV/AIDS educational sources. See Appendix B for sources, title and link of educational material identified. For analysis the educational materials were compiled into a single file for each disease with a total word count of 11,087 for TB and 13,993 for HIV/AIDS. Content analysis was used to systematically tabulate and organize the materials into categorical schema as recommended by Krippendorf (2004) and Neuendorff (2002). The PI developed a coding scheme based on the IMB model adapted for TB treatment adherence (Fisher & Fisher, 1992; Fisher et al., 2006) (see Table 4.1). The unit of analysis was a complete education messages summarized in one to two sentences. Similar or duplicate messages were deleted. These brief messages were coded based on the coding scheme using ATLAS.ti version 6 (GmbH, Berlin, 2009). Subcategories under each IMB category were identified to facilitate message review and the selection process. To crosscheck and augment message selection we drew from other credible sources: a TB specialist manual, WHO recommendations (World Health Organization, 2009a), and local patient TB educational material. The end product was a list of educational messages which were reviewed, selected, assessed for content validity and cultural and social appropriateness by the research team.

Table 4.1. Coding Scheme Based on IMB Model: Codes and Definitions

Codes	Definitions/examples
Adherence-related Information	
Disease	Accurate information regarding disease
Transmission	Ways disease transmitted
Symptoms	Disease symptoms
What constitutes adequate treatment adherence	Medication, treatment process/regimen, treatment strategies
Medication side effects and interactions	Drug effects and interactions to monitor
Adherence-related Motivation	
Personal motivation	Beliefs and attitudes towards adherence/ potential outcomes and suboptimal adherence
Social motivation	Support from others to follow treatment
Adherence-related Behavioral Skills: Objective and perceived abilities/efficacy	
Skills or tools to support self-efficacy	Skills, tools and self-reinforced strategies to perform and maintain adherence behavior, objective ability and perceived efficacy for performing critical adherence-related skills
Contextual factors	
Moderating factors	Living conditions, access to healthcare

Adapted from Fisher et al. (1992, 2006)

Results

The research team made multiple decisions, including final intervention components; timing and frequency of notification and educational texts; the content of educational texts, including adaptation to SMS format, Spanish translation, and ordering; and protocol to follow during intervention implementation (Figure 4.1). Steps that we used for decision making, such as, justifications, and considerations for decisions are described.

From the onset the team supported the idea of a text-messaging intervention as a method to support patients and monitor adherence during treatment. Texting was felt to be an acceptable medium to reach their population and it was noted that texting is in general more economical than phone calls. Our aim was to increase patient involvement

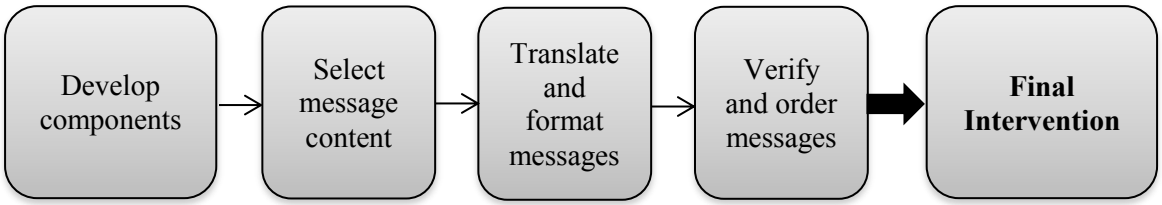

Figure 4.1. Intervention development process

in their care. The basis for having the patient text-in was for patients to become more fully engaged in their own care and not simply receive daily reminders or education. We wanted patients to be responsible for reporting with reminders being sent only to those who did not text-in. The initial idea was for patients to text in self-administration of TB medications daily and to receive weekly educational texts. The team added two components: an option for patients to text-in questions and a process for verifying receipt of text-in notification by sending a confirmation message. In addition, the team decided that more education was needed and planned for two educational text messages per week. *TextTB* was coined by a team member and agreed upon to give the program a name. The final intervention included four components (Figure 4.2).

Timing, Frequency and Not 'Too Automated'

Dosing for TB medication is daily. However, because the clinic was closed on weekends the decision was made that texting in on weekends or holidays was optional. Participants were notified that the service was only available during office hours. Educational text messages were delivered on Tuesdays and Thursdays because most holidays fell on Mondays and Fridays.

It is recommended that TB medication is taken after fasting, or in the morning, before eating, for best effectiveness (Caminero, 2003). Therefore, the team decided that

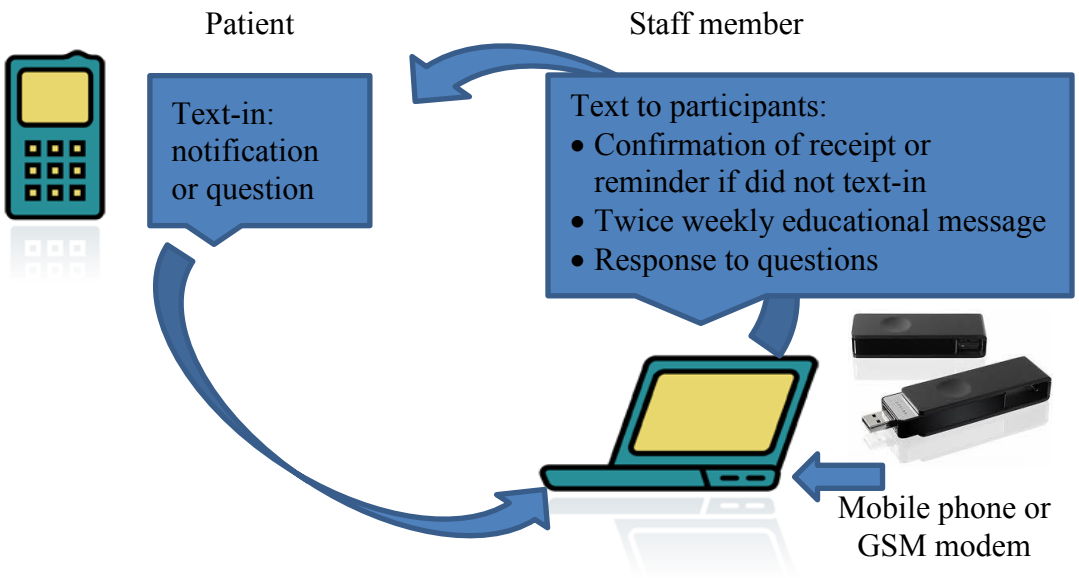

Figure 4.2. Intervention components

the staff member would review messages and responded to patients around 9:00 am and would further check messages throughout the clinic hours of operation. The staff member monitored the received messages daily to identify those who had not texted in and sent out any query texts that were necessary. With the texting platform used, this process could not be automated. A list of possible responding message options was composed to expedite the process.

The process to send a confirmation message of receipt of texting-in could be automated by setting key words. A concern of the team was that the intervention should not be what was labeled *too automated.* That is, messages could not be too repetitive and boring, and needed to be creative to engage participants. In response to the concern for not 'too automated,' a list of confirmation messages was produced in order to rotate automatic messages. A few examples include, "Thank you for notifying, keep it up!" or "Thank you for your collaboration." During intervention implementation the staff noted

that when the key word was not the first word in the message or there were any changes to the key word, for example an exclamation mark after word, the key word was not recognized. In these cases and when a patient did not use a key word a manual confirmation message was required.

Educational Text Messages

Education regarding TB itself was identified by research team and patients as often lacking during diagnosis and treatment delivery and was considered a critical component to treatment success. In ongoing meetings and discussions, we reviewed the recommendations from the patients, the list of educational messages identified from the content analysis of educational materials, and other resources until 16 messages (two per week for 2 months) were selected. The team reviewed the messages for accuracy.

Patients currently receiving treatment who participated in the development period (n=5) recommended educational topics of: (a) nutrition during treatment, (b) what to do when feeling bad (e.g., side effects–seek help from provider), (c) improvement of side effects of medication over time (often pass and gets easier), and (d) acknowledgement of challenges (e.g., that there are a lot of pills to take every day and for a long period). Ideas for text messages provided by patients included: "Continue, it is worth the effort to continue treatment," "If you feel bad go to the doctor so you can continue treatment," and "you are going to have a stomach ache but this will pass." Patients indicated that daily reminders to take medication could be an option. Initial meetings with the team also produced educational topics (e.g., continue to take medication even after feeling better, avoiding alcohol over the holidays).

Content analysis of compiled TB education material resulted in 145 verbatim quotes of potential educational messages coded according to the established coding scheme (see Appendix C). During coding subcategories (e.g., gender specific information, tools to minimize side effects or incorporate into daily living) were added for organizational purposes and to make review and selection easier for team. Having messages organized according to the IMB model allowed selection from each category or a combination. Messages were not taken verbatim from education material.

The identified HIV/AIDS patient education material was compiled, coded, and analyzed based on the IMB coding scheme as well to explore IMB-based language that could be adapted to TB education. The analysis identified examples such as, "You are not alone" in HIV material, that was not identified in TB education material. In addition, pronoun use of 'we' rather than 'you' was significantly higher in HIV/AIDS education (p=0.001) than in TB education.

Information regarding food and medication interactions with TB medication, not found in patient education material, was drawn from a TB provider manual (Caminero, 2003). Messages were selected and prioritized based on the IMB model and on the team's belief in the importance of the message. For example, the need for other family members to be tested (e.g., take care of you and your family), the importance of not spreading the disease (e.g., cough into tissues in well ventilated areas), presenting potential side effects of medication and which side effects warrant immediate medical attention were considered important information for patients to receive.

Cultural Adaptation and SMS Formatting

Once messages were selected we then needed to adapt them to the Spanish language and SMS format and decide on the order of the messages. During the Spanish translation process we discussed using the more common informal or more personal form of "you" singular in English. The team decided on using the informal "you" conjugation of *vos* so that the messages were more personal, rather than the formal *Usted* conjugation. Another cultural adaptation included team members stating that forms, such as the intake questionnaire, needed to be "Argentinized." The forms were translated by a native Spanish speaker who was from Mexico. Although the team members acknowledged that the Spanish was correct, the forms needed to be adapted to *Argentinian* Spanish. Team members also requested removal of the question on race/ethnicity because it is a question not understood or requested from Argentineans.

An SMS text message is in general limited to 160 characters. Messages had to be clear and concise to fit the word limit. The team identified common word abbreviations to accommodate more text, facilitate condensing messages and to meet the character limit. Examples of abbreviations used include: please (*por favor*) abbreviated as *X*; because (*porque*) abbreviated as *pq*; for (*por* or *para*) abbreviated as *p*; and that, what (*que*) abbreviated as *q* or *k*. In addition, the team decided to omit object pronouns (e.g., el, la, los, las) where possible. The process to reduce and distill the messages was time consuming and required many iterations.

Message Ordering

Ordering of the messages was an important consideration for the research team, thus priority ordering was completed. For example, shortly after starting one of the TB

medications, rifampin, the color of urine can change to reddish orange, which can be frightening for those who are not forewarned, or do not know that this is a normal, harmless side effect of the medication. Therefore, this message regarding color change was slotted for an initial message to be delivered to patients. Another initial message prioritized was regarding encouraging the patient to have family members or close contacts be tested for TB in order to detect infection early and help prevent further spread of the disease. Important time points identified by the team were at 1 and 2 months of treatment when follow-up with their primary provider was needed to evaluate treatment progress and are times recognized as susceptible to treatment abandonment because patients often start feeling better. Messages to reinforce follow-up visits and to continue medication even after a period of seeming recovery were scheduled to be delivered at these time points. Additional gender specific messages, such as, information on interaction of TB medication with oral contraceptives, was added. Table 4.2 provides examples of English translated messages (see Appendix D for full list in Spanish).

The need for operating procedures and materials for participants were identified as important aspects of protocol development. The team developed daily operating procedures and the PI integrated the procedures into a formal document. Operating procedures included steps to initiate SMS software and modem set-up, established times to review and respond to messages, documentation of patient tracking, and intervals to review patient and modem phone credit. Written information to accompany verbal instructions for participants in the intervention was developed into an instructional pamphlet which included key goals, expectations of the patient, and examples for how to text-in to report daily medication administration and the study phone number.

Table 4.2. Examples of SMS Educational Messages: Week Delivered, Type and Message

Week	IMB Message type* (subcategory)	Message
1	Information (transmission)	TB is contagious by cough or sneeze. Cough in well-ventilated places, cover your mouth and use a mask to not be contagious
	Information (medication side effect)	Rifampicine (red pill) can tint your urine, saliva or tears a color orange, this is normal. Be careful with contact lenses, they can become tinted too.
2	Information (transmission) + Motivation - personal	TB is not contagious by shaking hands, sharing glasses or plates. It is contagious by coughing or spitting. Remember TB can be cured!
	Motivation -social	Up to +/- 20 days of treatment you can still be contagious. Frequent contact and in close places increases the risk. Those who live with you should be tested.
7	Skills	Taking medication every day is a challenge! To remember: keep meds in one space, use an alarm, hang a note in the bathroom or on the fridge.
	Motivation - personal	Feeling better does not mean that you are cured. To be cured you need to continue treatment at least 6 months and take the meds regularly to not become sick again. You can do it!

Note. English translation of example messages. IMB message type based on Information-Motivation-Behavior model (Fisher & Fisher, 1992; Fisher et al., 2006).

Development of Daily Operating Procedures and Algorithm for Patient Tracking

Anticipatory guidance was also considered when developing materials for the study. Discussion regarding decision points for such instances as a participant did not text in to report medication administration initiated an algorithm design. The first step was to send messages of inquiry. It was recognized that phone signal coverage may be a potential barrier to send or receive messages, and power outages and other problems may arise. A set of possible inquiry message options was written that could be modified or personalized. These messages were written to not be accusatory, but rather to imply that

other possible challenges may have occurred. For example, "We know that you normally take your medication and notify daily but today we have not yet received notification, any problems?" If there was no response the team decided that the patient would receive inquiry messages for 3 days and then the staff member would attempt to call the patient. If contact could not be made the staff member would notify the nurse and social worker. The social worker would then contact the local healthcare center close to the patient to see if the patient could be tracked down locally and the RNs would notify the staff member if the patient came in to the clinic in order to speak with the patient directly.

Discussion and Conclusion

Discussion

This research adds to existent knowledge about collaborative research emphasizing text messaging intervention developed for patients with active TB, in Argentina, and specifically provides information on the research study process and protocol development integrating a theoretical foundation. We described decision making processes, justifications, and considerations as well as how we applied a theory to develop a coding scheme, analyze education material, and guide decision making for message content selection.

Although a number of studies report on SMS-based interventions to promote behavior change (Fjeldsoe et al., 2009; Lim, Hocking, Hellard, & Aitken, 2008; Pop-Eleches et al., 2011; Vervloet et al., 2012), few have described the process of development. Gold and colleague (2010) and Owens and colleagues (2010) worked collaboratively with others in their research, including service users, participants, and clinicians. The collaboration being reported in this paper parallels similar information

from Gold and colleagues (2010) and Owens and colleagues' 2010) collaborative work, but extends to a more comprehensive presentation of process detail for the development and implementation of an SMS- based intervention.

Regarding infectious disease medication adherence using SMS interventions, to date, published literature includes a focus in HIV/AIDS research. The interventions reported to improve antiretroviral therapy adherence for patients with HIV/AIDS included sending a text message asking "how are you?" (Lester et al., 2010) or sending text medication reminders (De Costa et al., 2010; Pop-Eleches et al., 2011). A study protocol outlines how they propose to use reminders with a motivational message and number to call if the patient needs help (Mbuagbaw et al., 2011), but authors do not describe how the weekly motivational reminder messages were designed. Person, Blain, Jiang, Rasmussen, and Stout (2011) found that patients attending TB and HIV clinics were generally receptive to text messaging for healthcare-related communication; however the TB studies identified used the mobile phone video feature (DeMaio et al., 2001; Hoffman et al., 2010). No studies were identified to use SMS to deliver educational messages or monitor adherence for patients with TB.

Contextual Appropriateness and Potential to Provide Patient Support

Mobile phones are increasingly relevant in resource-limited settings and incorporating their use has been identified as a priority by the WHO (World Health Organization, 2009c). In the current research, the team recognized that text-messaging was a contextually appropriate medium for a healthcare intervention in their setting. Supporting this assumption are national statistics thatt reveal that In 2010, with an estimated population of 40.9 million (Instituto Nacional de Estadistica y censos

(INDEC), 2001), there were 50.4 million mobile phones in service, in contrast to 9.2 million land lines, and 5.8 billion SMS text messages sent monthly (Instituto Nacional de Estadistica y censos (INDEC), 2010). By 2013, the number of mobile phones in service has increased to 59.6 million and the number of SMS text messages to 11.3 billion (Instituto Nacional de Estadistica y censos (INDEC), 2013). Argentina has an estimated population of 40.9 million (Instituto Nacional de Estadistica y censos (INDEC), 2001), indicating that there are more mobile phones in service than inhabitants.

Developing a strong patient-healthcare professional relationship through supervision and support has been identified as highly important in TB control efforts (Iribarren, Rubinstein, Discacciati, & Pearce, 2011; World Health Organization, 2006, 2009c), with the suggestion that improving relationships could potentially be achieved through telecommunication tools, such as texting (Barclay, 2009). In the current study, in order to elicit the potential relationship benefit the team agreed that the intervention must include the interactive function of SMS, not be 'too automated', and not simply 'sending reminders' or 'information' like reported in other studies (Chen, Fang, Chen, & Dai, 2008; Hanauer et al., 2009; Pop-Eleches et al., 2011; Vervloet et al., 2012). The intent for the intervention to not be 'too automated' was to establish a more personal relationship with the patients and be able to identify problems that could be dealt with. However, the tradeoff was increased work load on team and time needed to implement the intervention.

Although the direct observation of treatment (DOT), where a trained healthcare worker or treatment supporter observes medication ingestion daily, has been the WHO recommended intervention to assure drug adherence (World Health Organization, 2009a),

it continues to be challenging to apply for patients and healthcare services in many communities globally (Hill et al., 2005; Khan, Walley, Witter, Imran, & Safdar, 2002; Sanchez & Bertolozzi, 2009). In settings where self-administration is the standard treatment delivery, other options to supervise, provide support and promote patient-provider relationships are needed and TextTB is such an intervention.

Challenges and Benefits to Collaborative Intervention Development

The basic study premise was provided by the PI, but final drafting and decision making was left open for discussion and team agreement. The team drafted plans for daily operating procedures and an algorithm for follow-up during the implementation phase. Although the aim of this intervention development was to apply a collaborative approach, this can result in the slowdown of the intervention development for many reasons. First, participation in this process takes time away from team members' other daily duties. Second, as this was an international collaboration it required correspondence by email and then an extended time on site by the PI to work directly with team members to accomplish more than what could be by correspondence alone. The development phase did take longer than expected and delayed the initiation of patient recruitment, extending the onsite stay for the PI. Similarly, Owens et al. (2010) encountered extended development time by involving service users in the design and development of an intervention, which resulted in an intervention distinct from and not considered during initial planning. Although this initial developmental phase was written into the proposal in our case, participatory intervention development can be problematic when funding agencies typically expect well- formulated and established proposals. On

the other hand, engaging clinicians in the design phase can minimize problems and delays in study implementation.

Educational Content and Theoretical Considerations

Decision making for educational message content could have been more quickly made based on expert knowledge by the team alone. However, the added steps of applying a theory and using content analysis of educational material provided the team with an extensive list of message options. The theory helped organize messages into categories and facilitated combining message types and to guide decisions. This process made message content development more systematic and comprehensive.

Though the IMB model has been suggested as a promising theoretical model to promote TB medication adherence (Munro et al., 2007), it has yet to be applied and tested as such. In TB literature the model guided a study to assess healthcare workers TB infection control information, motivation and behavior skills (Kanjee et al., 2012) and to suggest examples of ways to manage latent TB (Franks J, 2005).

The model does make the assumption that individuals who are well-informed and motivated develop behavior skills needed for effective adherence, but also takes into consideration contextual factors, such as living conditions and access to healthcare (Fisher et al., 2006). Factors such as access to healthcare and stigma have been identified as a barrier to treatment adherence (Cramm, Finkenflugel, Moller, & Nieboer, 2010; Enarson & Billo, 2007). An underlying premise for using text-messaging as the mode of intervention delivery was to mitigate the barrier that limited access to healthcare presented. The team recognized that many of their patients who attend this clinic come from throughout the region and could travel a few hours to arrive. We included a

message acknowledging the stigma of TB in the general public. A number of patients responded and agreed with this message. Acknowledging challenges was a category coded under the contextual factor category and applied in a message combined with a behavior skill suggestion.

The timing and ordering of message delivery was also considered. Supporting the application of SMS patient contact at the initiation of treatment, a study by Mbuagbaw, Bonono-Momnougui, and Thabane (2012) assessing SMS as a potential tool for patients living with HIV found that it was during the initial period when patients were most forgetful.

Conclusion

This study supports the use of a collaborative approach and applying a theory for message development and to help guide decision making. Interventions for TB care should be standardized, but also flexible and based on the needs of the local community. Although using a collaborative approach involving local TB experts and patients during the design stage was more time consuming, the result was an intervention that was more responsive to patient needs, culturally appropriate and comprehensive. The process required flexibility, an open mind and willingness to adapt to the needs and schedules of others. Applying the IMB model to systematically identify key educational messages with adherence-related information, motivations and skill development and contextual language, along with expert knowledge and patient input, was useful in selecting the educational text content. Although health behavior theories can help guide the process of understanding underlying behavior change, more research is needed to test theory driven interventions to improve outcome for patients with TB. Additionally, text messaging as a

mode to foster patient-provider relationship and provide a supportive mode of treatment delivery warrants further exploration. The described intervention was applied in a randomized control pilot study, which is reported elsewhere.

Practice Implications

Collaboration among the multidisciplinary research team members and patients, with the research team implementing the intervention and patients who would potentially receive the intervention, is important in development of educational programs, regardless of the mode of delivery. Although potentially challenging during grant writing, planning for an extended time to collaborate with end users during design phase is necessary for successful intervention implementation. Specific to SMS mode of delivery, issues that must be taken into consideration during development include timing of delivery, adapting to SMS format by using accepted and recognized abbreviations to meet text limit, adapting language considering cultural nuances, and ordering of messages for optimum effect. Adaptation to SMS format will vary by country and language; therefore using local staff to develop messages is essential for content validity. Content analysis can serve as an organizational and analytic tool to sift through educational material. Applying a theory to develop a coding scheme to code a body of educational literature for elements of the theory can aid in systematically selecting educational content and provide structure and added depth to content to be used in an intervention. SMS is a basic feature common in most phones and its use in TB management and other health interventions warrants consideration and systematic investigation.

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CHAPTER 5

TEXTTB: A PARALLEL DESIGN RANDOMIZED CONTROL PILOT STUDY

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Abstract

Background

Investigators assessed the feasibility, acceptability and explored initial efficacy of a short message service (SMS) based intervention to promote TB treatment adherence.

Methods

A mixed-methods randomized controlled pilot-study was conducted in an outpatient clinic within a public pulmonary-specialized hospital in Argentina where self-administered treatment was usual care. Patients newly diagnosed, 18 or older, not identified as having drug resistance or HIV, having access to a mobile phone and opting to continue treatment at the hospital were randomization in a 1:1 allocation in blocks of 10. Participants received usual care plus medication calendar (control, *n*=19) or SMS-based intervention (intervention, *n*=18) for the first 2 months of treatment. We conducted interviews (*n*=12) and collected self-reported adherence, sputum microscopy and treatment outcomes.

Results

Feasibility was supported by high access to mobile phones and most knowing how to send an SMS; many (60%) indicating not being adequately informed about TB or treatment at diagnosis. Participants identified feeling *cared for*, *responsible for their treatment* and valued the intervention option to ask questions and receive quick answers. Most participants *highly recommended* intervention for others. A total of 1320 text messages were sent and 996 received. Patients in the SMS group responded 77% of the days (*SD* 23.5, range 22-100) whereas only 10 (53%) in the control returned calendars at

60 days. Initial efficacy was explored; there was no significant difference between groups in sputum or treatment outcomes.

Conclusion

Intervention was feasible to implement in this population and well received. Automatic daily reminders were not necessary. Further testing of its efficacy should be evaluated in a purposely designed clinical trial in a larger sample.

Introduction

The mobile phone is cited as the most rapidly adopted technology on the planet (ITU, 2009). The figure of 6.8 billion mobile phones subscribers in 2013 is nearing the number of people on earth (ITU, 2013). In an attempt to combat the continued challenges of tuberculosis (TB) as a major global health problem (World Health Organization, 2009a) researchers have proposed using short message service (SMS) or text messaging to improve TB treatment adherence (Barclay, 2009). TB treatment adherence remains a challenge in TB control efforts and nonadherence can lead to poor outcomes, such as prolonged infectivity, increase in the risk of relapse after treatment, generation and propagation of drug resistance, treatment failure, and increased mortality (Maartens & Wilkinson, 2007; Mitchison, 1998). Heightening TB patients' involvement in their own care and improving communication between patients and their healthcare team have been recommended to improve adherence (Barclay, 2009; Kaplan, 2006).

Argentina has high access to mobile phones and a need to improve TB treatment outcomes. With an estimated population of 40.8 million, there were a reported 59.6 million mobile phones in service and 11.3 billion SMS messages sent in January 2013

(Instituto Nacional de Estadistica y censos (INDEC), 2010). Argentina's National TB Program acknowledges that the overall TB treatment success has varied little and has made no significant improvement over the past 10 years (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2010). The World Health Organization (WHO) TB target success rate is 85%; however, in Argentina, the average reported treatment success rate was 46% (2008-2010) (World Health Organization, 2012). Furthermore, about half of the TB cases were reported to have received treatment by self-administration (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2010).

SMS interventions have been suggested to improve communication and lead to health behavior changes (Cole-Lewis & Kershaw, 2010; Fjeldsoe, Marshall, & Miller, 2009), yet few TB researchers have put it to the test. The only text message-based TB intervention identified in the literature was a nonrandomized study in India with 30 participants conducted by Mohammed et al. (2012) to understand user perceptions, acceptability, and engagement with an SMS system. The intervention involved sending daily text message reminders and asking participants to respond with texting-in the time they took their medication. Mohammed and colleagues report a mean response rate of texting back when patients reported taking their medication of 57% that trended from 62% at the beginning of the trial to 49% towards the end (Mohammed et al., 2012). Therefore, there is limited evidence of applying SMS as the mode of intervention delivery for TB management. Other researchers have tested the video feature of mobile phones to conduct directly observed therapy (DOT) or M-DOT (also reported as V-DOT for video phone) (DeMaio, Schwartz, Cooley, & Tice, 2001; Hoffman et al., 2010; Wade, Karnon, Eliott, & Hiller, 2012). In the US, DeMaio et al. (2001) found 95% adherence

with six TB patients using V-DOT. In a retrospective cohort study in Australia Wade et al. (2012) identified 18.9% (95% CI: 12.2-25.4) (N=128) fewer missed observations than in the traditional DOT using M-DOT and it was calculated to be cost-effective. Hoffman et al. (2010) evaluated M-DOT in Kenya with 13 patients and their supporters in a proof-of-concept study with 11 completing the 1-month trial; adherence data were not reported. In all of these studies the video capable mobile phones were provided to the participants and almost all participants found the model acceptable. In a third approach, Kunawarak et al. (2011) conducted a randomized control study in Thailand with 98 multidrug resistant (MDR) and nondrug resistant TB patients comparing outcomes from daily reminder calls to the patient's mobile phones by a TB center officer to DOT using a family member as the treatment observer. Researchers found a higher completion success rates in both groups who received daily calls to their mobile phones (MDR and nondrug resistant TB patients) (p<0.001), and a significantly higher sputum conversion rate in patients with MDR (p<0.001) receiving daily calls compared to the patients in the DOT with a family member observer.

Factors influencing adherence, and ultimately TB treatment success, are varied and may include limited family or healthcare system support, impact on patient's ability to work, lack of knowledge regarding disease and treatment, and social issues related to stigma (Cramm, Finkenflugel, Moller, & Nieboer, 2010; Iribarren, Pearce, Discacciati, & Rubinstein, 2010; Munro et al., 2007). The complexity of these factors suggests a multifaceted approach to its treatment management. To improve treatment success and promote treatment adherence alternative, innovative solutions that are readily accessible, convenient, flexible, personalized, and cost effective and that can empower individuals

need to be identified and systematically evaluated. The purpose of this presentation is to detail the results of a mixed method evaluation of an interactive multifaceted SMS-based intervention with patients receiving TB by self-administration. In this pilot study we aimed to assess issues of feasibility, acceptability, and explore initial results of efficacy of the TextTB intervention to promote adherence to TB treatment. The findings may be applicable to other treatment regimens or in settings with limited resources where self-administration of TB treatment is offered.

Methods

This study was a single center, parallel group, randomized controlled pilot study using mixed methods. Eligible participants were randomized in a 1:1 allocation ratio in blocks of 10 to one of two arms receiving usual care plus either: a text messaging based intervention (described below) or a medication administration calendar. Semistructured individual interviews were conducted with a subset of participants in the intervention arm at the end of the 2-month intervention period and outcome variable data were collected to explore initial results of efficacy.

Inclusion and Exclusion Criteria

Patients initiating TB treatment who met the inclusion criteria were recruited and enrolled consecutively from November 2011 to June 2012. Initial inclusion criteria included newly diagnosed confirmed TB patients ≥18 years of age who were initiating TB treatment for the first time; had no known TB drug resistance or HIV positive status (HIV status per self-report or medical record); elected to continue treatment and follow-up at the study site; owned or had personal access to a mobile phone; and were able to

operate the mobile phone to communicate using text-messaging. We excluded patients who were severely ill (i.e., requiring hospitalization) or who resided in the same household where another participant was already recruited.

We made an IRB- approved addendum to the eligibility criteria after trial commencement to include patients receiving treatment, who had previously completed or had abandoned treatment or had other forms of TB. This change was made because there were many patients being excluded for these reasons (n=15) and the research team felt they might benefit from the intervention.

Study Setting

Patients were recruited at a public pulmonary specialized reference hospital, Hospital Dr. A. Cetrangolo, located within Health Region V in the province of Buenos Aires, Argentina. Health Region V serves a large geographic region with a population of 3.13 million and accounts for about one third of the TB cases (incidence 49.2/100,000) within the province of Buenos Aires (Chirico, Kuriger, Etchevarria, Casamajor, & Morcillo, 2007). The regional reference hospital for respiratory pathologies serves both urban and suburban communities.

Informed Consent

This study was approved by the IRB from the University of Utah and Hospital Italiano, an independent IRB in Argentina. The PI provided all participants with a verbal and written description of the study and obtained informed consent in their primary language, Spanish. Participants were compensated for their time in the form of mobile phone credit, virtually added to their mobile phone account at the end of each month (~25

USD equivalent). Participants in intervention group received extra phone credit to cover the cost of the intervention and for participating in an interview.

Usual Care

All participants received the routine standard care provided by their healthcare provider at the out-patient clinic. This included routine clinical and laboratory tests and follow-up appointments according to their healthcare provider preferences. Patients received, in general, a month's supply of medication and were asked to return monthly for follow-up evaluations, or if they had any problems patients could schedule appointments prior to their follow-ups.

Intervention

The SMS intervention was developed in collaboration with a multidisciplinary research team and patients. It consisted of four components in which patients: (a) were instructed to text-in after medication administration (they received reminders if they did not); (b) received confirmation of receipt of notification; (c) had the option to text-in questions or concerns; and (d) received twice weekly educational texts which were based on the Information-Motivation-Behavior Skills model (Fisher & Fisher, 1992; Fisher, Fisher, Amico, & Harman, 2006). For full details of the intervention development, see Chapter 4. The intervention was delivered during the intensive treatment phase, which is the first 2 months of treatment. Participants in the intervention arm received verbal and written instructions at recruitment and were asked to send an initial text to test the program's receipt and function. Participants were informed that the intervention was

provided within a clinic based system and available during office hours (Monday through Friday) and that emergencies must be directed through standard routes.

FrontlineSMS, an open-source software (FrontlineSMS, 2011), was the text messaging platform used to store, send, and monitor text messages. A basic modem and laptop were used to perform the intervention. Hands-on training and written directions were provided for team members implementing the intervention. A staff member monitored the received messages daily to identify those who had not texted-in and sent out any query texts that were necessary, for example, "We know that you normally take your medication and notify daily but today we have not received notification, any problems?" Two pulmonologists were available for consult via text-messaging if a participant had a specific question or concern which staff member could not answer (e.g., recommendations for potential allergic reaction). A protocol and patient follow-up algorithm developed with the participatory research team was used to guide decision making (see Chapter 4).

To compare the groups based on self-reported adherence, participants in the control arm were asked to complete a paper-based medication calendar with spaces to indicate if medication was taken and the time taken (see Appendix E). Participants were given a demonstration on how to complete the report. Although there are inherent problems with collecting self-reported adherence data, such as overestimation of adherence (Wagner & Rabkin, 2000) using a calendar was the most practical method to assess adherence and more closely represented the standard practice. Patients were receiving treatment by self-administration, would return to follow-up according to provider's request, and could be

asked by providers or nurses if they were taking their medication regularly. Another option such as conducting a pill count would not have been feasible in this setting.

Process Measures

Process measures were *feasibility* and *acceptability* of the SMS-based intervention. Feasibility of delivering the intervention aimed to assess issues such as the number of eligible participants, the number of patients with cell phones, and the cost of text messages. *Feasibility* issues to be considered for conducting a larger trial, such as technical issues, are reported elsewhere in a socio-technical evaluation. *Acceptability* was considered the patient perceptions of the intervention, how to optimize the intervention, and how the intervention was used (e.g., types of messages sent/received, average number of questions, average number of reminders sent per patient, average number of side effects reported). We collected baseline information on socio-demographics, mobile phone access and diagnosis and conducted semistructured interviews (see Appendix F) at the end of the intervention period with participants in the SMS group.

Exploratory Outcomes

Exploratory outcomes included self-reported adherence, sputum smear or culture conversion, and treatment success. Self-reported adherence was measured by reviewing data collected in FrontlineSMS for the intervention group and the medication administration calendars for the control group. Sputum-smear or culture conversion from positive to negative and the treatment outcome was collected by reviewing the patient's medical record or outcome reports in the regional TB program records. Treatment

success rate was defined as the percent of patients who either completed treatment (without bacteriological confirmation) or were confirmed cured (negative sputum smear or culture in last month of treatment and on at least one previous occasion) (World Health Organization, 2009b).

Sample Size

We calculated the sample size of at least 17 per group in order to detect a response rate indicating that the intervention warranted further testing based on Schoenfeld's statistical considerations for pilot studies (Schoenfeld, 1980). We used the WHO target treatment success rate of 85% and the average treatment success rate in Argentina 46-65% from 2008-2010 (World Health Organization, 2012) to identify the desired improvement rate. The recommended cut off (clinical signal) to merit further testing of a pilot tested intervention in a larger trial was a 71% rate of response (successfully completing treatment) in the intervention group (Schoenfeld, 1980). A sample size of 40 was sought to account for attrition and for chi-square analysis requirements (Tabachnick & Fidell, 2006).

Randomization

Block randomization of 10 was used to ensure balanced representation in control and intervention arm. The random allocation sequence was generated using a computer-generated randomized list. Opaque envelopes sequentially numbered and sealed were used for treatment allocation concealment. Patients were recruited during medication retrieval at nurses' station after seeing the healthcare provider. Because of the nature of the intervention blinding of the group, allocation could not be conducted for research

staff, patients to other patients, or physicians to their patients. However, physicians were not made aware of the group allocation of their patient unless the patient informed them.

Analysis

With respect to the primary outcome of *feasibility*, we are reporting descriptive summary statistics of eligibility, enrollment and intake data, e.g., number of potential participants without cell phone, travel time to clinic, mobile phone types/access, and what they knew about TB. The semistructured interviews were transcribed verbatim in Spanish by a local, native Spanish speaker (Lincoln & Guba, 1985). Interviews and field notes were analyzed using descriptive content analysis to assess perceptions of the intervention and recommendations of how to optimize the intervention. Focused transcription Spanish-English translation was verified by the PI who is bilingual, and by Argentinian site supporter Dr. Rubinstein. To assess how the intervention was used a database using RedCap (Harris et al., 2009) was developed and the SMS data were coded for sender, day (e.g., weekday or holiday weekend), number of messages per day, and type of message (e.g., notification, question, or reminder) and entered into the database.

Baseline equivalence between groups was assessed using independent-sample *t* tests for continuous outcomes and chi-square test for dichotomous variables. Descriptive statistics included means (SD) and proportions. A p-value less than 0.05 was used to detect a statistically significant difference for all analyses. Computations were performed using IBM SPSS, version 20 (Chicago, IL). Self-reported adherence rates were calculated as the number of SMS notifications during clinic days of operation (e.g., Monday through Friday) divided by 60 days minus holidays and weekends. Notification sent with or without reminder was also assessed. We conducted a subgroup analysis to

explore adherence rates for those who had personal mobile phone access versus shared access.

Results

Feasibility of SMS-based Intervention

Between November, 2011 and June, 2012 we enrolled 37 participants from the 122 patients who were diagnosed with TB during the recruitment period (Figure 5.1). After screening, three patients were excluded because they did not have a mobile phone or have regular access to a mobile phone, three did not know how to send text messages (one was illiterate), and two declined participation. Fifteen patients were excluded due to initial inclusion criteria of first time TB treatment or extra pulmonary TB. Eighteen of the participants were randomly assigned to the SMS intervention and 19 to standard care. Two patients withdrew from the intervention group after random allocation. One required transfer of care to a local healthcare center where DOT was being provided because she could not afford travel cost to hospital outpatient clinic and was suffering from severe side effects and the other did not provide an explanation for withdrawal. Nine in-person semistructured interviews and three partial interviews with structured questions sent via text messaging were conducted. The in-person interviews lasted on average 25 minutes. There were no significant differences between the groups by baseline characteristics and demographic variables (Table 5.1). The average age of participants was 34.43 years with a range of 18-77, and 56.8% were females. Most participants (*n*=28, 75.7%) had individual (not shared) mobile phones and more had pay-as-you go, without contract service (59.5%) and basic cell phone features without internet (70%). There were 38% of the participants who indicated that they did not or did not

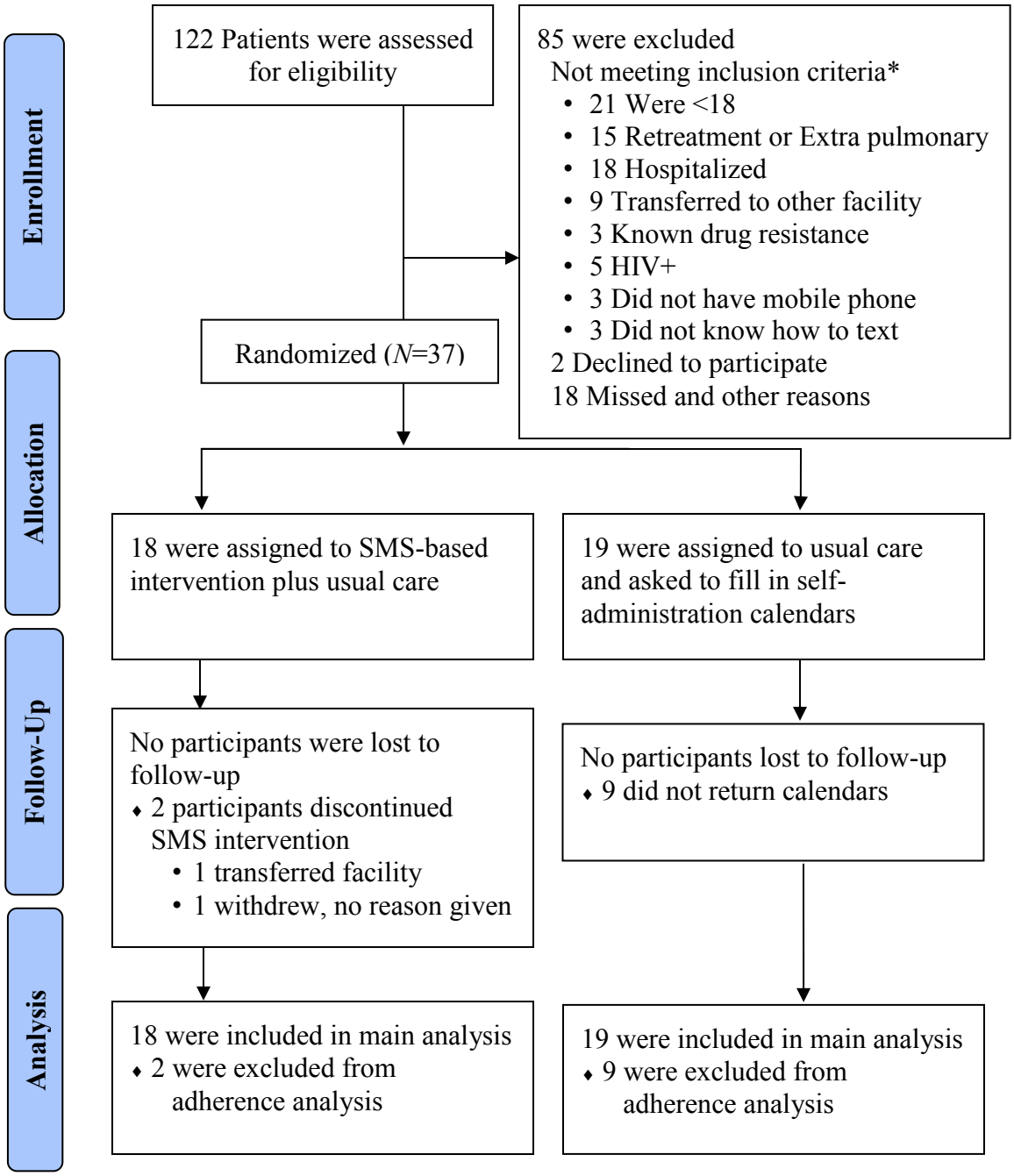

Figure 5.1. Patient flow diagram
*numbers do not add up because multiple criteria can apply for an individual

Table 5.1. Demographic and Baseline Characteristics

	Control group (*n*=19)	SMS group (*n*=18)	*p*
Age (years) (mean, *SD*, range)	35.05 (17,18-77)	33.78 (15,18-75)	0.81
Women	11 (58%)	10 (56%)	0.89
Education (completed)			0.19
Primary	7 (37%)	2 (11%)	
Secondary	10 (53%)	13 (72%)	
Postsecondary	2 (11%)	3 (17%)	
Travel time to clinic (minutes) (mean, *SD*, range)	63.93 (32.06,10-120)	69.06 (43.21,0-120)	0.71
Takes other medications daily	7 (37%)	2 (11%)	0.08
Monthly income covers basic needs (e.g., food, housing)	11 (58%)	12 (67%)	0.58
Mobile phone access			0.29
Personal	13 (68%)	15 (83%)	
Shared	6 (32%)	3 (17%)	
Basic feature mobile phone (not smart phone or with access to internet)	16 (84%)	10 (55%)	0.06
Prepaid mobile phone plan	13 (68%)	9 (50%)	0.25
Number of texts sent per day			0.45
<1/day	5 (26%)	3 (17%)	
1-10/day	8 (42%)	10 (56%)	
+10/day	6 (32%)	5 (28%)	
Not sufficiently informed about disease or treatment	13 (68%)	8 (44%)	0.37

Note. The number and percent are reported unless otherwise indicated.

always have enough income to cover basic needs (e.g., food, housing). The average commute time to get to the hospital based clinic was reported as 66.5 minutes (ranging from 0-120 minutes). Independent-sample *t*-tests were conducted for continuous variables (age, travel time) and chi-square test for categorical variables.

Baseline data were collected after diagnosis and their first appointment with a medical provider. On questionnaire 57% (*n*=22) of the participants reported that they were not well informed about the disease or treatment. When asked to describe what they

knew about TB some participants reported knowing very little. Statements included, "Zero," "nothing," "little to nothing," "very little," and "the doctor told me to 'take this' and nothing more." Two participants stated that they thought they contracted TB because, "I was drinking cold drinks, coca-cola" and "I ate out of the garbage when I was little." Others indicated that TB was "contagious," "contagious by cough and bacteria come out," "need to keep house open," "I have to take medication for a long time," and "long treatment but curable."

Acceptability of SMS-Based Intervention

Perceptions of Intervention

Text messages received during the intervention indicating acceptance included: "thank you for being there," "thank you for the information," and "thank you for responding to my question." During the interviews, when asked to rank if they would recommended the intervention for other patients diagnosed with TB, 9 of 12 would highly recommend, 2 had a low –moderate recommendation, and 1 participant did not respond.

All participants in the intervention group were asked to participate in an interview at the end of 2 months. Nine participants were able to conduct in-person interviews and 3 received the structured questions by text message because they were unable to attend in person. Overall the participants interviewed indicated in the qualitative interviews that they felt "accompanied," "cared for," "had a friend when all others wanted nothing to do with them," and felt "responsible for my treatment" by texting in daily. Common themes were being thankful for the support and valuing having someone available to answer their questions. Two participants discussed not forgetting to take the medication because they

knew that someone would be checking. One stated "It's like alone it is very complicated there are many pills, a long time…if you don't have someone following you it is likely you will fail treatment." Three indicated that they would rather send messages daily than go to a clinic daily to receive medication. One patient stated "the experience for me was splendid," while another indicated that we (the research team) were "more interested in the numbers" because this was a study.

Most Helpful Component

When asked what component of the intervention was most helpful 9 of 12 indicated all intervention components were helpful. The other three reported notifying daily and being able to consult (n=1); educational messages and reminders (n=1); and educational messages were the most helpful (n=1). During the intervention some participants responded to educational text messages. For example, the educational text message regarding TB stigma received a few text replies from participants. One participant texted back "yes many people are even scared to call" and another wrote "often one does not become aware of a disease until they suffer from it. Then ones sees and notes the ignorance that we have regarding it and the degree of discrimination that exists!" During the in-person interviews, participants described the educational text messages as helpful. One participant indicated that she shared the educational text messages with family and friends to help educate them on the disease.

Recommendations of How to Optimize the Intervention

During the qualitative interviews recommendations from participants on how to optimize the intervention included continuing the intervention for the full course of

treatment; providing more information, including messages from other patients; possibly texting in less often, e.g., once per week; having option to email messages; and offering in-person consultation in addition to text messaging intervention when patients come to clinic to pick up medication. One participant who inconsistently texted-in, partly due to technical/ modem problems (see Chapter 6 for the socio-technical evaluation) stated "might be better to call to see how the person is doing."

How Intervention Was Used

A total of 1320 text messages were sent and 996 were received during the study period (Table 5.2.). On average there were about three questions (ranging from 0-9) and two side effects (0-11) reported during the intervention period. Examples of questions texted in included: "I want to know how to take the pills bc there are 8 of them each day. can I take 1 every hour?," "Is it normal that urine changes reddish?," "how is TB contagious, if don't talk or breathe in a room can still spread?," "how many days or wks do I have to use a facemask to prevent spread?," "my knees hurt, could this be related to

Table 5.2. Types of Messages Sent and Received During Intervention

Type of SMS message	*N*	*Mean*	*sd*	*Range*
Text messages received from patients	996	55.00	33.50	2-131
Questions	46	2.87	2.55	0-9
Report side effects	32	2.00	3.50	0-11
Days continued to notify after intervention	109	7.79	13.74	0-53
Test messages sent by researchers	1320	73.00	28.5	18-154
Reminders per patient	170	9.44	6.59	0-21
Automatic confirmation of notification	307	17.05	14.11	0-40
Manual confirmation of notification	128	7.11	6.66	0-21
Educational messages	277	15.39	3.42	7-19
Personalized /respond to questions	113	6.28	4.16	0-14

Note. Mean is average per person

tx?," "can any of the meds cause allergies rashes?," "at some point will my cough go away?" The most common side effects reported via text messages are in Table 5.3. The intervention was also used by patients to report going to their appointments, the results of tests of family members and problems with their mobile phone.

Confirmatory text messages were sent to participants after a notification was received. Staff also used this opportunity to incorporate a motivational message such as, "keep it up!" within the confirmatory text. These messages were sent to the patient either automatically, using keywords or manually when keywords were not identified by the FrontlineSMS program. Of the confirmation text messages sent, 70.1% were sent automatically and 29% were sent manually.

In addition to answering questions, the TB program staff utilized the text messaging system to notify participants when medication was available to pick up. During the study period there was an unexpected regional and country wide shortage of TB medication. At one point, there was no Ethambutol or Rifampin in liquid form, or some of the second line medications. The shortage began December 1, 2012 and the last text message (n=6), which indicated that Ethambutol had arrived and could be picked up, was sent on March 20, 2012. Because of the shortage patients were allocated medication for shorter periods, for example 5 days or 2 weeks depending on availability to make the medication last.

Table 5.3. Side Effects Reported in Text Messages

Side effect	*N*
Stomach problems	10
Rash	4
Muscle ache / pain	3
Low energy	3
Urine color change	2

Patients were informed to keep checking in for when the missing medication would arrive. This unexpected event likely had an impact on the pilot study.

Initial Efficacy

Notification or Self-reported Adherence Rates (texting in)

The mean notification (texted-in) of the SMS group was 77% (*SD* 23.5, range 22-100) (Figure 5.2). Of the notification (*n*=407), 83% were sent without a reminder. In the SMS group one participant notified the team (texted in) that she was not taking medications because they were on hold by provider for a week due to having side effects from the medication. During the interviews three participants indicated that they had family members or significant others respond on their behalf. The participants who notified less than 50% of the time were 2 of the 3 who shared a phone. These 2 participants reported a change in access to the mobile phone. For one the shared phone was stolen while the other indicated that his relationship with his girlfriend, with whom he shared the phone, changed and he no longer had access to a phone. The latter obtained a personal mobile phone and reinitiated notifying staff.

Reasons for not notifying were texted in by some participants and included texting in the next day “Sorry I didn’t notify my cell phone fell but I fixed it don’t worry I took my meds thank you for caring I say it from my heart greetings to all,” another “Yes I am continuing to take my medication I didn't respond bc my phone got wet and I had to put chip in another phone.” Two texted, “if I don't send msg means that I have ran out of credit” and “I took the meds forgot to send msg” and others texted in that the mobile phone battery ran out during an extended power outage or that they were out of town

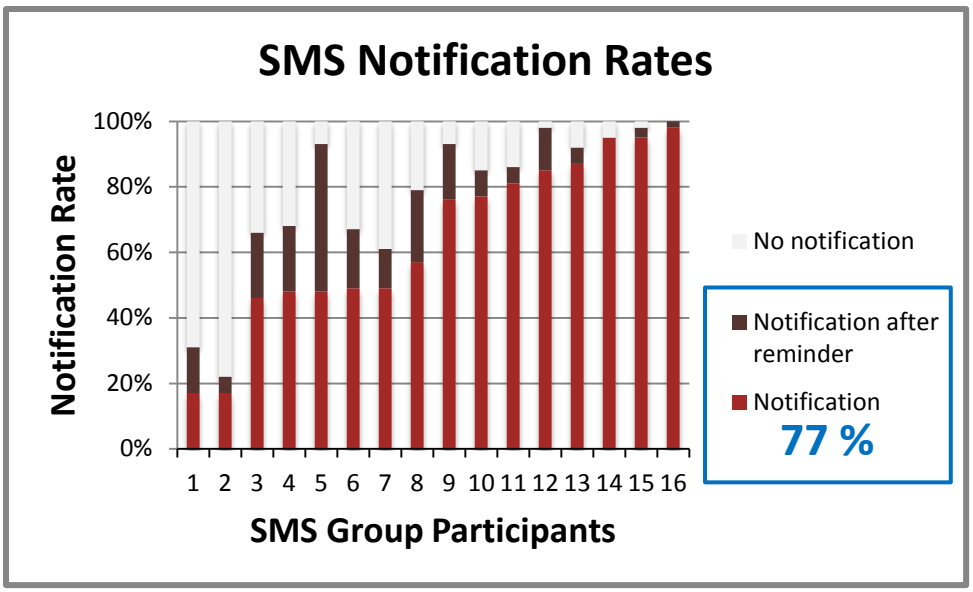

Figure 5.2. SMS notification rates in access to mobile phone

without mobile phone reception. During the interview 1 stated "I know it is me that lacks motivation to send message daily" and recommended notifying less often or calling to check on her rather than asking her to text in daily.

Although participants were not required to do so, some texted in on weekends or on the next workday after a weekend or holiday, notifying that they had taken their medication for the prior days (e.g., "took medication today and Saturday and Sunday as well") (mean 4.3 text messages *SD* 3.3, 0-10, with on average 8 weekends over 60 days period).

In the control group, 12 (63%) and 10 (53%) returned calendars for the first and second month, respectively. Therefore, the self-reported adherence rates could not be compared between the groups due to missing information. Of those who did return the calendar there was a 100% self-reported adherence. On the calendars 1 participant reported going to the emergency room due to fever and another indicated that he did not take ethambutol because it was not available for 2 days due to the medication shortage.

Conversion Rates

Follow-up microscopy testing was low with only 15 (41%) participants having a follow-up test reported (Table 5.4). Because of the low rate tests of significance could not be conducted, but it appears that there was no difference.

Treatment Outcomes

Final treatment outcomes were collected from participant medical records (Table 5.5). Treatment success was high in both groups with 34/37 (92%) completing treatment successfully. Two (.05%) participants abandoned treatment, 1 was diagnosed with a nontuberculosis mycobacterium after being treated for TB, and no participants failed treatment or died from TB. There were 5 participants who were reported to have transferred to another healthcare facility, but treatment outcomes were documented in their medical record. At the point of final treatment collection, 1 participant in the SMS group was reported to have abandoned treatment. However, this participant had continued to notify (text-in) after the documented abandonment date, and during the exit interview this participant reported transferring care to a local healthcare facility.

Table 5.4. Sputum or Culture Conversion by Group

Sputum smear or culture	Calendar (*n*)	SMS (*n*)
Remained positive	2	2
Converted to negative	6	5
Not evaluated	11	11

Note. Not evaluated: records indicated no sputum production or no follow-up test ordered

Table 5.5. Treatment Outcomes by Group

Treatment outcome	Calendar (*n*)	SMS (*n*)
Treatment success (Cured or Completed)	17	17
Failure / Continuing treatment	0	0
Death	0	0
Treatment Interrupted / Abandoned	1	1
Transferred out / no data	0	0
Other	1	0

Note. Other represented a participant diagnosed with nontuberculosis mycobacterium after completing TB treatment for an extended period

Discussion

The investigators in this study explored issues of feasibility, patient acceptability, and initial efficacy of implementing an SMS-based intervention. The multiple component interactive intervention was developed as a comprehensive package in a low-resource setting in which patients routinely receive TB treatment by self-administration. To our knowledge this is the first study with TB patients to trial a mobile phone-based intervention, which goes beyond reminders, and may be applicable for resource limited setting where video access is not yet commonly accessible and DOT is costly and challenging. Our findings suggest the TextTB intervention was feasible and well accepted. Further, there was greater adherence with reporting in the SMS group than with the use of a medication diary. However, assessing the success of adherence in the research is obscured by low numbers of patients in the control arm returning their calendars. In addition, outcomes of initial efficacy have yet to be determined given a limitation of low rates of follow-up tests for sputum or culture conversion. However, according to the power analysis (Schoenfeld, 1980) a response rate of 71% would indicate that further testing of the intervention is warranted and our overall notification

rate was 77%. This trial was not powered to assess the degree to which each component of the intervention contributed to any observable difference.

Feasibility

Access to mobile phones was high and most knew how to use the SMS feature. Those without mobile phones indicated that they were willing to participate if they had a phone or a phone was provided. One participant lived alone and did not have anyone close to share a phone with and another had recently had her mobile phone stolen and did not anticipate replacing it immediately. There was also a low refusal rate, which demonstrates potential feasibility of conducting a larger study. Those who consented to participate seemed interested in intervention and eager to have support, which may be a potential reason for low refusal rates. One potential participant who refused indicated that she did so because she did not have time to discuss the study; another indicated that she did not know how to text and was not interested in learning for the study. There were 2 patients who were angry because of delay in diagnosis and clinic nurses did not want to approach them about the study, and another potential patient wanted to go home and think about it and did not return; therefore, they were not invited to participate.

Of the newly diagnosed TB cases identified during the recruitment period the largest group who were excluded were those under 18 years of age. Younger people have been reported to be less compliant with the long treatment (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2011). The use of SMS technology as part of everyday communication is high in the younger population, warranting further testing in this age group. In addition, a number of patients were being treated for TB for a second or third

time. As previously described, we modified the initial inclusion criteria to be more inclusive of these patients.

Having access to care and travel time has been previously identified as barriers to TB treatment success (Hill et al., 2005; Khan, Walley, Witter, Shah, & Javeed, 2005). In our study patients traveled on average 1 hour and up to 2 in order to be attended to at the regional pulmonary reference hospital. Anecdotal evidence from discussions with patients points to having more confidence in the larger facilities compared to smaller clinics, which have varied staff composition and resources. Although the average travel time was substantial, patients indicated that they would rather travel farther and they perceived the larger hospital provided better care than the smaller clinics in closer geographic proximity. However, 1 of the participants who withdrew from this study had to transfer care to a local healthcare center after 2 weeks in the intervention due to inability to pay for transportation to the hospital-based clinic for follow-up evaluation for severe side effects.

Our study supported text messaging as a feasible intervention option. Although technology will continue to change, currently only 30% reported having mobile phones with internet access or smart phones. Therefore, the ability to use the mobile phone video feature, as previously described from other studies (DeMaio et al., 2001; Hoffman et al., 2010; Wade et al., 2012), would have been limited in our population at the time of this study. Our participants were not asked if the video feature would have been an acceptable option for treatment monitoring, but it could be considered for future studies. Of the researchers who have reported use of video, those who tested the video feature all reported the video to be overall accepted.

Acceptability

Overall, the intervention was accepted by the participants and the research team. An aim of the TextTB intervention was to promote a supportive patient-healthcare professional relationship. A strong patient-healthcare professional relationship has been identified as highly important in TB control efforts (Iribarren, Rubinstein, Discacciati, & Pearce, 2011; World Health Organization, 2006a, 2009c). The main themes described by participants in the interviews and in the text message were feeling *cared for* and *supported by staff*. Similarly, other researchers using text-messaging interventions report patient acceptance and being well received (Lester et al., 2010; Mohammed et al., 2012; Person, Blain, Jiang, Rasmussen, & Stout, 2011). Most participants indicated that they would highly recommend the intervention to other patients starting TB treatment. Although patients were notified at the end of the 2 months that they no longer were required to text in daily, some continued to text in notification for as long as 53 days. One participant continued to text in daily for nearly 2 months.

Concerns with health-related information regarding diagnosis being seen by those it was not intended for and associated stigma has been reported as a potential drawback to using mobile phones (Kaplan, 2006; Lester et al., 2010; Mbuagbaw, Bonono-Momnougui, & Thabane, 2012; Mohammed et al., 2012). Sharing a mobile phone could increase this risk. In our study, however, there were no privacy issues reported and as previously mentioned few researchers have applied mobile phone interventions with patients with TB to identify if this as a barrier. As previously described there were participants who shared a mobile phone with a family member or significant other. The problems reported by 2 individuals with shared phones were related to access to the

phone rather than concerns with information being received by others. Two of the shared users reported having a family member or significant other send the text message notification on their behalf at times, therefore having others actively participate in their treatment.

Initial Efficacy

As previously indicated there have been few researchers who evaluated the use of text messaging for TB management. Mohammed and colleagues (2012) were the only researchers identified in the literature to have specifically applied text messaging. Some important differences in our study from that conducted by Mohammed et al. (2012) were that our study was a randomized controlled parallel design and the intervention was conducted during the first 2 months of treatment compared to participants who had been on treatment for an average of 3 months. In addition, for our intervention we did not send daily reminders automatically. Patients were asked to notify on their own and received a reminder or inquiry if a notification was not received. TextTB also included educational messages and encouraged patients to text in questions. Our study results differed in that we had a higher overall reported notification rate and those who shared a mobile phone had the lowest notification rates, in contrast to Mohammed and colleagues, who reported lower response rates for those who owned their own mobile phone. Similar findings included having participants report family members assisted in sending text messages and having participants overall indicate acceptance and being supported by the text messaging intervention. Because our intervention did not automatically send reminders, we were able to detect that many participants notified on their own and used the system to ask questions regarding treatment or what to do after experiencing side

effects. In addition, TextTB provided an opportunity for ongoing education regarding TB treatment.

We did encounter challenges in assessing the outcomes of rate of reporting treatment adherence and sputum or culture conversion. To enable the comparison of reporting treatment adherence across the groups, the control arm was provided with medication calendars. It was recognized by the research team that adding the calendar was in itself an intervention; however, it was determined to be the least invasive way to compare adherence across groups. Only about half of the participants in this group returned the calendars and, of those who did, the self-reported adherence rate was 100%, making it hard to compare groups based on this variable. Similarly, in a randomized control trial conducted by Wamalwa and colleagues (2009) in Kenya, there was lower self-reported adherence observed in the medication diary group as compared to receiving counseling alone to improve adherence to antiretroviral therapy. In addition, there was a lack of information on how the calendars were completed by the participants. For example, if the data were entered on the calendars daily or at the end of the month. Information on why calendars were not returned was not collected.

In order to more objectively identify if patients were adhering to medication, the outcome of sputum or culture conversion and treatment outcomes were evaluated. Sputum or culture conversion was selected to provide a measure of initial efficacy of the intervention. However, in our study we found that providers did not consistently request follow-up sputum or culture specimens and less than half of all participants had results for this outcome. Given the low rate of sputum or culture testing (15 out of 37), the potential significance of this type of intervention, especially in settings where self-

administered treatment is the usual care, may be enhance through early identification of nonadherence to treatment. According to the WHO, patients should be monitored for response to treatment by conducting follow-up sputum tests after the initial 2- month intensive phase, then at 5 months and the end of treatment (World Health Organization, 2006b). Notations in 4 participants' records indicated that they no longer had a productive cough, in 2 there were indications of the test ordered but not submitted by the participant, and in the remainder of those without sputum or culture results there was no notation of the test being ordered. Given the low rates of follow-up sputum or culture tests the initial efficacy based on conversion rates could not be adequately assessed. However, using conversion rates as an outcome indicator may be an issue since treatment success is considered either cure with bacteriologic confirmation or treatment completion without bacteriological confirmation (World Health Organization, 2006b). In a study conducted by Lopez et al. (2013) assessing the accuracy of follow-up sputum smears to predict outcome only 56% (n=526) of the population had confirmed conversion.

There are no significant differences in treatment outcomes between the groups, but conclusions are limited by the small sample size. Paper charting delayed verifying treatment outcomes at the regional level. Even 1 year after patients initiated treatment, it was challenging to collect final treatment outcomes. Treatment success was high in both groups; however the most recent regional report, analyzing data up to 2011, reported a regional treatment success of 77.6%. Therefore, both interventions seemed to improve treatment success compared to historical regional data.

Recommendations for Improvement and Issues to Consider for Larger Trial

Reflecting on recommendations from participants, this intervention could be expanded to include other options to make notifying and maintaining contact with healthcare staff more convenient. For example, having the option to email notifications or questions could be added to the intervention. This, however, could add to the workload of the staff member and possibly be limited due to power outages or loss of internet access. Nonetheless, it could provide both the staff and the patient with a backup option if mobile phone credit runs out or the phone is lost.

Limitations

Although this was a small pilot study most participants utilized the interactive intervention to meet their needs. Specific factors, applicable to this setting and other resource-limited settings where mobile phone access is high, are highlighted. Nonetheless, this study has some important limitations. First, self-reporting is subject to systematic biases that are prone to overstating medication regimen adherence (Garber, Nau, Erickson, Aikens, & Lawrence, 2004). Phone credit compensation was intended to have been an incentive for the control group to return calendars, but only about half did so to redeem their phone credit. We do not know how self-reporting influenced the control group who reported 100% adherence for those who submitted calendars. In the intervention group, however, conducting a daily assessment rather than over multiple days or a month may limit the bias of overstating adherence.

Our aim was to assess sputum or culture conversion and treatment completion rates for objective measures. However, because of the low number of follow-up tests

conducted after 2 months of treatment, we were limited in our ability to compare groups based on the sputum or culture conversion rates. Nonetheless, there appears to be no significant difference between the two groups. Final treatment success rates were high in both groups. It is possible that those who agreed to participate were more likely to be adherent with treatment.

Other potential contributing factors to improved outcomes in both groups could include increased visits to clinic due to the medication shortage and additional education received at the onset of the study. The period during which some TB medication was scarce or not available changed the medication allocation intervals. When medication was available patients standardly received a month supply and when there was a shortage the allocation varied from 3 days to 2 weeks' worth depending on the amount of medication available. Therefore, the amount of contact with the patient and a healthcare team member may have changed during this period.

At recruitment nearly 60% of the participants indicated that they were not well informed by providers on the disease or its treatment and some describe inaccurate causes of TB transmission. During recruitment participants were given the opportunity to ask questions, therefore possibly providing an additional educational benefit to both groups. In future studies TB understanding might be better elucidated by asking specific TB knowledge questions at baseline and after intervention to more accurately capture what was learned from educational text messages. In addition, future studies could tailor messages based on baseline knowledge.

Conclusions

New strategies are needed to improve patient adherence to TB treatment to prevent the spread of disease, drug resistance and poor treatment outcomes, especially in settings where self-administration of treatment is common. To promote treatment adherence and support patients with TB the TextTB mobile phone-based intervention was trialed and our results suggest that it was feasible and overall well-received. An aim was to empower patients to engage in the management of their own care in a setting where self-administration was the standard. Asking patients to text in after self-administering medication, rather than sending patients daily reminders, was supported. In this study, for some having a shared mobile phone represented a barrier. There was greater reporting of adherence using text messaging than with the use of a medication diary. Final treatment outcomes were similar in both groups. Patient tracking was paper based and collecting the final treatment outcomes was resource intensive and time consuming, highlighting organizational challenges faced by the TB program. Although there is no clear evidence that the SMS intervention was more efficacious than calendar use, feasibility and acceptability results in this study suggest that there is value in assessing this intervention in a larger-scale research project. In addition, further testing in patients who are under 18, which was the largest group to be excluded in the cohort of patients diagnosed with TB during the recruitment period and is often recognized as a population with high mobile phone usage, is warranted. In this population the use of the video feature or other advanced phone features may be available in the near future and being flexible and adapting to quickly changing technology will be required to leverage the benefits that new technologies will provide.

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CHAPTER 6

SOCIO-TECHNICAL EVALUATION: CONSIDERATIONS FOR CONDUCTING A LARGER TRIAL

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Abstract

Purpose

A text messaging based intervention to promote active tuberculosis (TB) medication adherence was introduced into a clinic setting workflow of a public pulmonary specialized hospital in Argentina in a randomized control pilot study. This evaluation focused on identifying feasibility issues to be considered for conducting a larger trial.

Methods

The study design was a socio-technical evaluation using mixed methods. A qualitative approach complemented the quantitative RCT study. Emerging issues were grouped into three categories: technical, human and organizational. Our findings are reported using the STARE-HI (Statement on Reporting of Evaluation Studies in Health Informatics) guidelines.

Results

The intervention was integrated into the working practice of the regional TB office for nine months and was received by participating patients randomized to the text messaging group (n=18) for the first 2 months of their TB treatment. The PI observed 115 working days of intervention and analyzed study process notes, verbal and written input from team members, and the text messages. A TB technician managed the daily patient interactions, and three other team members were trained and able to operate the program at various levels of comfort. A total of 1320 text messages were sent and 996 were received during the study period. A summary of the findings structured by the socio-technical evaluation framework is provided.

Conclusions

Considerations for implementing the intervention in a larger trial included reducing the barriers of text message cost, improving the automated process of sending educational messages, and strengthening capacity to return patients back to treatment. Technical feasibility issues are highlighted and suggestions to improve the intervention are offered.

Keywords: Telemedicine, text-messaging, tuberculosis, socio-technical evaluation, primary care, RCT, mHealth

Introduction

Scientific Background

Tuberculosis (TB) remains a major contributor to the global burden of disease and in some settings targeted outcomes, such as treatment adherence, are not being met (World Health Organization, 2010). To assure TB treatment adherence the World Health Organization (WHO) and others have called for more integrated, patient-centered approaches to promote patients as partners while individualizing and tailoring interventions to meet patient needs (Barclay, 2009; Kaplan, 2006; Tuberculosis Coalition for Technical Assistance, 2009; World Health Organization, 2009). Mobile phone technology supports patient-centered approaches and holds potential to impact tuberculosis (TB) treatment outcomes (Barclay, 2009). However, despite the broad application of mobile phone based interventions in some chronic or infectious diseases (Cole-Lewis & Kershaw, 2010; Fjeldsoe, Marshall, & Miller, 2009), uptake has been slow in TB management.

Some researchers have focused on providing *directly observed therapy* (DOT) using the video feature of mobile phones (DeMaio, Schwartz, Cooley, & Tice, 2001; Hoffman

et al., 2010; Wade, Karnon, Eliott, & Hiller, 2012). DOT, a recommended treatment strategy, requires that a healthcare worker or a trained individual observes the patient swallowing every dose of medication. These researchers suggest that the video feature was a feasible means to provide DOT and found it to be overall acceptable to users (DeMaio et al., 2001; Hoffman et al., 2010; Wade et al., 2012). Wade et al. (2012) identified fewer missed observations than traditional DOT and calculated the cost savings of $1.32 Australian dollars (1.38 USD) per day of successful observation (N=128). DeMaio et al. (2001) observed 95% adherence in their six- patient cohort and Hoffman et al., 2010) found the method to be technically feasible with 13 patients. Other investigators have used individual calls and text messages in their mobile phone interventions. Kunawarak et al. (2011) conducted a randomized control study with 98 multidrug resistant (MDR) and nondrug resistant TB patients in Thailand divided into four groups. The researchers compared outcomes from daily reminder calls to the patient's mobile phone by an officer in a TB center to DOT with a family member participating as the treatment observer for MDR and nondrug resistant TB groups. They found a higher completion success rates in both intervention groups (p<0.001), significantly higher sputum conversion rate in patients with MDR TB (p<0.001), but a nonsignificant difference between the two interventions in the non-MDR patients. Mohammed and colleagues (2012) conducted a nonrandomized study with 30 participants in India sending daily text message reminders and asking participants to respond with texting-in the time they took their medication. Patients responded that they took their medication 57% of the time over a 1-month period (Mohammed et al., 2012).

Despite suggesting feasibility and patient acceptability, only a few studies report challenges in implementing a mobile phone based intervention. For example, Hoffman et al. (2010) reported challenges of internet access in Kenya, such as downtime due to issues of frayed ethernet cables, slow system access, and technical issues with transmissions resulting in loss of an estimated 25% of data. Wade et al. (2012) reported ongoing technical difficulties such as temporary freezing and drop out of video calls identified as due to variable signal strength. Therefore, an in-depth exploration of feasibility issues while implementing a mobile phone based intervention is justified.

Given the increase in ICT globally, and the ubiquitous movement of and reliance on technology in everyday life, a parallel movement of ICT into healthcare, including utilization in interventions, is readily apparent in the literature. Researchers need to evaluate ICT interventions during implementation to inform users, researchers and developers on successful applications and to identify unintended and intended consequences of the technology itself, and its use (Talmon et al., 2009).

Why the Socio-technical Approach?

The evaluation of an intervention is an important step in system development and helps meet overall organizational goals, in this case specifically the clinical outcome to improve TB treatment adherence. The socio-technical framework is an approach to systems design that recognizes the complex interaction between people and technology in organizations. The approach is grounded in both social theory and information technology (IT) and sees technological innovation as a social process; the approach makes use of in-depth formative evaluations to achieve improvements in system design and implementation (Berg, Aarts, & van der Lei, 2003). A formal evaluation includes

recognizing complaints, challenges, and shifts in relationships or user acceptability. The framework provides researchers with a guide to accommodate identification of variables and relations within the context of use, which can influence perceptions about usability. Functionality and technical aspects of an information and communication technology-based intervention are important, but the value and usefulness also depend on the individuals and organizations who will use and adapt to the intervention (Berg, 1999). Insufficient evaluation can lead to unintended consequences, and may undermine quality and safety, leading to implementation failure and therefore less positive outcomes (Berg et al., 2003; Harrison, Koppel, & Bar-Lev, 2007). The socio-technical framework provides researchers with a way to organize formative evaluations of technology- based interventions taking into account the technical aspects, human perspective, and organizational context (Barber, Cornford, & Klecun, 2007; Cornford, Doukidis, & Forster, 1994). Examining a technical intervention while in use can provide an opportunity to understand and respond to user and provider needs and improve the intervention (Harrison et al., 2007).

Rationale for the Study

Improving treatment adherence for patients is challenging, and adding new technical tools can be as well. The purpose for this study was to examine the implementation of a Sort Message Service (SMS)-based intervention using a socio-technical approach. The purpose of the intervention was to promote adherence to TB treatment in an out-patient clinic in Argentina where the standard treatment modality for patients with TB was self-administration of medication. The research was the first of its kind, using mobile-phone based interventions, to be implemented in this setting.

Objective

The objective of this evaluation was to identify challenges of integrating the intervention into the clinic setting from system, human, and organizational perspectives and to provide insight into the issues to consider in conducting a larger trial. This study, which was a component of a phased pilot study, was approved by the Institutional Review Boards (IRB) of the University of Utah and Hospital Italiano, an independent IRB in Argentina.

Study Context

Organizational Setting

Tuberculosis remains a major public health problem in Argentina (World Health Organization, 2012). Countrywide the incidence rate is 26/100,000 (World Health Organization, 2012); however the distribution of TB between regions varies greatly, from 1-199.1 cases/100,000 (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2011). Treatment success rate is defined as cure with microbial confirmation two times during the course of treatment, or treatment completion (World Health Organization, 2003). The World Health Organization (WHO) target success rate for TB treatment is 85% of cases (World Health Organization, 2003). In Argentina, the average treatment success rate from 2008 to 2010 was 46% of sputum smear-positive cases (confirmed pulmonary TB diagnosis) (World Health Organization, 2012). Furthermore, about half of the TB cases are reported to receive treatment by self-administration (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2010). According to the National TB Program in Argentina there has been little improvement in treatment success over the past 10 years (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2010).

Argentina suffered a tremendous socioeconomic crisis in 1990-2002, which left nearly 60% of the country's population below the poverty line and resulted in a historically high rate of unemployment at 21.5% in 2002 (Zeballos, 2003). Possible health effects attributed to the crisis specific to TB included higher rates of complications and death, increased resistance and spread of resistant strains, and unfavorable short- and long- term epidemiological scenarios (Zeballos, 2003). Prior to the economic crisis, Argentina was considered a successful reference, or role model, for other Latin American countries and the world. Aside from the residual effect of the economic crisis in Argentina, the cause for low TB treatment success rates is not well understood.

In Argentina TB treatment is provided free of charge in the public healthcare system. The public healthcare system is decentralized and consists of provincial, regional, and municipal healthcare facilities and peripheral healthcare centers. The intervention was implemented in a regional TB program office located within a public pulmonary-specialized reference hospital, Hospital Dr. A. Cetrangolo, in the province of Buenos Aires, Argentina. This hospital serves both urban and suburban communities and resides within Health Region V, which serves a population of about 3.13 million across a large geographic region (Instituto Nacional de Estadistica y censos (INDEC), 2010). Region V accounts for about one quarter of the TB cases within the province of Buenos Aires (Chirico, Kuriger, Etchevarria, Casamajor, & Morcillo, 2007). In 2010, the rate of treatment abandonment was reported at 15.3%. In this hospital the routine standard of care for patients with TB is provided in the out-patient clinic by pulmonary specialized healthcare providers (N=20). In general, patients receive a month's supply of TB medication and are asked to return monthly for follow-up evaluations according to their

healthcare provider preferences. Routine clinical and laboratory tests are scheduled by the healthcare providers. A monetary subsidy is provided to patients with TB who do not have a medical insurance and who have resided in the province of Buenos Aires for at least 2 years. In order to receive the subsidy the patients must return a signed slip from their provider at the scheduled visits.

System in Use and the TextTB SMS-Based Intervention

The system in use for monitoring medication adherence is paper based. A 4x6 in. card is filled out with patient information (e.g., age, medication ordered, type of TB diagnosed) when the patient brings a notification form from the provider to the nurses' station to pick up treatment. When patients return to providers they receive another prescription to continue treatment and the notification card is updated with the date when the patient picked up the medication.

The intervention, which was labeled TextTB, was developed using the FrontlineSMS open-source free software version 1.6.16.3 (FrontlineSMS, 2011) installed on a laptop, along with a GSM modem and a SIM card. The FrontlineSMS software (2011) enables the user to send, receive, and manage text messages (Figure 6.1). The TextTB research used the contacts, keywords, messages, phone manager, translation (Spanish), and reminders features. A GSM modem is a type of modem that accepts a SIM card from a mobile operator and can be connected to a computer, supporting computer communication across a mobile network (Now Wireless Limited, 2013). Essentially the GSM modem enables the functionality of the computer to work like a phone, and can be used to provide mobile internet connectivity or send and receive messages. A mobile phone can be used instead of the GSM modem to operate the FrontlineSMS software.

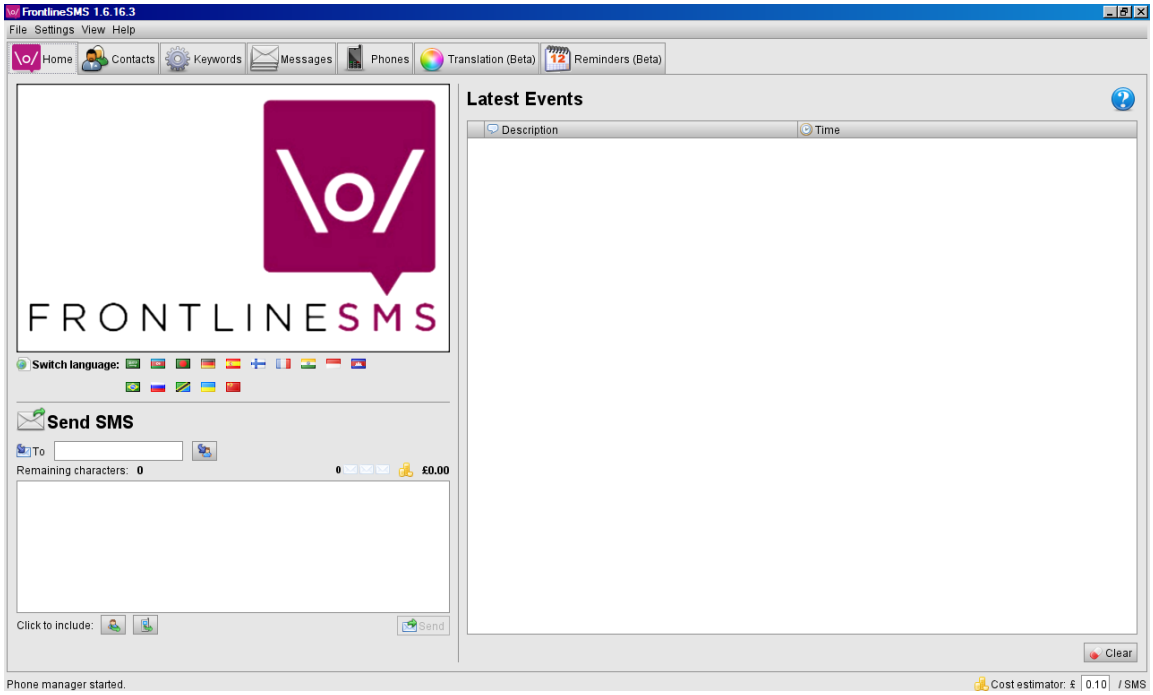

Figure 6.1. Screenshot displaying features of FrontlineSMS

TextTB Intervention

The aim of the TextTB program was to monitor self-reported adherence and provide support to TB patients who were receiving treatment by self-administration. The intervention was developed with a multidisciplinary, collaborative research team and patients in treatment. For full details of the intervention development, see Chapter 4. In brief, the key components of the intervention included medication adherence monitoring, provision of TB related information, and a platform for patients to ask questions and providers to respond. There were 37 participants enrolled in the pilot study and randomized in a 1:1 allocation in blocks of 10 to the control group (n=19) and the intervention group (n=18). Participants randomized to the control arm were instructed to complete a medication administration calendar to submit to the research team at their monthly appointment. Patients randomized to the text-messaging intervention were

asked to 'text in' daily after medication administration (they received reminders if they did not); received confirmation that their text-in was received; were encouraged to text in questions or concerns; and received twice weekly educational texts messages based on the Information-Motivation-Behavior Skills model (Fisher & Fisher, 1992; Fisher, Fisher, Amico, & Harman, 2006). Intervention group participants were asked at enrollment to text in an initial text to confirm receipt of their number and connection with the system. The participants received the interventions during the first 2 months of treatment. There was greater reporting of adherence using text messaging than with the use of a medication diary. The text-messaging intervention was found to be feasible to implement in this population, was overall well received and findings indicated that further testing using the intervention was warranted (see Chapter 5 for complete results).

Methods

Study Design

We conducted a socio-technical evaluation (Berg et al., 2003; Cornford et al., 1994) synchronously as part of the intervention implementation phase of the randomized control pilot study using mixed methods (Johnson & Onwuegbuzie, 2004). This evaluation focused on identifying feasibility issues to be considered for conducting a larger trial. A qualitative approach was integrated for data collection, complementing the mixed-methods randomized controlled trial (RCT) study. The intervention was in operation for 9 months in which time patients were enrolled and received the intervention for the first 2 months of their TB treatment. Findings are reported using the STARE-HI (Statement on Reporting of Evaluation Studies in Health Informatics) guidelines (Talmon et al., 2009). The STARE-HI guidelines aim to improve the quality of evaluation studies

in Health Informatics by providing a comprehensive list of principles to be described during reporting (Talmon et al., 2009).

In regard to reporting potential bias, this study may include a risk of 'circular inference' bias. Circular interference is identified as arising when a technique, method or framework was developed on the basis of a population and then applied to the same group (Brender, 2006). By intrinsic nature, an assessment based learning approach method can constitute a type of circular inference (Brender, 2006). That is, the "lessons are incorporated into the basis for the further process" (Brender, 2006, p. 267). Therefore, conclusions beyond the technique and setting in which the intervention was applied are drawn with caution. In addition, having deep prior knowledge of a system or having become acquainted with the functionality may lead to unintentional omission of problems that new users may experience (Brender, 2006). The software was not built specifically for the application for which it was used in this research. The PI did have prior knowledge of the software by viewing user tutorials and conducting trials with the software. The rest of the team had no prior exposure to the software prior to training and intervention implementation. Because of the nature of the pilot study the PI worked in close collaboration with the team and participated in trouble shooting when infrastructure or software issues arose during the implementation process.

Theoretical Background of the Study

The socio-technical approach (Berg et al., 2003) as adapted from Conford et al. (1994) and Barber et al. (2007), guided this evaluation of the SMS-based intervention (Table 6.1). The categories of structure, process, and outcomes were observed through system function (technical), and human perspective and organizational context (social)

Table 6.1. Theoretical and Evaluation Framework Based on the Socio-Technical Approach

	Technical	**Social**	
	System Function	**Human Perspective**	**Organizational Context**
Structure	*Technical detail* *Content: Computer based intervention details* • Hardware and software setup • User requirements for the intervention	*Adapting work conditions / requirements of intervention implementation* • Skill level or training needed (e.g., computer skills) • Work conditions and staff patterns	*Requirements for sustainability: costs, management and equipment needs* • Cost of the intervention • Organizational / technical support for management and equipment • Management (e.g., team required)
Process	*Information processing* • What system can capture • How organized • Correct and valid • Functions of software	*Participation of patient/health care team social interaction* • Team's participation in tasks • Process of sending, receiving, responding to text messages • Shift in attitudes / beliefs of supervision	*Altered practice and delivery of service* • Aspects of intervention (how fits) • Protocol: process / steps when patient not responding • Communication interactions • Workflow changes and monitoring
Outcome	*Technical performance: efficiency and reliability* • Hardware/software issues • Reliable system • Sending and receiving text messages, and the ability to store and retrieve data • Intervention appropriateness	*Quality of service and individual outcomes* • Perceptions of quality (patients, staff) • Outcomes for individuals (e.g., adaption by staff) • Changes in workflow, workload • Text message relevance	*Global effect; lessons learned, potential application to other settings* • Lessons learned • Process involved in implementing • Balance tech/human perspective • Steps needed to implement intervention in larger trial

Note. Adapted from Conford et al. (1994) and Barber et al. (2007)

lenses. Representing the three major areas, *structure* includes the components that make up the system, *process* involves actions taken and reflects how structural components interact, and *outcome* encompasses the result of the interaction of processes that occur within a structure.

Participants

The primary feasibility evaluation was conducted from a healthcare provider perspective, but was augmented with feedback from patients during the implementation. The participants were the multidisciplinary team members who were engaged in the collaborative intervention development and implementation process. The team consisted of: a regional TB director/pulmonologist, the lead regional TB social worker, a regional TB staff member, two TB-specialized clinic RNs, and the hospital TB program director/pulmonologist. All team members contributed to the intervention development and varying aspects of implementation. The regional TB director was involved from the initial drafting of the grant proposal. The final intervention development was achieved with the regional director, lead social worker, nurses, and regional TB staff member. The TB staff member was the primary interventionist, but utilized other team members as resources. The patients were those randomly assigned to the intervention group (n=18).

User Training

The PI provided hands on training to four of the team members and written directions in Spanish on how to use the FrontlineSMS program. The PI was available on-site for 6 months and remotely the remainder of the 9 months the intervention was in process. The intervention was introduced to hospital staff during an oral Power Point

presentation at a hospital wide conference focusing on TB case presentations and current and future goals for TB management at this regional hospital. However, the healthcare providers were not made aware when their patients were enrolled in the intervention or of the group allocation of the patient unless the patient informed them.

Study Flow

The intervention was trialed and implemented from December, 2011 until August, 2012 when the last recruited participant completed the 2- month intervention period (see Figure 6.2). The research team developed a protocol and patient follow-up algorithm to guide decision making. A staff member monitored the received messages daily to identify those who had not texted in and sent out any query texts or reminders that were necessary, managed the educational text messages, and responded to questions texted in. Two pulmonologists were available in person or by text messaging to the intervention staff member to respond to specific questions or concerns that the staff member could not answer (e.g., recommendations for potential allergic reaction).

Measures

The feasibility issues were categorized at the technical, human and organizational levels. Technical issues evaluated the performance (efficiency, applicability and reliability), and extent of conformance to user requirements of the text messaging software package. Human issues concerned perceptions of the quality of the intervention, changes in the workflow and workload, and user training needed. The organizational level examined requirements for sustainability and organizational impact. Patient acceptability and initial efficacy of the intervention are reported elsewhere (Chapter 5).

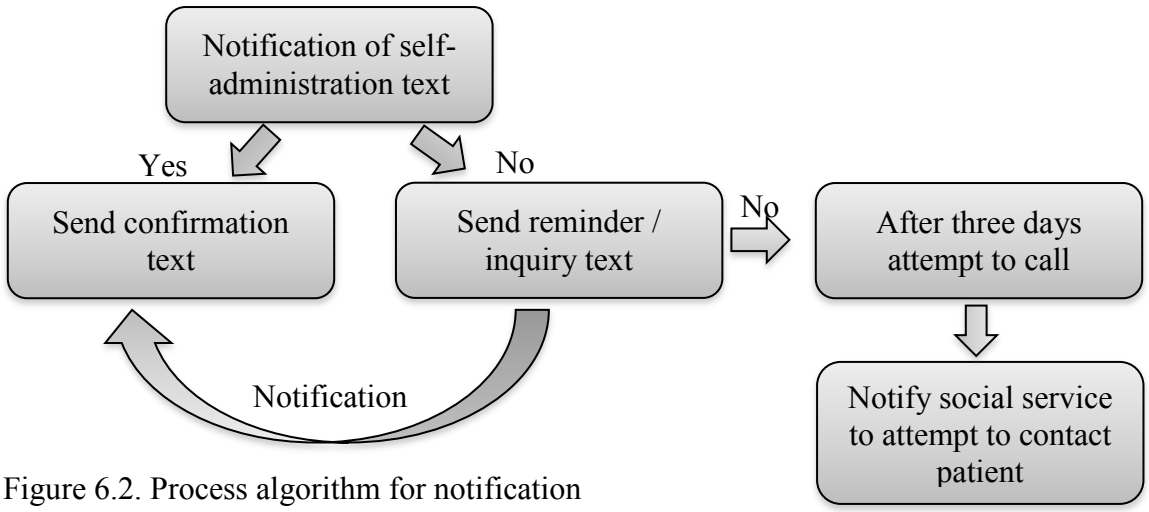

Figure 6.2. Process algorithm for notification

Methods of Data Acquisition and Analysis

The PI maintained an observational log of the study implementation process as the primary data source. This log included observations of issues, barriers and glitches, meeting notes, one-on-one conversations, and informal team discussions during intervention implementation. The participating healthcare team members were also asked to provide input on technical, human and organizational feasibility of the intervention and discuss their experience as a measure of validation and verification of the observational data. Table 6.2 provides examples of what the team was asked to consider. Notes and issues were organized into the socio-technical matrix during intervention implementation. The setting of the observation was in the regional TB office and the nurse's office on a daily basis for about 6 months. This long-term observation allowed the PI to gather detailed data on the workflow of the clinic, and the interactions of hospital and regional staff.

The primary approach in the evaluation of the observational log was qualitative in nature (Denzin & Lincoln, 2000; Sandelowski, 2000, 2010). The log was examined and

Table 6.2. Guide to Healthcare Team Members to Describe Intervention

Perspective	**Suggested questions and focus areas to describe intervention**
Technical / system	Challenges with the computer, organization of the messages, issues related to program What were some usability issues of the software? What were the useful functions or characteristics of the program? How could we improve the characteristics of the program?
Human	Discuss the training required to use the program, challenges with implementation, attitudes towards the program /intervention and time needed. What were some of the barriers to using the intervention? What were some of the facilitators?
Organization	Type of support from national program level, the team required, the process to implement on a larger scale, security issues What are the practical issues of the intervention in this setting? Is it an intervention which could improve services to patients? Could this intervention manage a larger number of TB patients?

data were categorized, separating *structure*, *process* and *outcome* at the *system*, *human* and *organizational* levels. The text messages sent and received during the intervention were also evaluated for technical problems, system errors, or other issues that surfaced within the text messages themselves. The text messages were coded using ATLAS.ti version 6 (GmbH, Berlin, 2009).

Results

Overview

The TextTB text messaging based intervention was integrated into the working practice of the regional TB office for patients being attended to at the outpatient clinics for 9 months. One TB staff member managed the daily patient interactions, but three other team members were trained and able to operate the program at various levels of comfort. That is, because they did not use the program on a regular basis they felt that they would need more guidance and training if they were to manage the system

independently. A total of 1320 text messages were sent and 996 were received during the study period. The PI observed 115 working days of intervention and analyzed 20 typed pages of study process notes and written input from three study staff. A summary of the findings structured by the evaluation framework are detailed in Table 6.3 and are further discussed below.

Technical / System Functions

Infrastructure / Software

The SMS system was available only when it was manually "powered on" by a user at the clinic. We identified that the initial GSM modem employed for the first 2 months inconsistently delivered text messages to the FrontlineSMS program. Reminders were sent when the patient notifications were actually received by the modem software. It was recognized that messages would transfer to the FrontlineSMS program depending on the order of opening the software, e.g., modem first versus FrontlineSMS program, or depending on when the messages were sent. That is, if the message was sent prior to the computer and programs being "powered on" the messages would go to the modem only and not be delivered to the research staff. Once this issue was identified the modem inbox was reviewed daily and the messages (n=55) were transferred into a combined text message database. There were messages sent by patients (n=15), which indicated that a message had previously been sent after a reminder was received by the patient. In addition, we identified that the modem stored a maximum of 34 messages in the inbox after which no new messages were received. Only after the modem inbox was emptied could new messages be received. The PI purchased a new modem after these issues could not be resolved and there were fewer instances of data not being received, and

Table 6.3. Feasibility Issues by Category and Level

	Technical	**Social**	
	System Function	**Human Perspective**	**Organizational Context**
Structure	*Technical detail* ➢ Software to manage text messages open source, free ➢ Requirements: computer, local SIM card, mobile phone or GSM modem ➢ Mobile phone credit virtually uploaded at local kiosks	*Adapting work conditions/requirements* ➢ Collaboration for development and implementation ➢ In person and written training ➢ A doctor, social worker, nurses and a technician trained on software ➢ Technician elected to be primary intervention operator ➢ Ongoing technical support provided	*Requirements for sustainability* ➢ Cost 12.80 – 29.44 USD/patient ➢ One able to manage intervention ➢ Mobile network coverage varied ➢ Most patients had access to mobile phones and were able to text ➢ Most had basic feature phones (70%) and pay-as-you-go plans (59%)
Process	*Information processing* ➢ Program organizes SMS by patient with multiple view options ➢ Technical issues identified ➢ Initial modem software captured data requiring manual data review	*Participation* ➢ Challenges for RNs to manage intervention ➢ Some patients used phone credit early ➢ Some texted in when not required ➢ Collaboration to respond to questions	*Altered practice and delivery of service* ➢ Belief that self-administration 'functioned well' ➢ Not all convinced quick follow-up needed when patients failed to notify ➢ Patient tracking challenges ➢ Cases abandoning treatment identified as having self-transferred
Outcome	*Technical performance* ➢ Software problems identified ➢ Changing modem improved reliability of receipt of messages ➢ Facilitated communication ➢ Questions answered quickly	*Quality of service* ➢ Real world tested/integrated into workflow ➢ Patients asked questions, report side effects and requested advice ➢ Considered valuable to identify problems early	*Global effects* ➢ Research considerations identified ➢ Many strengths identified ➢ Patients indicate appreciation of personal attention ➢ Shared phone limiting for some

when it was identified that messages were not received it appeared to be an issue with service coverage rather than modem issues.

Software Issues Regarding Message Review, Creation and Delivery

The FrontlineSMS software facilitated the review of text messages and allowed multiple view options. For example, incoming texts could be separated by contact, sent or received, or displayed together on a main screen. However, initially separating messages by receiver could not be accomplished until it was identified that a '0' needed to be added to the beginning of each mobile phone number in the contact list in order for the automated program to match the messages to the individual.

The FrontlineSMS provided a character count box that counted down the allowable number of characters for one message (160) and an icon of an envelope, which indicated the message would be sent in one, two, or three text messages, along with an estimated cost in British pounds. When accents marks, which are commonly used in the Spanish language, were used in a message a discrepancy in the character count was generated. For example, when a text message under 160 characters included accent marks the program indicated that multiple text messages were required to send the message. See Figure 6.3 for an example which indicates three text messages are needed to send when accents are included and one when the accent marks are removed. Once this was identified the Spanish educational messages were adapted to not include accent marks.

Issue of Using Keyword for Auto-Confirmation of Receipt of Notifications

The FrontlineSMS *keywords* option was maximized to set up auto-confirmation of receipt of notifications. It was identified that in order for the confirmation message to be

sent automatically a *keyword* must be entered as the first word of the message with exact spelling and was sensitive to accent marks and punctuation, like exclamation marks. For example, if the keyword was listed without an accent and the word was texted in with an accent mark, the program did not recognize it and the auto-confirmation was not sent. Although at the onset of the intervention the participants received both verbal and written instructions on how to send notification text messages (e.g., "Tome 3R 4B" for I took 3 red and 4 white pills), many started the message with other words, such as 'hello' or 'good day'. We added a total of 16 keywords in response to the different ways participants texted in notification. For example, the same word was entered with and without an accent (e.g., tome and tomé) and tailored keywords to the patterns of each patient (e.g., hola!!!). However, the number and variety of keywords also lead to auto-confirmation messages sent in error (n=17) when, for example, a question rather than a notification was submitted.

The *keyword* function used for auto-confirmation was also an issue when notifications were sent over the weekend and the system provided a delayed response. For example, if the patient was notified on Saturday and Sunday, on Monday morning when the program was powered on the patient would receive two auto-confirmations at the same time. In some instances this led to some confusion, as evidenced when the patient texted back that the medications had not yet been taken for that day. This is because of the limitation of having the SMS system available only when the program was "powered on" by a user at the clinic. Because of security issues the laptop needed to be closed and locked up within the locked office. The issue of insecurity prevented trialing the intervention with the computer continuously powered on.

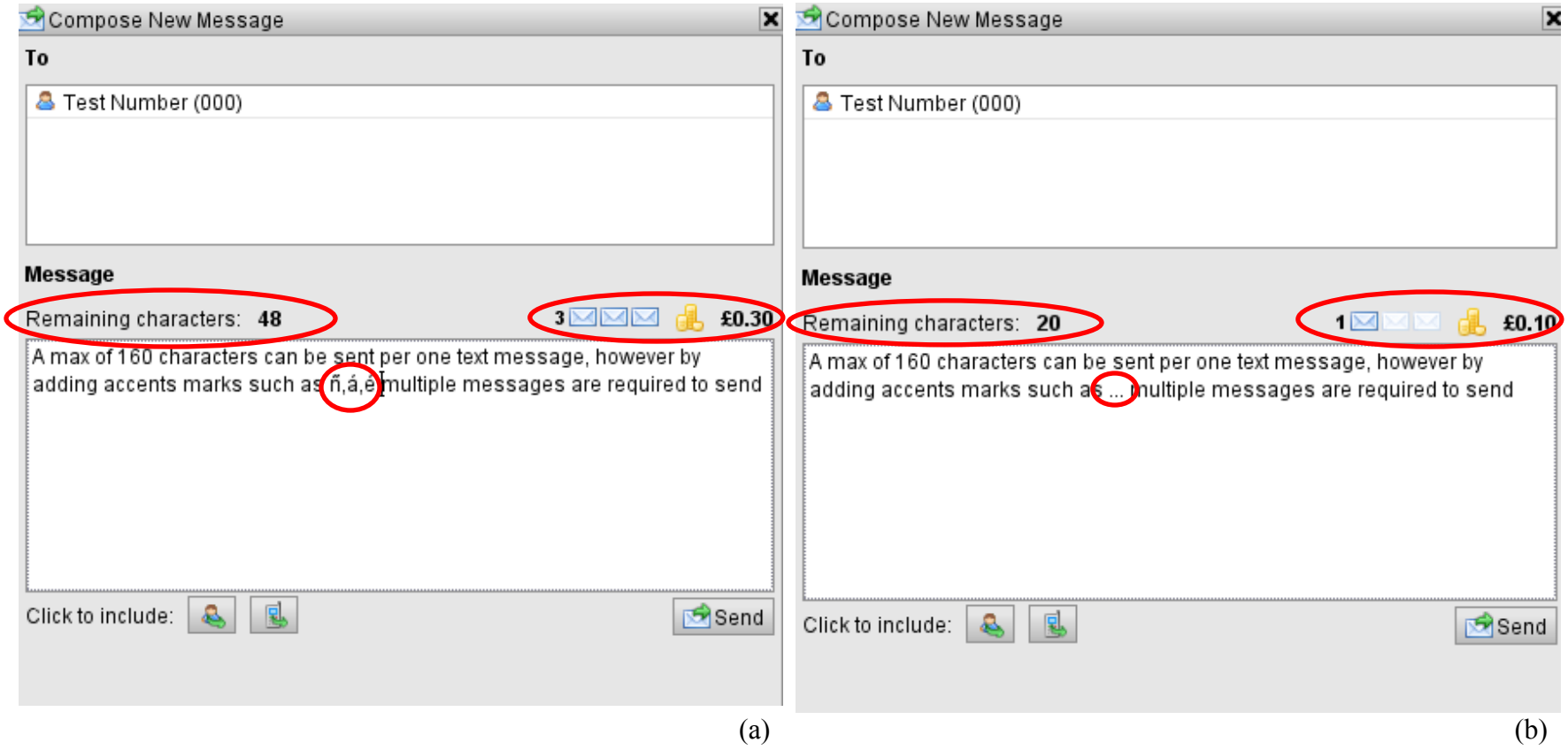

Figure 6.3. Number of texts required to send with (a) and without (b) accents

Software Issues Regarding Time Commitment

The *Reminders* feature was used to automatically send the educational text messages as a package. The *Reminders* feature enabled messages to be entered into the program when patients started the intervention and be set up to be sent at a prespecified time and date. A total of 16 educational messages, or two messages per week, were created per patient. Although setting up the messages as a package assured that each patient received the same messages at the same time intervals, the set up process proved to be time-consuming. Steps to enter a new message into the *Reminder* Manager included selecting the message frequency, the date and time, the recipient, the mode of delivery, and the message (Figure 6.4). Because patients enrolled in the study on different days, each set of messages had to be created uniquely for each patient. It took from 15-20 minutes per participant to enter the set of messages.

In addition, the messages were not consistently delivered at prespecified time and date. We identified that not all messages that were sent as reminders were being sent as scheduled. When reminders were sent a green check is seen to the left of the message row in the software window. The reminders had to be reviewed and if not checked, were sent using the 're-send selected' button. In addition, after being unable to enter new messages into the *Reminders* feature, we identified that there was a software max capacity of 100 allowable reminders saved in the program at a time. From the point at which this was discovered to be a problem, sent messages had to be deleted at regular intervals before new ones could be created.

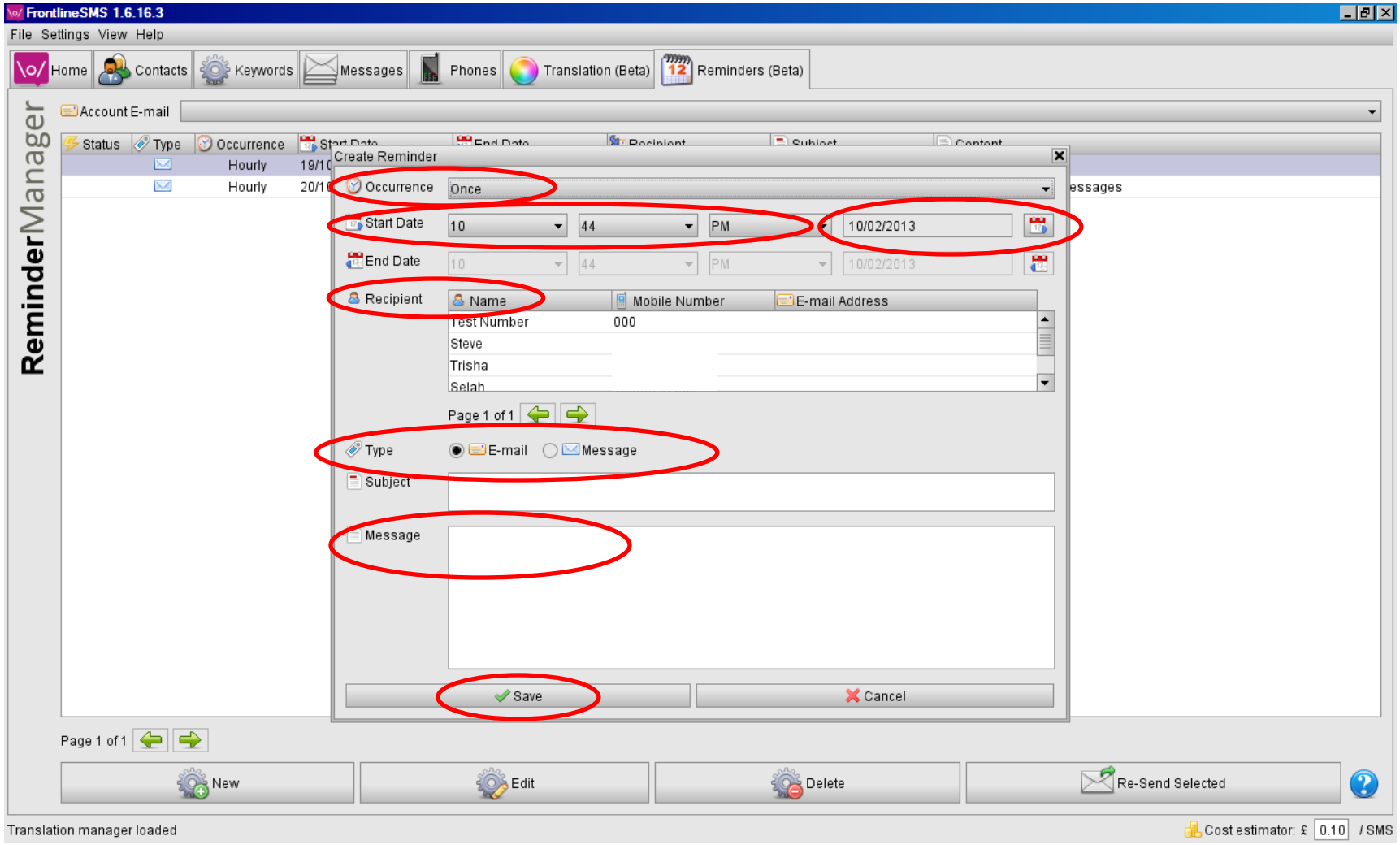

Figure 6.4. Steps required to input and create an automatic educational text message

Software Issues Regarding Data Analysis

Text messages were time stamped 2 hours earlier than when they were actually sent or received. This discrepancy was recognized when some of the messages being received in the modem software were also received in the FrontlineSMS software (described above), but the time stamp was 2 hours different. Consultation with the FrontlineSMS staff helped to identify that this issue could not be corrected with this version of the FrontlineSMS software possibly because the computer itself was set up in a time zone different from that in which the program was being implemented. However, changing the time zone on the computer did not remedy the problem.

Data stored in the FrontlineSMS software can be exported into an excel file. However, words written with accent marks were changed to unrecognizable characters. For example, the word in Spanish for 'I took', Tomé changed to "TomÃ©" after being exported to an excel file. Therefore, the text messages had to be reviewed in the software and corrected in the exported data file. In addition, because more in-depth quantitative and qualitative analysis of the text messages was sought in this study, such as message types and how the intervention was used, the PI developed a database using RedCap (Research Electronic Data Capture) (Harris et al., 2009). RedCap is an electronic data capture tool allowing database development, data entry, and downloading to common statistical packages (Harris et al., 2009), such as IBM SPSS Statistical software. This process was time consuming and required manual review, entry, and coding of the text messages. However, open source software that provides electronic transfer of data and codes for type of message may be challenging to find.

Human

Training

Training was provided by the PI to the regional TB director/ physician, a social worker, two nurses, and a technician. One nurse and the technician were computer novices, and thus needed orientation on basic functions of a computer and software (e.g., how to save a file, how to copy/paste text). The original plan was for the nurses to implement and manage the intervention. However, due to concerns of computer security in the nurse's office the study computer was moved to the regional TB office, located upstairs in the same building. The nurses were unable to consistently leave their office to go upstairs to the regional TB office to run the program due to daily responsibilities, workflow requirements, and covering for vacation or sick leave. There were only two nurses to manage the entire patient load and clinic needs. At the onset the regional director managed the intervention when others were away on vacation. A new staff member joined the TB program team and volunteered to be the primary operator of the intervention. All of the trained team members were able to review and send text messages using the program.

Workflow

The research team supported the idea of a text-messaging intervention as a method to support patients and monitor adherence during treatment. Texting was felt to be an acceptable medium to reach their population and it was noted that texting is, in general, more economical than phone calls. However, because the standard treatment delivery was self-administration this intervention was a new task that had to be incorporated into the daily workflow of the staff members. They recognized that a dedicated staff member

was required to manage the intervention. Time to become familiarized with the software features and repeated instructions from the PI were required during the initial learning period. The technician indicated that it probably took him more time to become familiar with the program because of his inexperience with using a computer. Although a step-by-step instruction set was provided the technician indicated that it was helpful for him to take handwritten notes during demonstration on how to start and use the program.

The technician estimated between 15 minutes to 1 hour per day was required to review and respond to the text messages. This time was broken up into two to three intervals because part of the time the technician worked in another area of the hospital. He would arrive in the morning, start the program and review text messages, make sure confirmation of notifications were delivered or would send them manually, and send educational messages on set days (Tuesdays and Thursdays). After returning from his other duties he would review the messages again, send reminders or inquiries to those who had not texted in their notification, and respond to any questions. The PI developed an excel database to help visually track each patient as they entered and to provide a tool to mark notification for each patient to clearly identify who did not text in. The technician preferred to keep a daily paper tally of patients texting in and if they received a response and then transfer that information to the excel file.

It was observed that responding to patients' questions was often a collaborative process. The office is without walls or dividers and other staff members are seated nearby. Some questions would be posed to everyone, discussion ensued, and a response based on collective input was drafted. In our study the staff members included two pulmonologists specializing in TB management who were available to field the more

technical or medically-related questions. Having the pulmonologist available provided support to the nonmedically trained staff member when needed. In addition, the responses to questions often went through a few iterations to meet the word count requirement of a text message and assure that the message was clear. Common word abbreviations were often used.

While on-site for 6 months the PI managed the phone credit, which was later taken over by the technician, adding an additional task for the ending 3 months. Participants were provided mobile phone credit to compensate for cost of texting in daily and an additional amount for participation in the study at the end of each month. Although adding mobile phone credit is easy and convenient, it requires leaving the hospital. Almost all kiosks have the capacity to add mobile phone credit virtually with the name of the mobile phone provider and the phone number. This task is also complicated because patients entered into the study at various times and cash was required for the transaction.

Potential Barriers

Potential barriers to the intervention were discussed during the intervention development phase. The team identified that the patients could possibly lose their mobile phones, change their phone numbers, or use up mobile phone credit provided before the end of the month and that likely there might be wide variation across these potential issues. There were in fact instances during the pilot study when phones were lost or stolen (n=2) and credit was used up sooner than anticipated. One participant texted in using her mother's phone and indicated that she used all of her credit within 10 days. She informed staff that her usual mobile phone habit was to purchase a package that allowed unlimited calls and text for 5 days when she had funds. This participant transferred to a

local healthcare center that provided directly observed treatment (DOT) and therefore was disqualified to continue in the pilot study. Therefore, further evaluation regarding the credit use issue was not identified in this case. Other participants texted in that they were low on credit a few days before they were due credit for the next month and it was added early.

Organizational Context

In team members' written feedback and in group and one-to-one conversations with the PI, the team strongly agreed that the intervention was of benefit in supporting patients receiving treatment by self-administration, especially for those who lived in rural or semirural settings where access to care was challenging. The team members indicated that the ideal situation was for all patients diagnosed with TB to be referred to local healthcare centers close to where they live to receive more supervised treatment. However, patients in this cohort, with an average of 1 hour of travel time, indicated that they felt that they could get better care at the pulmonary reference hospital and preferred to travel the long distance once per month.

The technician who managed the intervention indicated that he felt that he was truly helping the patients and that it seemed to be very useful for them, especially in the cases in which patients had many questions and needed recommendations. Both the research team members and patients identified that there was inadequate information regarding the disease, symptoms, treatment, or treatment side effects provided during provider visits. The intervention provided some of this information in the educational messages. The benefits of the program are, however, dependent on the sustainability of the program (e.g., cost of intervention, availability of computers in other areas to conduct a similar

intervention). For example, the regional director indicated that most healthcare centers do not have access to a computer.

It was identified within the text messages from patients that healthcare provider recommendations for how to take the TB medication varied substantially. For example, discrepancies in instructions included instructions to take some of the medication in the morning and the rest in the evening, take some before each meal, take with and without food, or take on an empty stomach in the morning. One participant indicated that his provider instructed him to take medication between meals and sent notification in the evenings.

Network Coverage and Infrastructure

Network coverage issues and infrastructure problems occurred during intervention implementation. In our setting, the mobile telephone infrastructure was in place and mobile phone usage was high, but network coverage varied. There were four dominant mobile phone providers in Argentina. As described above there were initial technical problems with the modem in which messages were not received consistently, but there were also coverage issues identified in the text messages. There were text messages that indicated that the participant had been out of town without mobile phone service (n=2), resulting in days missed for notifying. When discussing problems on the FrontlineSMS forum of not receiving messages when participants indicated that they were sent, a researcher in Argentina using the same software indicated that they also experienced issues, perhaps with the coverage and particularly from certain mobile phone service providers. There were 3 days in which one of the main mobile phone service providers had an outage and no messages could be sent or received. The company provided an

automatic compensation of 10 pesos (about 3.5 USD) for the loss in service, but cost to the research overall in terms of sustained intervention and outcomes is indeterminable.

Access to the internet is required to download the FrontlineSMS program but after it is installed onto a computer, internet access is no longer required. There were 10 days logged in the field notes in which there was no internet access and a number of days in which electricity was out for all or part of the work day, but an accurate count was not recorded. If the source of mobile phone credit had been from an online provider the messages would not have been sent on the days without internet access. However, opting to use the local SIM card and add credit as needed allowed continued messaging without intervention interruption. The loss of electricity did not cause a delay in messages being received or sent because of long battery life of the computer, but potentially loss of electricity could have caused major problems with the research. In addition, when the radio was on in the office and a text message was being received there was a notable static disturbance in the music. Although considered a negative in terms of office aesthetics, there was a positive consequence for the research in that this change in sound served to assist in quick review of the text message inbox.

Estimated Intervention Cost

In Argentina, text messages are free to receive and varied from 0.60 – 1 peso (0.10 - .23 US) to send for pay-as-you-go service plans, according to the patients and mobile phone service provider websites. Based on the text message cost of 0.10 to 0.23 US per text, the average cost per patient for sending and receiving text messages during the first 2 months of treatment was 12.80 – 29.44 USD. Because the intervention was incorporated into the daily workflow of a staff member this cost estimate did not factor in

time of staff; such estimates are recommended in future research. Almost 60% of the patients enrolled in the pilot study indicated that they had a pay-as-you-go mobile phone plan. However, these fees could vary substantially because mobile phone service providers ran special promotions frequently. For example, a text message promotion would indicate that the phone credit would be doubled or tripled depending on the amount of credit added to the number, or packages with unlimited text messaging for a given number of days could be purchased for a set rate. In addition, not all messages could be condensed into 160 characters, therefore increasing the cost of a single message when more than a single message was required to send complete information or respond to a question. There were text messages from both the participants and the technician responding to questions that extended into two or three messages due to the length of response.

FrontlineSMS has the option to use an online mobile phone credit service provider to send text messages at a discounted rate. Initially credit was purchased as a bundle from one of the suggested online mobile phone credit providers. However, on location it was identified that in order to use the credit the phone number had to remain a US or European number. This would have required the patients to send messages to an international number. Therefore, because of the potential increased cost and the possibility of the patients not recognizing the number as a local number, the option to use a SIM card with a local phone number was chosen. In addition, the choice to use a GSM modem and SIM card enabled service for any days that the internet was inaccessible. Another problem identified was that when mobile phone credit was depleted, messages were still shown to have been sent in the FrontlineSMS program. That is, there was no

link with credit amount remaining on the SIM card account and the FrontlineSMS program. Therefore, the mobile phone service account was regularly checked on the service provider website to assure that there was credit remaining and messages were actually being sent.

Challenges to Tracking Patient When Not Texting In

Self-administration has been the usual treatment delivery method at this site. Despite a documented high rate of treatment abandonment, there was the belief by some of the staff that self-administration functioned well. For example, after initiating the protocol to track participants who were not notifying or who were unable to be contacted on their mobile phone, there was hesitation to act before a full month had passed. In one case the patient contact information was not entered in the medical record and therefore follow-up could not be initiated. There were no cases that were returned to intervention by means of contacting a healthcare center close to where the patient lived. In all cases that missed notifying they either later returned to clinic or started to text in notification after calls or text reminders. The intervention did serve to identify a patient who had been documented in the notification records as abandoning treatment but actually transferred to a different healthcare facility to pick up medication and receive follow-up care.

Unexpected Events

An unexpected event during the study was that there was a TB medication shortage at the regional and national TB program levels. At one point there was no Ethambutol or Rifampicin in liquid form and some of the second line medications ran low. It was documented in the study log that the shortage began December 1, 2012 and the last text

message (*n*=6) recorded regarding the medication shortage was sent on March 20. Because of the shortage to make the medication last patients were allocated medication for shorter periods, for example 5 days or 2 weeks depending on availability. There were patients who were allocated only one of the medications and told to keep checking back in for when the missing medication would arrive. This unexpected event may have impacted the pilot study outcomes of self-reported adherence by increasing the number of patient-provider contacts. However, for those who participated in the pilot study there were no days identified when patients did not have at least one medication to take. Another unintended consequence, which is not the focus of the texting work, is the impact the medication shortage may have had on patients' overall tuberculosis treatment. It is conceivable there may have been some impact on length of infectivity due to this shortage. However, the TB staff indicated that a prior medication shortage had not occurred for many years.

Discussion

Overview

Improving treatment success, especially where self-administration is the treatment standard, requires new patient support options that are feasible and acceptable. The TextTB intervention was identified to be feasible to conduct and acceptable to patients (Chapter 5). The socio-technical model helps guide the evaluation of how a health informatics systems functions within a given context and environment (Berg et al., 2003; Cornford et al., 1994). This facet of the research, from a structured socio-technical evaluation of the TextTB intervention, was to identify technical feasibility and acceptability issues from the healthcare team and patient perspective. Findings from this

study add to the literature by highlighting specific technical and acceptability issues, within socio-technical constructs, to inform larger scale implementation and testing of a text messaging intervention aimed to promote adherence and provide support to TB patients.

Because there are few TB studies in which researchers have used the mobile phone, and specifically the text messaging feature, or who have applied the socio-technical approach, comparisons to this study are limited. This may be due to DOT having been the central strategy to improve treatment adherence since the 1950s (Bayer & Wilkinson, 1995; Morris, 1997). Some researchers argue that DOT is necessary to assure cure rates (Frieden & Sbarbaro, 2007b) and others emphasize a patient-centered, individualized approach to monitor treatment adherence which can be a modality different from DOT (Macq, Theobald, Dick, & Dembele, 2003; Pope & Chaisson, 2003; Tuberculosis Coalition for Technical Assistance, 2009; Volmink, Matchaba, & Garner, 2000). However, for reasons such as limited resources, expense to operate and burden to travel daily to a clinic or a house, the administering of DOT has been challenging for patients and healthcare services in many communities globally (Hill et al., 2005; Khan, Walley, Witter, Imran, & Safdar, 2002; Sanchez & Bertolozzi, 2009). Interventions for TB care should be standardized, but also flexible and based on the needs of patients and healthcare providers.

It can be argued that the use of a mobile phone or videophone is another method of intervention delivery that works for those who would complete treatment anyway. Wade et al. (2012) reported that the videophone service did not improve the number of direct observations missed due to patient absence or refusal. However, they did find video

observation more cost effective than DOT provided by a public health nurse visiting the patient's home (Wade et al., 2012). In addition, all researchers who used the video feature reported it overall acceptable to users and suggest that it is a means to direct observation (DeMaio et al., 2001; Hoffman et al., 2010; Wade et al., 2012). Similarly, Mohammed et al. (2012) identified acceptability but found a modest utilization with a text messaging system, and did not highlight any technical feasibility issues. Nonetheless, when a notification was not received the staff was alerted to the patient who may be at risk for defaulting, or stopping medication before full treatment term. It is recognized that a method for regular supervision and support promotes greater opportunities for education, resolution of barriers, and quick detection of nonadherence and monitoring of reactions or worsening symptoms (World Health Organization, 2009).

Technical

Despite demonstrating feasibility in implementing the intervention in this population, many technical issues were encountered during its implementation. Variable receipt of messages likely affected the overall notification rate. This could be a barrier to accurate monitoring and possibly an annoyance to participants if their messages were not consistently received. The known loss of data capture, which was partly resolved with the modem change, was a major frustration and likely a source of data inaccuracy in study findings. Similarly, Hoffman et al. (2010) reported technical issues with transmissions resulting in loss of data, an estimated 25% due to technical problems. Patients coming from more rural settings or being away on vacation in other provinces may have also contributed to the variability in service coverage and messages received. Wade et al. (2012) also reported technical problems with variable signal strength, which

was improved by identifying locations in the house with stronger signal strength or installing a higher-gain antenna.

The issues regarding the software, such as the 2- hour time log difference, limited number of reminder texts allowed, and discrepancy in character count when using an accent mark, were more a nuisance rather than a limiting factor in using this software. Once identified, adjustments could be made by not including accent marks in messages and recognizing the time difference and setting messages for 2 hours ahead. To help resolve issues and share experiences, FrontlineSMS provides an electronic forum in which staff and other members can post and respond to posts by other users. Attempting to resolve issues encountered during implementation, the PI posted on 23 occasions to the FrontlineSMS forum. The FrontlineSMS staff was quick to respond and offer suggestions for the questions posted. For example, from their suggestion the modem was changed. It is a collaborative forum and another researcher using the FrontlineSMS software was able to provide feedback regarding local issues in Argentina. However, we were unable to reset the time stamp or identify why the educational messages that were set up within the Reminders feature were not being consistently sent.

Although patients were provided, both verbally and in written instructions, established options to text in notification of having taken their medication, they often added words at the beginning of text, which limited the software's ability to recognize the keyword for automatic response. Future studies would include having established first words for notification and questions. This would decrease time required to assure that everyone received a confirmation text.

Using this software to send the educational package of sixteen messages appears to not be feasible, at least using the prior software version. Inhibiting factors include uploading each message one by one with seven steps required to save a new reminder, the 100 stored message limit, and not consistently sending messages automatically requiring manual review and resending of messages. This process was time consuming and left ample room for errors in copying messages or entering wrong date. A possible alternative might be to look into the option of using a Hosted SMS or SMS Gateway site. With this option we would to be able to add individuals to the program as they entered into study and schedule messages automatically on set days (e.g., Tuesday and Thursday) or have participants send a text with a single word to opt into the messaging service, which would automatically schedule messages to be sent at predetermined intervals. Although there were two fee-based services identified, neither provided services yet in Argentina and this option could not be further investigated.

In addition, there is a limitation related to the automation of the data and the ability to analyze the data from a researcher perspective. In order to identify types of messages sent a new database was built and messages were entered into the new format to be able to code and classify types of messages sent and received. However, this may not be uncommon when programs are built for other purposes.

Currently a new version of FrontlineSMS, version 2, is presented as more intuitive, easier to create and manage messages, and capable of managing larger volumes of messages (FrontlineSMS, 2011). It is unclear if these updated features would decrease some of the issues we faced in our study. However, features in the new version, such as

translation manager or reminders that we used, are indicated to be added at a later date. The redesigned software can still be used without the internet.

Human

The functional fit of the system and the clinical workflow was not initially congruent in this setting. Ideally a nurse, who is trained in patient management and education and who would likely be able to respond to patients easily, was to manage the intervention. Due to concerns of computer security the study computer was transferred upstairs to the TB regional office where there was always a staff member present. Having to leave their office daily to monitor the messages turned out to not be feasible. As was the case in our study, nurses are often overburdened with multiple tasks and frequent patient interruptions. Easy access to the system is an essential feature for workflow integration.

Although the individual who ended up running the program was a technician and had never managed patients before he was able to successfully manage the intervention. Initially, he was not familiar with computers or their basic functions and required extended hands-on program training by the PI. However, through repetition, taking notes, and functioning independently to self-identify problems he was able to become proficient with the program and take the necessary steps to use other team members as resources to answer patient questions in a timely manner and accurately. He requested assistance when needed from the physicians, social worker, and the nurses. This finding indicates that with the right staff composition a nurse would not necessarily have to be the individual managing the text messages. This approach may be more cost-effective. Because this intervention was implemented as a pilot study and used with relatively few patients it is unclear the number of patients that one technician or nurse could manage

using the software. The software does have the capacity to store a large number of contacts. Although there was the attempt to make the intervention as automated as possible, the team also wanted to assure that it could allow personalized communication with the patients and not be too automated. Eliciting further IT support to develop an added component that would highlight or notify staff of those who did not text in notification could decrease the manual review process. In addition, as previously mentioned having structured first word notifications would support the automatic sending of the confirmation text. These actions would likely free up time to focus on answering patient questions and providing support to a larger number of patients.

Organizational

Internet and electrical outages, challenges to mobile phone credit management, and patient tracking when not notifying were some of the organizational level issues encountered. There were a number of days, and at one point 1 full week, in which the hospital and regional office were without electricity or internet services. Similarly, Hoffman et al. (2010) reported experiencing challenges of internet access in Kenya, such as downtime due to issues of frayed ethernet cables and slow system access. However, in our study, because a feature of the program was that internet access was not required to operate, the internet outages were not a limiting factor to the continuity of intervention delivery. In addition, some resources must be in place to deliver this intervention. It was reported that most clinics within the health region where the study was conducted are not equipped with a computer.

Adding phone credit for each patient by going to kiosks was feasible for a pilot study, but would likely be prohibitive for implementation at a larger scale due to time

constraints and the tracking required to identify when each patient has credit due. Establishing a contract with a mobile phone provider and having logistical negotiating support from the national level could be beneficial. Although providing payment incentives, such as mobile phone credit in our study, has been suggested as a strategy to promote treatment adherence (Macq et al., 2003; Pope & Chaisson, 2003; Tuberculosis Coalition for Technical Assistance, 2009; Volmink et al., 2000), a plan for "free-of-charge to text in" would alleviate some of the challenges to mobile phone credit management. During a Skype meeting with the National TB Director of Chili, we consulted about the Chilean text messaging intervention to provide patients with education about TB. We were informed that a plan and contract were established with a mobile phone service provider and patients could text in the week of treatment and receive information appropriate to that week of treatment. At that time no outcome measures had been evaluated. Nonetheless, the Chilean National TB Director could serve as a good resource for further implementation at a larger scale.

When trying to follow-up with patients who did not notify according to established protocol, weaknesses within the healthcare system were identified. In one case when the social worker started follow-up on a patient she found the patient's medical record was missing the address and any other contact information. Discussions for future studies identified the option to transfer or refer patients to a local healthcare facility if they had difficulty with texting in their notification. Other potential components to integrate into the intervention could include involving the patients' physicians when patients report side effects, increasing case contact, and assuring or confirming arrival of a transferred patient to a new healthcare facility. Further evaluation will be needed to identify if other

healthcare teams and leaders are interested in collaborating and investing in this novel approach to TB management.

Considerations for Potential Application to a Larger Setting

Pilot studies are important to identify feasibility issues prior to launching a larger scale intervention study. These identified barriers can either be overcome or may inhibit further use of the intervention. It is inevitable that there are glitches when implementing a new system; Table 6.4 is a summary of feasibility issues and possible solutions.

Table 6.4. Identified Feasibility Issues and Their Possible Solutions

Identified feasibility issue	Possible solutions
Inconsistent receipt of text messages	Identify if the cause is due to modem, service coverage, or mobile phone service provider issue
Not feasible to charge each patient's mobile phone credit manually	➢ Negotiate a contract with a mobile phone service provider
Challenges to track patient who did not notify	➢ Strengthen capacity to track patient, including collaborating with local healthcare centers, assuring accuracy of patient records and convincing staff that one month is too long to wait for assuring treatment adherence ➢ Refer patient to local healthcare center for closer monitoring
Resources needed for intervention	➢ Computers, most healthcare centers do not have computers ➢ Adequate modems
Software problems (e.g., too much time to manually upload patient education package one message at a time)	➢ Encourage patients to use a key word for the first word in notification ➢ Trial the updated version of the FrontlineSMS software ➢ Better software ➢ Identify / create a program in which a phone number and start date can be added and on scheduled days the educational messages are sent

Limitations

Although the results of this study using text messaging to promote TB treatment adherence were encouraging and seem to be promising, there were several limitations to the study. Some of the technical issues may have been resolved more quickly if the team included an IT specialist. Issues were resolved by trial and error and by contacting software or IT personnel. Sample size was small (*N*=38), and the study was conducted at a single center, making it potentially easier to follow the participants more closely, answer questions and provide support when requested. Participants, however, did come from all parts of the health region. The convenience sample of TB staff, some of whom were involved from the inception of the grant writing phase, can be a source of bias in the study. The regional TB program staff strives to improve TB control measures in their area and being involved in the study would be no exception. Activating the protocol steps for when patient did not text in was challenging for a few reasons. Social workers, who were responsible for patient management activities, were aware of the intervention and study, but were not research team members and therefore did not participate in the protocol development. Some of the challenges encountered could be rectified in future studies to assure agreement amongst all staff for quick activation of protocol steps. Nonetheless, missing data in medical records, such as patient contact information, did limit the social worker's ability to attempt to contact patient or healthcare personnel close to where the patient lived. This lack of data may be a rare occurrence that happened to be picked up during this study.

Conclusions

Utilizing the mobile phone as a tool to provide support for patients with TB may be valuable in improving treatment outcomes. In order to identify technical feasibility issues to consider for conducting a larger trial we conducted a socio-technical evaluation of a text messaging- based intervention. The functionality of the SMS system is limited by being available only when manually "powered on" by a user at the clinic. We identified that reducing the barriers of text message cost; improving the automated process of sending educational messages; and strengthening capacity to return patients back to treatment were the primary considerations for implementing the intervention in a larger trial. Partnering with a mobile phone service provider to establish a contract that would allow patients to text in free-of-charge could counter the limitation some of our participants encountered when they ran out of credit and the challenges to manage patient credit. A separate software program may be necessary to improve the automation of delivery of the educational text messages and better data capture for research purpose. Encouraging patients to use a keyword as the first word in their message could improve automated delivery and accuracy of confirmatory messages. Strengthening capacity to return patients who are not notifying back to treatment could include improving patient record documentation, solidifying protocol with staff, and collaborating with local healthcare centers where the patient could be referred or where staff is better able to look for a patient not continuing with treatment. Important components of the intervention were that it was individualized, interactive, and operated off-line. Technical feasibility issues are highlighted and suggestions for improvement and issues to consider in

conducting a larger trial are offered. Table 6.5. highlights the summary of what was already known before this study and what this study has added to our knowledge.

Authors' Contributions

The PI contributed to the research development, implementation, analysis, and manuscript drafting. K.S. contributed to the development and adapting of the theoretical framework, final analysis, and manuscript preparation. S.B., P.P. and D.T. contributed to protocol development, analysis and manuscript preparation. C.C. contributed to data collection, manuscript preparation, and verification of findings.

Table 6.5. Summary

What was already known before this study	• A proposed method to improve TB adherence is through text messaging, using short message service (SMS) • A socio-technical approach can highlight issues to be improve for further implementation and improvement of an intervention • Text message monitoring of TB medication adherence has the potential to access difficult to reach populations with mobile phone use high and accessible globally
What this study has added to our knowledge	• Implementing a text messaging based intervention to support patients with TB is an acceptable method to monitor treatment adherence but there are technical feasibility issues to be addressed prior to implementing in a larger sample • Being flexible and adapting to quickly changing technology will be required to leverage the benefits that new technologies will provide • Technology-mediated approaches applied in low- or middle-income countries may pose challenges and require feasibility testing in each setting

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Conflict of Interest

The authors declare that they have no conflict of interest.

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CHAPTER 7

SUMMARY

Introduction

Improving TB treatment adherence and treatment success helps to prevent the spread of the disease, drug resistance, and poor treatment outcomes (World Health Organization, 2009a). To improve TB treatment adherence authorities and researchers recognize that patient-centered approaches are needed to empower and support patients and to improve the relationship between the patient and provider (Macq, Theobald, Dick, & Dembele, 2003; World Health Organization, 2009a; Xu et al., 2009). Mobile phones have gained increasing recognition as a potentially powerful tool to deliver healthcare interventions (Cole-Lewis & Kershaw, 2010; Fjeldsoe, Marshall, & Miller, 2009) and to improve TB treatment adherence (Barclay, 2009; Kaplan, 2006). The rapid expansion and uptake of mobile phones globally, and particularly in low and middle income countries where TB is the most common, makes implementing mobile phone based interventions potentially more feasible (International Telecommunication Union, 2013). Text messaging is the least expensive but most widely adopted mobile phone feature (International Telecommunication Union, 2013). However, the mobile phone feature of text messaging as a method to promote TB treatment adherence has so far surfaced very little in the TB research literature (Mohammed et al., 2012). This may be changing. For example, a

protocol for a systematic review has been published planning to evaluate the impact of text messaging for TB treatment adherence (Nglazi, Bekker, Wood, Hussey, & Wiysonge, 2013).

In addition to the lack of application of text messaging- based interventions in TB management, it has also been noted that few researchers have described how text messaging- based interventions were developed (Cole-Lewis & Kershaw, 2010). Text message content has been evaluated by end users (Gold, Lim, Hellard, Hocking, & Keogh, 2010) and intervention components have been selected using patients and experts in the field along with seeking a theory to support the intervention (Owens et al., 2010).

In prior TB research using mobile devices, researchers have focused on providing directly observed therapy (DOT) using the video feature of mobile phones (DeMaio, Schwartz, Cooley, & Tice, 2001; Hoffman et al., 2010; Wade, Karnon, Eliott, & Hiller, 2012). Participant sample sizes were 6 (DeMaio et al., 2001), 13 (Hoffman et al., 2010), and 128 (Wade et al., 2012). Only Wade et al. (2012) in a retrospective design study conducted in Australia included a control group in their evaluation. Mohammed et al. (2012) were the only researchers identified to have evaluated text messaging to support TB treatment adherence. Important differences in the study conducted by Mohammed et al. (2012) and this study were that Mohammed et al. applied the intervention to patients who were already in treatment for an average of 3 months, daily automatic reminders were sent, and the study was nonrandomized.

The objectives of this study were to finalize development of an interactive SMS-based intervention in collaboration with patients in treatment and a TB specialized team and to pilot the intervention in order to assess feasibility, acceptability, and initial

efficacy. To assess the intervention during implementation a socio-technical evaluation was conducted to identify issues to be considered for conducting a larger study using this intervention.

This study adds to the body of TB research by reporting the SMS-based intervention development process and an in-depth evaluation of its implementation. Developing an intervention is a major component of the research process. Reporting steps taken with a collaborative multidisciplinary team and patients in treatment to finalize intervention components, identifying educational topics, and applying an adherence- based theory for educational message selection, along with formatting and assuring cultural appropriateness, could aid others in the development of other SMS- based interventions. By understanding the rationale for decisions made and the challenges experienced, improvements in applying this intervention might be made more quickly. Another way this study adds to the TB literature is by exploring how patients accepted and used the implemented text messaging- based intervention. Text messaging may improve TB adherence in a number of ways. For example, patient and healthcare provider relationships may be improved; accurate and informative education may be allocated quickly; and healthcare providers might be more quickly alerted to nonadherence to TB treatment and be able to work with patients to solve the problems that are preventing treatment adherence. The purpose of this chapter is to provide an overview and synthesis of this two- phased research project, which was segmented into three parts. The specific aims and findings from each analysis are highlighted, study limitations are reviewed, and implications for practice and research are offered.

Results

Sample

Thirty-seven participants were enrolled in this study, 19 in the control and 18 in the SMS intervention group. The average age of participants was 34.43 years with a range of 18-77, and 56.8% were females. Most participants recruited in this study (*n*=28, 75.7%) had individual, not shared, mobile phones and in the intervention group 3 had shared phones. Over half of the phone plans were pay-as-you go, without contract service (59.5%) and most phones had basic mobile phone features (70%) defined as not a smart phone or without internet. Fourteen (37.8%) of the participants indicated that they did not or did not always have enough income to cover basic needs (e.g., food, housing). The average commute time to arrive to the hospital- based clinic was 66.5 minutes (ranging from 0-120 minutes). When participants were asked if they were adequately informed about TB and its treatment, 22 (59%) indicated that they were not. None of the baseline characteristics and demographic variables resulted in a significant difference between the groups.

Phase 1: Intervention Development

Aim: To describe the development of a collaborative, theory-guided short message service (SMS)-based intervention to promote tuberculosis (TB) treatment adherence.

In this study a text messaging intervention, coined TextTB, was developed in collaboration with a TB specialized team and patients. In the development phase, decisions were made on the final intervention components, what educational text messages would be included, and how to respond to specific situations during the implementation phase. The challenges to working on a collaborative initiative included

finding time to meet as a group, coming to an agreement on message selection, and identifying who would manage the intervention. Querying patients in active TB treatment and involving the TB team in the process was an essential part of the project. The process required periods of waiting for patients in order to approach them to request their input on topics they identified as important for people receiving TB treatment. It also required persistence and the presence of the PI on a daily basis and working around other team members' schedules. Although the process was time consuming, it resulted in a more comprehensive and culturally appropriate intervention.

We created the educational messages by combining topics identified as important by patients, as well as the research team members, with the information from the literature coded by applying the Information-Motivation-Behavior skills (IMB) model. The IMB model served to guide and focus educational components aimed to encourage TB medication adherence. Purposeful selection to include messages with each of the elements of the model helped provide direction and theoretical backing to the educational component of the intervention. The purpose of this study was not to validate the IMB model for TB medication adherence. However, because medication adherence is complex, a comprehensive behavior change framework provided guidance for the design of the educational component of the intervention.

Condensing the educational messages into the word limit allotment of one text message was another challenge in establishing the educational component of the intervention. Many words are commonly abbreviated during text messaging. Using the common abbreviations helped condense, make the message more concise, and allow for a fuller message. However, multiple iterations were needed in the process to make clear

and concise messages. Collaborating with local native speakers helped in the translation and cultural appropriateness of the messages. There are distinct Spanish language variations across Spanish speaking countries and the local language nuances need to be taken into consideration. However, the messages should also be written clearly and with basic terms for a broader audience and for lower literacy levels.

When planning for collaborative efforts in the design of an intervention, researchers should allow for substantial time. Although more time consuming, the process of including end users during the design phase is necessary for a successful intervention. Content analysis can serve as an organizational and analytic tool to sift through a large amount of educational material. Moreover, applying a theory to develop a coding scheme and then using the coding scheme to code educational literature for elements of the theory can aid to systematically select, provide structure, and add depth to content to be used in an educational intervention.

Phase 2: Exploratory Pilot Study

Aim 1: Evaluate the structure, process and feasibility of conducting a trial with an SMS intervention in Argentina (e.g., the number of eligible participants, number consenting, number completing, log of issues, barriers, glitches and key informant interviews with providers and TB program director).

In this study the intervention was identified to be feasible for this population. Details of the feasibility of conducting a trial with the SMS intervention are described in Chapter 5. Access to mobile phones was high and most participants knew how to use the SMS feature. Of the 122 newly diagnosed patients during the recruitment period, three potential participants did not have mobile phones, one of which had been recently stolen

and was not planned to be replaced right away, another had never had one, and one did not have regular access to a mobile phone. Three did not know how to send text messages, one of whom was illiterate. The low refusal rate to participate in this study also demonstrated potential feasibility in this population. Only two declined to participate because they were too busy or not interested in learning how to use the text message function. However, there were a number of potential participants missed (*n*=18) due to various reasons, including a physician who picked up the medication and did not send his patients to the nurse's station, nonresearch team study nurses in the nursing office not notifying when new patients started treatment, patients being angry and upset about diagnosis and nurses not wanting to approach them about the study at the time and others not returning after being introduced to the study and going home to think about it. Because patients were in general allocated a month supply of medication, if they were missed on the first day of starting treatment they were likely not seen again for another month. Fifteen potential patients were excluded due to initial inclusion criteria. They either had been previously treated for TB or had extra pulmonary TB. The largest group of patients who were excluded were those who were under 18 years of age (*n*=21). There were also a number of potential participants with severe cases (*n*=18) who were admitted directly into the hospital for various lengths of stay. In general, patients with the severe cases were directly referred to local healthcare centers for DOT or closer monitoring.

Our study supported text messaging as a feasible intervention option. Because only 11 (30%) reported having smart mobile phones or phones with internet access, options to send video would likely have been limited. In addition, with the average travel time to clinic of 66.5 minutes the feasibility of applying DOT in this setting was highly unlikely.

Ideally patients are transferred to local healthcare centers to continue treatment with closer monitoring. However, when discussing this option with the participants they indicated that they preferred to travel and felt more confident in the care they received at the larger reference hospital. At the regional level, however, it was noted that there are higher rates of treatment completion at outlying clinics where staff are thought to be more motivated and better positioned to attend to patients.

A lack of education or information about TB was recognized as a barrier by patients and the research team. When asked if they were adequately informed by providers on the disease and its treatment, 60% of the participants indicated that they were not. And when asked what they knew about TB, some participants described inaccurate causes of TB transmission. A positively received feature of the intervention was having the option to text in questions. Participants described the value of being able to ask questions and receiving answers quickly. A range of questions was asked: how long the face mask should be worn, how the medication should be taken, what should be done when experiencing a specific side effect, or if it would be ok to sleep in the same bed with a family member while receiving treatment.

Two of the participants who had been randomized to the intervention withdrew from the study. One participant was transferred to a local healthcare center where DOT was being provided because she was suffering from severe side effects and was unable to afford travel expenses to hospital outpatient clinic. The other participant withdrew from the study without providing an explanation.

Aim 2: Explore the initial efficacy of the intervention comparing usual care and a medication calendar, to usual care plus a patient-mediated, mobile phone text

messaging-based intervention on outcomes of: (a) adherence rates (e.g., patterns of adherence, percent of days reporting adherence); (b) sputum-smear conversion rates; and (c) final treatment outcome (added as an additional outcome).

The primary outcomes of this study concerned evaluation feasibility and acceptability of the intervention. The exploration of the initial efficacy of the intervention, which is also detailed in Chapter 5, was a secondary outcome. Because of the nature of a pilot study, which was not powered to identify statistical significance, it was recognized that outcomes of initial efficacy were to describe how patients responded to the intervention. Notification of self-administered treatment in the intervention group (*n*=16 analyzed) was on average 77% (*SD* 23.5, range 22-100) of the nonweekend / nonholiday days during the first 2 months of their treatment. Fourteen of the sixteen participants (87.5%) notified self-administration of treatment 61% of the days or greater. Of the notifications of self-administered treatment received (*n*=407), 83% were received without a reminder and 17% were received after a reminder was sent. As opposed to the study by Mohammed et al. (2012), who found lower response rates with those who owned their phone, the 2 participants with the lowest response rates (22 and 31%) were 2 of the 3 participants who shared a phone. Both of these participants indicated that they lost access to the mobile phone during the study period. One was stolen and the other's relationship with the person with whom he shared the phone changed. The latter purchased his own mobile phone and began to maintain contact with the research team more consistently for the last 2 weeks of the 2- month period. There was greater reporting of adherence using text messaging than with the use of a medication diary.

However, because of the low return rate of calendars (10 of the 19) there is limited evidence to support increased adherence in the SMS group.

Given the low rate of sputum or culture testing (15 out of 37), the potential significance of this type of intervention, especially in settings where self-administered treatment is the usual care, may be enhanced through early identification of nonadherence to treatment. Nonetheless, the low rates of sputum smear or culture follow-up testing limited our ability to clearly assess initial efficacy based on conversion rates. Because this outcome variable was not helpful to evaluate initial efficacy, the IRB was amended to add another outcome variable, final treatment outcome. Collecting the final treatment outcomes was challenging due to paper charting and delay in final notification to the regional office. The final treatment outcomes were collected about one year after diagnosis and treatment initiation. Treatment success was high in both groups with 34/37 (92%) completing treatment successfully. Two (5%) participants abandoned treatment, 1 was diagnosed with a nontuberculosis mycobacterium after being treated for TB, and no participants failed treatment or died from TB. Five participants were reported to have transferred to another healthcare facility, but treatment outcomes were documented. At the point of final treatment collection, 1 participant in the SMS group was reported to have abandoned treatment. However this participant had continued to notify (text in) after the documented abandonment date, and during the exit interview this participant reported transferring care to a local healthcare facility.

Aim 3: Evaluate perceptions of intervention acceptance, acceptability, and feasibility (including intervention cost), and how to optimize the intervention from the perspective of the patients and TB-specialized healthcare team.

The evaluation of perceptions of acceptance and how to optimize the intervention was presented in Chapter 5. To identify feasibility issues to consider for conducting a larger trial, including intervention cost using text-messaging based intervention, a socio-technical evaluation was conducted and was presented in Chapter 6.

From interviews and in the evaluation of the text messages the intervention was identified to be overall accepted by the participants and the research team. Most participants indicated that they would highly recommend the intervention to other patients starting TB treatment. Participants described being *thankful for the research team's involvement in their treatment*, feeling *cared for* and *supported by staff* and feeling that *they were responsible for their treatment by reporting in*. Similarly, other researchers using text-messaging interventions report patient acceptance and being well received (Lester et al., 2010; Mohammed et al., 2012; Person, Blain, Jiang, Rasmussen, & Stout, 2011). To develop an intervention that is more patient-centered, where patients are encouraged to contribute to their care, we did not want to automatically send daily reminders. In addition, establishing a strong patient-healthcare professional relationship has been identified as highly important in promoting TB treatment adherence (Iribarren, Rubinstein, Discacciati, & Pearce, 2011; World Health Organization, 2006, 2009b). Nonetheless, sending reminders daily would have been technically easier. In the FrontlineSMS Software daily reminders can be sent to all contacts at a set time daily. Therefore, manually reviewing messages daily to assess who had notified and sending a reminder or query text message took time, but was an intentional part of the interventions' interactivity and personalization.

Another example of acceptance of the intervention was that some patients continued to notify daily at the end of the 2 months after they were informed that they no longer were required to text in daily (*n*=109 texts, mean 7.79, range 0-53). The result of most participants texting-in without a reminder indicated that patients were willing to take the initiative to participate in their treatment management via text messaging. To improve the intervention it was suggested to continue the intervention for the full duration of the treatment course and that possibly having the notifications or checking less frequently could be helpful. Although prior researchers have reported concerns of stigma as a potential drawback to using mobile phones (Kaplan, 2006; Lester et al., 2010; Mbuagbaw, Bonono-Momnougui, & Thabane, 2012; Mohammed et al., 2012), in this study there were no privacy issues reported. In fact, some participants indicated that they shared the educational text messages with others and reported having a family member or significant other send text message notification on their behalf at times, therefore having others actively participate in their treatment.

The socio-technical evaluation of the intervention reported in Chapter 6 highlighted issues encountered during implementation. These issues were categorized into: technical, human and organizational. A number of software issues were identified, some of which could be resolved and others not. For example, some of the positive aspects of the software included enabling the research team to view the text messages in multiple ways (e.g., by individual, by sent/received, by date, or all new messages), and it allowed interactivity, personalization, and functionality without requiring access to the internet. Having the program function without access to the internet proved to be important to the continuity of the intervention as there were multiple days in which there was no internet

access and at times no electricity. Some of the drawbacks of the software were that there was a time stamp discrepancy that could not be resolved, the computer and the program had to be powered on for it to function and powering on after the weekend resulted in automatic text messages sent out of sync with the patients' notifications, and there were multiple time consuming steps required to set up the automated delivery of the educational text message package. In addition, in order to analyze the text messaging data according to the aims of this study a database had to be built in another program in order to capture more relevant detail of the intervention use.

Some staff required more training because they were computer novices, and thus needed orientation on basic functions of a computer and software such as how to save a file and how to copy and paste text. Nonetheless, the program was able to be integrated into the workflow of the team members and operated without assistance by the PI.

The average cost per patient for sending and receiving text messages during the first 2 months of treatment was estimated to be between 12.80 – 29.44 USD. This estimate was based on the average number of texts sent and received per patient (n=128) and the text message cost of 0.10 to 0.23 US per text identified from the websites of the supporting mobile phone service providers for service plans without a contract. In Argentina, text messages are free to receive. Other considerations for using this intervention in a larger population are presented below.

Access to technology is continuously changing; therefore there is a need to be flexible and adapt quickly to technological changes within a population to best meet their needs. In the population evaluated in this study, the use of the video feature or other

advanced phone features may be available in the near future. However, at the time of this study using the common and basic feature of text-messaging was feasible.

Limitations

Some of the overarching limitations are as follows. Innate to a pilot study with a small sample size, the investigator's ability to predict or test for statistically significant differences between groups was limited. Patients used the intervention by texting in questions, side effects, and when attending visits to the physician. Although the emphasis in this study was to understand the intervention's acceptability and feasibility for patients, the workplace and the organization, outcome measures to explore initial efficacy were also evaluated. However, because of the low return rate of the medication diaries and the low rate of follow-up sputum or culture collection the comparative analyses of self-reported adherence and conversion rates were limited. Collecting the medication calendars was challenging because many patients were seen daily in the nurse's office and often the nursing staff did not recall who the participants in the study were and therefore did not query them or the patients did not bring in the calendars. In general patients attended clinic about once a month and the number of opportunities to identify the patients and request calendars was limited. In addition, the use of the medication calendar in itself is an intervention and could have potentially improved self-reporting to comply with the study, potentially diluting the results of the SMS based intervention. Self-reporting is subject to systematic biases, which is prone to overstating medication regimen adherence (Garber, Nau, Erickson, Aikens, & Lawrence, 2004). Another strategy to identify medication adherence may have been a better outcome indicator: using a medication recall questionnaire or reviewing if the patient returned for

medication. It is unclear why providers did not order sputum or culture follow-up tests more frequently. Some charts indicated that the patient no longer had a cough or there was no mention of why a follow-up examination was not conducted. Therefore, the treatment outcome variable was added. Another limitation to identifying a difference between groups is that at recruitment if participants in either group asked questions regarding the disease or treatment, the PI answered them, thereby possibly providing an additional educational benefit to both groups.

The first 2 months of treatment are challenging because of patients potentially experiencing medication side effects, having to take a number of pills each day, and coping with the ramifications of TB diagnosis. However, it is recognized that a vulnerable time for patients to abandon treatment is when they are feeling better (Garner, Smith, Munro, & Volmink, 2007; Gebremariam, Bjune, & Frich, 2010). Patients often report feeling better near or after 2 months of treatment; therefore the data collection period in this study may potentially not fully capture the ability of the intervention to retain patients in treatment. Ending the intervention after 2 months of treatment is, however, a natural evaluation point because the treatment schedule and the number of medications prescribed changes during the maintenance phase (the last 4 to 6 months) (World Health Organization, 2003). In addition, the recommendation for providing directly observed therapy or DOT according to the WHO is daily for the first 2 months and then two to three times per week during the maintenance phase (World Health Organization, 2003). Some participants in this study did indicate that the intervention should continue the full duration of the treatment course. See Chapters 4, 5 and 6 for detailed limitations for each evaluation.

Possible Improvements to Apply in a Larger Trial

In order to conduct a study with a larger population using the text messaging intervention described in this dissertation, it would be necessary to reduce the patient cost to text in notifications or questions. Not texting-in due to running out of credit was reported by participants and the process to add mobile phone credit on an ongoing, staggered basis required time to leave the hospital and organization to track each patient's time in intervention. A likely scenario would be to set up a contract with one of the wireless service providers to allow the cost of the text messages to be accrued by the number being sent to rather than the sender or to negotiate an unlimited text message contract. Setting up a contract with a mobile phone provider would decrease the workload of researchers and prevent patients from not texting in due to insufficient credit. Involving the National TB Program staff in this endeavor could be beneficial. As compensation to participants for their time the mobile phone credit was useful.

For sending the educational messages the intervention should be more automated. Although 20 minutes per patient to set up the educational message package in the FrontlineSMS program may not be excessive for a personalized intervention, implementing in a larger population would be time consuming. In addition, if the inconsistency of sending the messages automatically within FrontlineSMS cannot be resolved, time would be wasted in reviewing and monitoring these messages and there would be a possibility that not all messages would be delivered. Consistent application of the intervention to all participants is essential. Another option may be to test a separate system that would automatically send the educational messages at scheduled intervals after a mobile phone number is added. However, if the messages are sent by

another provider with a distinct phone number from that of the rest of the intervention, patients may become confused and if they were to use the reply to message option their response messages may be missed by researcher. In this study there were multiple occasions in which the participants responded to educational messages with comments and personal experiences. In addition, intentional design by the research team was to provide an interactive intervention that was not be 'too' automated. The intervention as it is provides the option to be responsive to patients' questions and personalize the intervention when needed.

Adaptation to SMS format will vary by country and language; therefore using local staff, who are also experts in the field, to develop messages can aid in assuring cultural appropriateness and content validity. If this intervention was to be applied in another population the cultural appropriateness of the educational messages will likely need to be modified to accommodate for local language variation.

In addition, strengthening the capacity of the healthcare team to track patients who do not notify and return them to treatment would also be needed. Patients not notifying may signal nonadherence to TB treatment, which warrants a prompt response for further evaluation. All participating healthcare team members would need to be in agreement as to how the response should be pursued. Waiting until a month's time to start to contact the patient would not be a viable option.

Implications for Practice

Practitioners and the National TB Program should consider partnering with researchers to further evaluate patient-centered programs, such as mobile phone text messaging, as a means for promoting TB treatment adherence. Because the evidence is

still limited as to the effectiveness of text messaging to promote TB treatment adherence, further research is needed before widespread adoption of this or similar interventions. Clinics and hospitals, especially where self-administered therapy is the usual treatment delivery option, should further evaluate programs that aid healthcare teams to provide patient support, monitor for signs of nonadherence, and improve the patient and provider relationship. Clinics and hospitals also need to improve strategies to track patients or refer them to smaller centers for closer monitoring if they are identified as having difficulty with adhering to treatment. For developing and testing a text messaging based intervention, collaboration with a multidisciplinary team is recommended. During development of a text messaging based intervention issues to consider should include timing of delivery, adapting to SMS format by using accepted and recognized abbreviations to meet text limit, adapting language considering cultural nuances, and ordering of messages for optimum effect.

Implications for Research

Further research, including larger RCTs, using TextTB or similar text messaging-based interventions to promote TB treatment adherence is needed. Future research could include testing using the latest FrontlineSMS version to identify if some of the barriers and glitches experienced in this study have been resolved in the updated software. Due to the high rate of patients reporting a lack of TB knowledge and understanding, TextTB could be strengthened by including more educational messages and extending the intervention to the full treatment course as recommended by some participants. In future research the cost calculation should be more comprehensive and include staff member time to conduct intervention, and patient and equipment costs. It is recognized that the

burden of TB in adolescents and children is difficult to estimate and that these are important populations that need further understanding (World Health Organization, 2012). Therefore further research should be conducted with adolescent populations and with persons who care for children and infants with TB. Young people tend to use SMS technology as part of everyday communication and this is of particular importance since TB has increased in people between the ages of 20 and 45 and young people tend to be less compliant with the long TB treatment (Instituto Nacional de Enfermidades Respiratorias E. Coni, 2011). There is also a need for further evidence describing text-messaging intervention development, the intervention's acceptability and cultural appropriateness, and methods to make the intervention more feasible for use in a larger population.

Conclusions

In conclusion this dissertation research successfully designed and piloted a patient-centered, personalized and interactive text messaging- based intervention. Overall the intervention was well accepted and feasible and used by patients to ask questions, report side effects, and report on treatment progress. The option to ask questions and receive quick answers was valued. Through text messaging, interaction between patients and healthcare team was fostered and education was provided. Although treatment success was high in both groups resulting in unclear evidence that the SMS intervention was more efficacious, the treatment success rate was also higher than prior data from this region and hospital. Still feasibility and acceptability results in this study suggest that there is value in assessing this interactive SMS intervention in a larger-scale research project.

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APPENDIX A

DEMOGRAPHIC QUESTIONNAIRE

Directions: Please answer all of these questions accurately. The information you provide will be used only for this project and will not be seen by anyone else.

1. Today's date: _____/_____/_____
   Month Day Year
2. Your age: _____ (years)

3. Gender: Male Female (circle)

4. Your ethnic and racial background:
   Ethnic _____ Racial _____

5. Your marital status:
   _____ (1) Single (never married)
   _____ (2) Separated or divorced
   _____ (3) Widow or widower
   _____ (4) Married/partnered

6. Highest grade of school you completed:
   _____ (1) 8th grade or less
   _____ (2) Some high school
   _____ (3) High school graduate
   _____ (4) Technical school graduate
   _____ (5) Some college
   _____ (6) College graduate
   _____ (7) Postgraduate or professional

7. What best describes your employment status?
   _____ (1) Full-time
   _____ (2) Part-time
   _____ (3) Unemployed
   _____ (4) Retired
   _____ (5) Full-time homemaker

8. How far away do you live from the hospital (km)?
   _____ (1) <1
   _____ (2) 1-5
   _____ (3) 6-10
   ___(4) 11-15
   ___(5) 16-20
   ___(6) Other (please specify)

9. What is your means of transportation?

___ (1) Local bus
___ (2) Private car
___ (3) Walk
___ (4) Bicycle
___ (5) Train
___ (6) Taxi
___ (7) Other (please specify) _____

10. What (if any) type of other health problems do you have? Check all that apply.

_____ (1) Heart disease
_____ (2) Diabetes
_____ (3) Lung disease
_____ (4) Kidney disease
____ (5) High blood pressure
____ (6) Disease of the nervous system
____ (7) Other (please specify): _____
_____(8) None

APPENDIX C continued

11. What is your monthly household income before taxes (Argentinean Peso)?
1USD=3.93 Argentine Peso?

_____ (1) $0 - $600
_____ (2) $601 - $1500
_____ (3) $1501 - $2000
_____(4) $2001and above
_____(5) No answer/Unknown

12. What are your present sources of financial support? Check all that apply.

_____ (1) Savings
_____ (2) Retirement
_____ (3) Stock/bonds
____ (4) Family support
_____ (5) Employment
_____ (6) Other (please specify) _____

13. How would you describe your current financial situation?

_____ (1) I have problems making ends meet.
_____ (2) My financial situation is comfortable.
_____ (3) My income is more than adequate to meet my needs.

14. Do you have private health insurance?

_____ (1) No _____ (2) Yes please specify: _____

15. Do you currently (before starting TB treatment) take any medication on a daily basis?

___ (1) Yes ___ (2) No

16. How long have you owned a mobile phone?

_____ months

17. What is your level of comfort in using a mobile phone?

Very comfortable	Somewhat comfortable	Neither comfortable or uncomfortable	Somewhat uncomfortable	Very uncomfortable

18. What is your level of comfort in sending and receiving text messages?

Very comfortable	Somewhat	Neither	Somewhat	Very

	comfortable	comfortable or uncomfortable	uncomfortable	uncomfortable

19. How often do you use text messaging?

Once per week or les	1 or 2 times per day	3 to 5 times per day	6 to 10 times per day	> than 10 times per day

20. How often do you have a drink containing alcohol?

Never	Monthly or less	Two to four times per month	Two to three times per week	Four or more times per week

21. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2	3 or 4	5 or 6	7,8,or 9	10 or more

22. How likely do you think it is that you will avoid alcohol while you are receiving treatment?

APPENDIX B

TB AND HIV/AIDS EDUCATION SOURCE, TITLE AND LINK

TB Education Source, Title and Link

Source	Title	Link/reference
JAMA Patient Page	Tuberculosis	http:jama.ama-assn.org/*JAMA*.2008;300(4):464. doi: 0.1001/jama.300.4.464
American Family Physicians	Tuberculosis: What You Should Know	http://www.aafp.org/afp/2008/0815/p469.html
Minnesota DOH	Active TB Disease	www.health.state.mn.us/tb
CDC	Get the facts about TB disease	http://www.cdc.gov/tb
CDC	Tuberculosis: Get the Facts!	http://www.cdc.gov/tb
CDC TB Elimination	Tuberculosis: General Information	http://www.cdc.gov/tb
CDC	What you need to know about TB infection	http://www.cdc.gov/tb
CDC	Staying on track with TB medicine	http://www.cdc.gov/tb
CDC	Tuberculosis facts - TB can be treated	http://www.cdc.gov/tb
A Healthy Roads Media project	What You Should Know About Taking TB Medicines	www.healthyroadsmedia.org
Virginia DOH	What You Should Know About Taking TB Medicines	http://www.vdh.state.va.us/epi/tb
A Healthy Roads Media project	TB DISEASE -You Need Treatment To Make You Well	www.healthyroadsmedia.org

HIV/AIDS Education Source, Title and Link

Source	Title	Link/reference
FamilyDoctor.org	HIV and AIDS | Treatment	http://familydoctor.org/familydoctor/en/diseases-conditions/hiv-and-aids/treatment.html
FamilyDoctor.org	HIV and AIDS | How to take HIV medicines	http://familydoctor.org/familydoctor/en/diseases-conditions/hiv-and-aids/treatment/how-to-take-hiv-medicines.html
JAMA Patient Page	HIV Infection: The Basics	http:jama.ama-assn.org/*JAMA. 2010;304(3):364.doi:10.1001/jama.304.3.364*
JAMA Patient Page	HIV/AIDS: Drug treatment options for HIV	http:jama.ama-assn.org/ *JAMA.1998;280(1):106.doi:10.1001/jama.280.1.106*
	Now you are on ART	
The Complete HIV/AIDS Resource	How do you make sense of your treatment options	TheBody.com/treatment
NIH/NIAID	Treatment of HIV Infection	http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Treatment/Pages/default.aspx
UCSF Medical Center	HIV Treatment	http://www.ucsfhealth.org/conditions/hiv/treatment.html

APPENDIX C

CONTENT ANALYSIS RESULTS OF PATIENT EDUCATION MATERIAL

Adherence-related Information:

General information regarding disease

- TB usually affects the lungs, but it sometimes affects other parts of the body
- active infection, there is damage to organs
- TB is a serious disease that can be cured with the right treatment and medicine
- TB disease can cause permanent body damage and death.
- Anyone can get TB
- TB germs are strong and live a long time
- As long as you have TB germs in your body, they can wake-up, multiply, and make you sick with TB disease.
- Even if you had the BCG vaccine, you can still go on to get TB
- You got sick from TB when the germs "woke up" and started to grow and hurt your body. This is "active TB disease"
- The treatment you receive for TB infection only treats the TB germs in your body now. There is the possibility that you can be around someone else with TB disease and get new TB germs

Disease risk factors, those at higher risk

- Babies, young children, and elderly people have a much higher chance of getting TB disease if infected with TB germs
- Children younger than four years and people who live in nursing homes, mental institutions, or jails have a higher risk
- not treated correctly for TB infection in the past
- Abuses alcohol or illegal / injectable drugs.
- Has other health problems, like diabetes, that make it hard for the body to fight germ

Transmission

- Anyone can breathe in TB germs and get TB infection
- TB germs are spread from person to person through the air
- The TB germs are passed through the air when someone who is sick with TB disease coughs, laughs, sings, or sneezes

- People with TB disease are most likely to spread the germs to people they spend time with every day, such as family members or coworkers.
- typically occurs after repeated or prolonged exposure to the coughing of an actively infected person
- type of TB arises from improper or incomplete treatment of TB infection or through exposure to a person infected with this type of bacterium
- You cannot get TB germs from: Sharing drinking containers or eating utensils or Saliva shared from kissing
- NOT spread by sharing silverware or cups, sharing cigarettes, or sharing saliva when kissing someone
- NOT spread through shaking someone's hand, sharing food, touching bed linens or toilet seats, or sharing toothbrushes
- TB germs can sometimes stay alive in the air for a few hours, especially in small places with no fresh air.
- You may see healthcare providers wearing a mask around you so they won't get TB germs from you
- If TB disease is in your lungs or throat, you can give TB germs to your family and friends
- You may have to be separated from other people until you can't spread TB germs

Symptoms

- Symptoms vary depending on the patient's age and which organs are infected. Without treatment, usually get worse
- Fever and sweating (particularly at night)
- Unexplained weight loss
- Loss of appetite
- Fatigue
- Persistent cough that may be associated with bloody sputum
- Difficulty breathing or chest pain with breathing
- Losing weight without trying.

What constitutes adequate treatment adherence

- To be sure that all of the TB germs are killed, you must keep taking TB medicines for at least 6-9 months
- regimen of 3 to 4 antibiotics taken daily
- TB germs are strong, and it can take a long time for them to die
- If you miss one dose or forget to take the pills ONE TIME, don't worry. Just take the next dose when you are able to
- Take your medicine the right way, as your doctor or healthcare provider tells you
- You will feel better a few weeks after you start to take the TB medicines
- Multidrug-resistant TB is resistant to (cannot be killed by) standard antibiotics
- Treatment of multidrug-resistant TB requires additional medications and may last several years

- TB that is resistant to drugs is harder and more expensive to treat

Treatment Follow-up

- your doctor may ask for blood, phlegm, or urine tests while you are on treatment
- tests will help show if your TB medicines are working the right way and how your body is handling the medicine.
- you may also get additional chest x-rays.
- Your doctor will tell you when you can return to work, school, or other activities

Follow medical advice

- It is very important that people who have TB disease finish the medicine, and take the drugs exactly as they are told.
- Follow your health care provider's directions for taking your pills.
- It is very important to take all of your medicines for as long as directed by your health care provider
- You will need to take your medicines the right way, just as your doctor or healthcare provider tells you
- Take your pills exactly the way your doctor tells you
- Take your medicine the right way, as your doctor or healthcare provider tells you
- Follow your doctor's advice and take the medicine as prescribed.
- It is very important that people who have TB disease finish the medicine, and take the drugs exactly as they are told.
- Always follow your doctor's instructions.

Medication Side effects and Interactions

- Most people can take medicines for TB without any problems
- If you are taking Rifampin, you should know that: your urine, saliva, or tears can become orange in color.
- medicines for TB are usually safe, but some people have side effects
- Less appetite or no appetite for food.
- An upset stomach, nausea, or stomach cramps.
- Vomiting.
- Yellow skin or eyes.
- Aches or tingling in your fingers or toes.
- Fever.
- Your skin may become more sensitive to the sun.
- Don't drink beer, wine or liquor while taking TB medicines
- Sometimes taking certain medicines together can make you have a reaction.

- It is important for your doctor to know all of the medicines you are taking
- Tell your doctor if you are, or think you are pregnant or breastfeeding before you start any medicines some birth control pills may not work as well when you take them with medicines for TB.
- Women should use a back-up form of birth control, such as condoms, while taking rifampin.

Adherence-related Motivation:

Personal Motivation-related: Optimal Adherence

- Protect yourself, your family and friends from TB. Finish your TB treatment!
- Even if you feel better after a few weeks on the TB medicines, it does not mean all the TB germs are dead
- Even if you start to feel better, you will need to stay on medicine to be cured
- Remind yourself you are staying on your treatment plan to kill all the TB germs.
- You have done other tough things in your life and you can do this too!
- you know that you can do this-one day at a time

Personal Motivation-related: Suboptimal Adherence

- If you don't take all of your medicine correctly, you could become sick again and spread TB to other people
- TB can be cured, but without proper treatment you could die.
- If you do not take your medicine correctly, your TB could become even stronger. You would have to take stronger medicines for a longer time
- If you don't take the pills the right way: It can be harder or not possible to cure your TB
- You can pass TB germs to your family, friends, and others around you if you don't take TB medicine the right way

Social motivation-related

- Talk to family and friends about TB let them know: Anyone can get TB. You are taking your TB pills the right way.
- Ask your healthcare provider and your family and friends for help along the way
- DOT cures TB!
- Your healthcare provider will help find a plan that will work for you.
- Remember to take your pills.
- Do not stop taking your pills too soon.
- Remember-TB can be prevented, treated, and cured.
- Remember TB can be cured!
- The longest journey begins with a single step.

APPENDIX C continued

- you know that you can do this-one day at a time
- Together-you will succeed!
- Follow the treatment to get cured from TB.

Adherence-related Behavioral Skills: Self-Efficacy

To acquire information

- Learn how TB is spread ask your doctor or nurse whether your TB can spread to others (is contagious)
- Learn all you can about TB and share what you learn with your family and friends.
- For further information on TB, contact your local health department.
- Ask your healthcare provider any questions that you, your family, friends, classmates, or co-workers may have.
- If you are taking medicine for TB infection, write any questions you have to share with your doctor

To acquire support

- Talk to your doctor if you have trouble remembering to take your medicines
- ask a family member or friend to remind you
- Ask your family and friends for support
- If you have side effects that bother you, tell your doctor
- Talk to your healthcare provider if your TB medicine is making you feel sick

To incorporate into daily life / Reinforce

- Take all of your TB medicine at the same time every day.
- Keep telling yourself that the pills can help you beat TB.
- I made a plan to finish this medicine because I want to stay healthy for my family.
- Use a pillbox and put a week's worth of pills in the box
- Keep your medicine in one place, where you can't miss it.
- Write yourself a note. Put it on your bathroom mirror or on your refrigerator.
- take steps to remember to take your pills
- Write the names and amount of medicine you are taking each day to kill the TB germs
- Use a calendar to check off the days you have taken your medicine
- setting an alarm on your watch
- asking a family member or friend to remind you
- using a special pill box
- hanging a note on the bathroom mirror or refrigerator

APPENDIX C continued

- Wear a watch to keep track of time. Set your watch alarm for the time you need to take your pills.
- put a note in my wallet next to a picture of my family that said "James-stay healthy for your family
- If you forget your medicine more than one time, call your doctor or healthcare provider BEFORE you take the next dose scheduled.

To Minimize Side Effects

- Call your healthcare provider right away if you have side effects:
- Use sunscreen and cover skin that might be exposed to the sun.
- Talk to your healthcare provider if your medicine is making you feel sick.
- I should just have a little food before I take my pills
- I have some crackers or a piece of bread before I take my medicine and I don't have stomach aches anymore.

To prevent transmission

- Fresh air and sunlight make it harder for TB germs to stay alive.
- fresh air scatters the germs and the sunlight kills them
- Wear a special mask if your doctor says it is needed.
- If you are not wearing a mask, cover your mouth and nose with a tissue when you cough or sneeze
- Keep windows open in your home, if possible, until your doctor says you cannot pass TB germs to others.
- Don't spend time in closed spaces with others until your doctor or healthcare provider says you can't pass TB germs
- If you have TB disease, you may want to talk to your friends and family about it
- Usually after you have been on the TB medicine for several weeks no longer passing TB germs to others
- Explain that you are taking medicine
- Stay at home until your doctor or healthcare provider says you may return to school or work.
- Ask friends not to visit until your doctor or healthcare provider says you can have visitors.
- Put all tissues in a trash bag. Close the bag until you can throw it away.
- Keep windows open in your home, if possible, until your doctor says you cannot pass TB germs to others.

Contextual Factors

Acknowledging challenge

- Taking medicine regularly can be a challenge.
- It takes a lot of work to stay on a medicine plan
- Letting people know you have TB disease is not always easy
- Taking medicine each day can be difficult.
- All of this information is a lot to take in at once. Take each day-one day at a time as you work toward treating your TB infection.

APPENDIX D

EDUCATIONAL TEXT MESSAGES IN SPANISH

Week	Msg type*	Msg from**	Message
1	Information (transmission)	L/PQ [160]	Tbc se contagia a traves de la tos o estornudo de una persona enferma. Toser en lugar ventilado-no cerrado, cubrirse la boca y/o utilizar barbijo x no contagiar
	Information (drug interaction)	L [130]	Tomar las drogas en ayunas. Con alimentos, sobre todo si son abundantes en azucar y harinas, su accion disminuye 25-60%
2	Information (medication side effect)	L	La Rifampicina (rojas) tiñe la orina, saliva o lagrimas color naranja o roja, esto es normal. Precaucion con lentes de contacto, los tiñe también
	Information (transmission) + Motivation - personal	L/PQ [136]	La tbc no contagia al dar la mano, compartir vasos o platos. Se contagia solamente con la tos o al escupir. Recuerda ¡La TBC se cura!
3	Motivation -social	PQ [158]	Hasta + o - 20 dias en tratamiento aun se puede contagiar. Contacto frecuente y lugares cerrados aumenta el riesgo. A los convivientes debe hacerse un control
	Information (medication side effects)	L [159]	Efectos de las drogas puede ser nauseas, vomitos, picazon, perdida de apetito. Si piel, ojos se ponen amarillentos o cambios en la vision hacer pronta consulta
4	Information (simptoms)	PQ [131]	Es posible seguir con sintomas (x ej. fiebre, sudores nocturnos, tos y catarro) durante los primeros 20-30 dias del tratamiento. Continua con tu tratamiento!
	Information (side effect)	L [160]	Por los medicamentos su piel puede estar mas sensible al sol. Use crema solar y trate de cubrirse. Muy Bien! Ya cumpliste con un mes de tratamiento. Adelante!
	esputo		Es importante y recomendado un control de catarro al mes de comenzar tto, como parte del programa, no dejes de avisarnos los resutados
5	Motivation - social	L [156]	Mantener una dieta completa y variada y que incluya todos los componentes: carbohidratos (pan, pastas, harinas), grasas, proteínas, fibra, fruta y verduras.
	Motivation –	PQ	Existe discriminacion y falta de conocimiento sobre tbc x eso hay gente temerosa. Hace falta

	acknowledgement	[140]	realizar difusion para crear mas conciencia. Todos podemos enfermar
6	Motivation - personal	L/PQ [160]	El estudio de catarro a 1 o 2 meses verifica si no contagias y si podes volver al trabajo, pero x curarte necesitas continuar con el tratamiento los 6 meses. Adelante!
	Motivation - personal	[159]	Insistir en q tiene q seguir el tratamiento en forma regular. La irregularidad en la toma hace a la bacteria resistente a las drogas y un tratamiento mas largo.
Week	Msg type*	Msg from**	Message
7	Motivation – social / Skills	L [158]	Cuenta con personal de su lugar de atencion x solucionar inconvenientes: Entre todos podemos resolvar problemas. Ayudenos a controlar la enfermidad y curarse!
	Skills	L [158]	Tomar las drogas todos los dias es un desafio! Para acordarse: Mantengalas en un lugar, use alarma (x ej. tu celular), coloque una nota en el espejo o refrig
8	Motivation - personal	L [157]	La mejoria no significa q estas curado. Para curarse necesitas seguir el tratamiento 6 meses y tomar las drogas regularmente p no volver enfermar. Adelante!
	Information (follow-up)	L [134]	A los 2 meses cambia el regimen, es mas facil son menos drogas. Continua con controles y examen del catarro para verificar q vas bien

Other messages for specific populations

Smokers/ Fumadores	• Lo mejor es no fumar. El Tabaco provoca una baja de las defensas. En estos momentos las defensas ya están disminuidas por la enfermedad. (136) • Hay un equipo que trabaja para dejar de fumar aquí en el hospital
Women/ Mujeres	• Remedios anticonceptivos no trabajan bien cuando se toma rifampicina (la roja) consultar con tu medico para justar la medicación
Drug interactions	• Las bebidas alcohólicos más el tratamiento de la tuberculosis aumentan la toxicidad en especial en el hígado

* Message type based on Information-Motivation-Behavior model (citation)

** Message identified from literature (L) or patient question (PQ)

Message from a patient	Mensaje de una paciente en tratamiento: queridos amigos, soy una más entre ustedes, deseo que puedan sobrellevar la enfermedad con todos sus síntomas y que por nada dejen de tomar los remedios demos las gracias de ellos para nuestra salvación y agradezcamos que existe Sarah y un equipo de gente que cada día nos ayuda y contiene aún a la distancia los quiero a todos y les mandó un beso. Msj de una pcte en tto: queridos amigos, soy una mas, deseo que puedan sobrellevar la enfermedad con todos sus sintomas y q x nada dejen de tomar los remedios

APPENDIX E

CALENDAR EXAMPLE

Marzo 2012

ID del programa # _____

ID del paciente (N° celular) _____

Mes 1 o 2

Indicación:			
		Triple (Rojo)	4 compr./dia
		Etambutol (Blanco)	4 o 5 compr./dia

Por favor entregar en vacunación o Programa de TBC (1° piso)

domingo	lunes	martes	miercoles	jueves	viernes	sabido
ejemplo __ Roja Si/No __ Blanca Si/No Hora __:__				1 __ Roja Si/No __ Blanca Si/No Hora __:__	2 __ Roja Si/No __ Blanca Si/No Hora __:__	3 __ Roja Si/No __ Blanca Si/No Hora __:__
4 __ Roja Si/No __ Blanca Si/No Hora __:__	5 __ Roja Si/No __ Blanca Si/No Hora __:__	6 __ Roja Si/No __ Blanca Si/No Hora __:__	7 __ Roja Si/No __ Blanca Si/No Hora __:__	8 __ Roja Si/No __ Blanca Si/No Hora __:__	9 __ Roja Si/No __ Blanca Si/No Hora __:__	10 __ Roja Si/No __ Blanca Si/No Hora __:__
11 __ Roja Si/No __ Blanca Si/No Hora __:__	12 __ Roja Si/No __ Blanca Si/No Hora __:__	13 __ Roja Si/No __ Blanca Si/No Hora __:__	14 __ Roja Si/No __ Blanca Si/No Hora __:__	15 __ Roja Si/No __ Blanca Si/No Hora __:__	16 __ Roja Si/No __ Blanca Si/No Hora __:__	17 __ Roja Si/No __ Blanca Si/No Hora __:__
18 __ Roja Si/No __ Blanca Si/No Hora __:__	19 __ Roja Si/No __ Blanca Si/No Hora __:__	20 __ Roja Si/No __ Blanca Si/No Hora __:__	21 __ Roja Si/No __ Blanca Si/No Hora __:__	22 __ Roja Si/No __ Blanca Si/No Hora __:__	23 __ Roja Si/No __ Blanca Si/No Hora __:__	24 __ Roja Si/No __ Blanca Si/No Hora __:__
25 __ Roja Si/No __ Blanca Si/No Hora __:__	26 __ Blanca Si/No	27 __ Roja Si/No __ Blanca Si/No Hora __:__	28 __ Roja Si/No __ Blanca Si/No Hora __:__	29 __ Roja Si/No __ Blanca Si/No Hora __:__	30 __ Roja Si/No __ Blanca Si/No Hora __:__	31 __ Roja Si/No __ Blanca Si/No Hora __:__

APPENDIX F

INTERVIEW GUIDE

Questions
Tell me about how you usually use your mobile phone (e.g., talk, text, photos, internet, etc)?
What was it like using your mobile phone to report when you took your medicine?
Did you have technical problems using your mobile phone to report taking your medications? Any other problems?
How helpful was the phone system?
What worked well and what didn't?
Which part of the phone system was the most helpful, least helpful? 1) Educational Messages; 2) Texting in daily after taking medication, 3) Reminders if you forgot to take your medication or text in.
How did you find the education messages?
How did you find texting in daily after taking medication?
How did you find the medication reminders if/when you forgot to take your medication or forgot to text in?
Did you ever miss taking your medication? If so, why?
What other interventions might help you continue to take your medication daily?
Questions related to cost of intervention • What is the cost of one text message on your plan? • How much is it to drive to clinic (one way)? How much time does it take to arrive to clinic? • Any miscellaneous costs associated with TB treatment?
What would you recommend to improve the intervention?
Tell me about your overall experience with the text-messaging based intervention?
Would you recommend the intervention to others? 1-5 (e.g., 5=highly recommend, 1= do not recommend)
Anything else you would like to add?