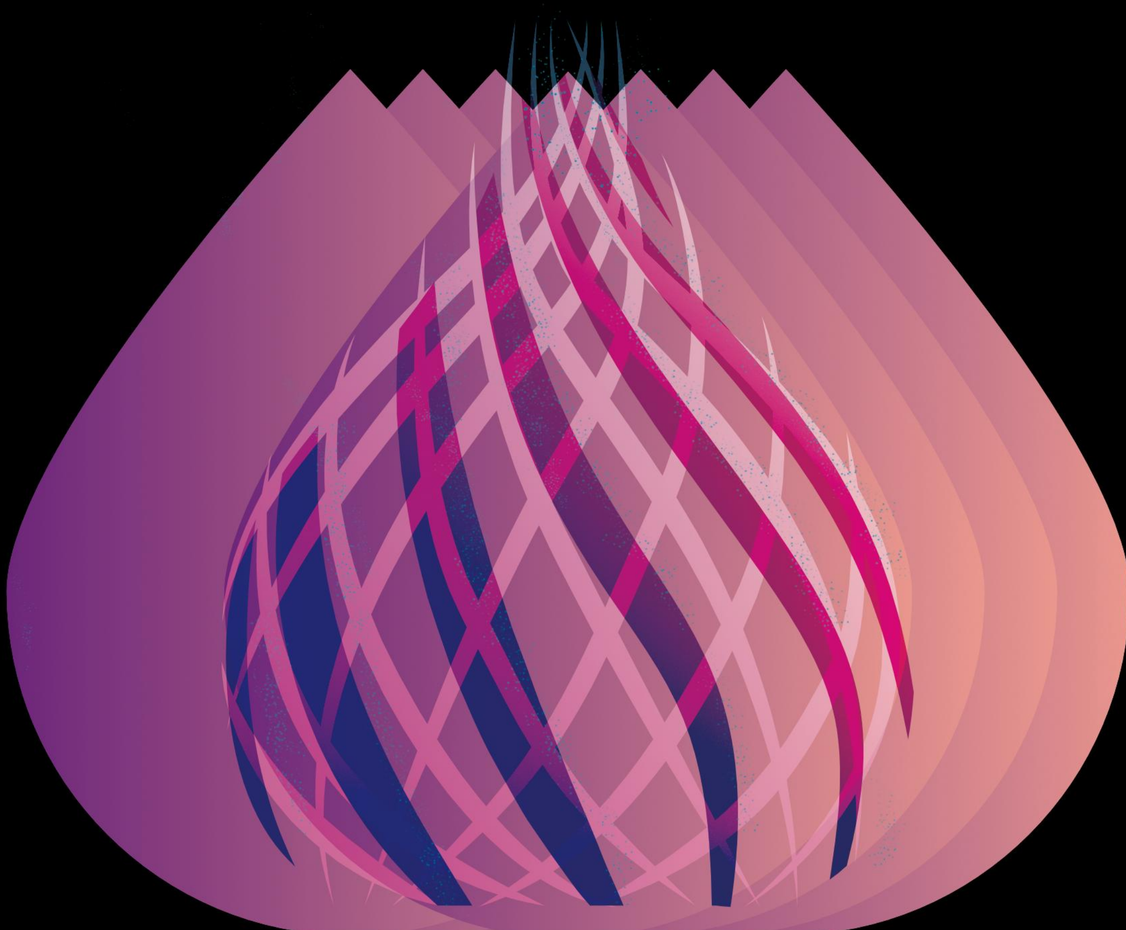
HANDBOOK FOR THE USE OF DIGITAL TECHNOLOGIES TO SUPPORT TUBERCULOSIS MEDICATION ADHERENCE.



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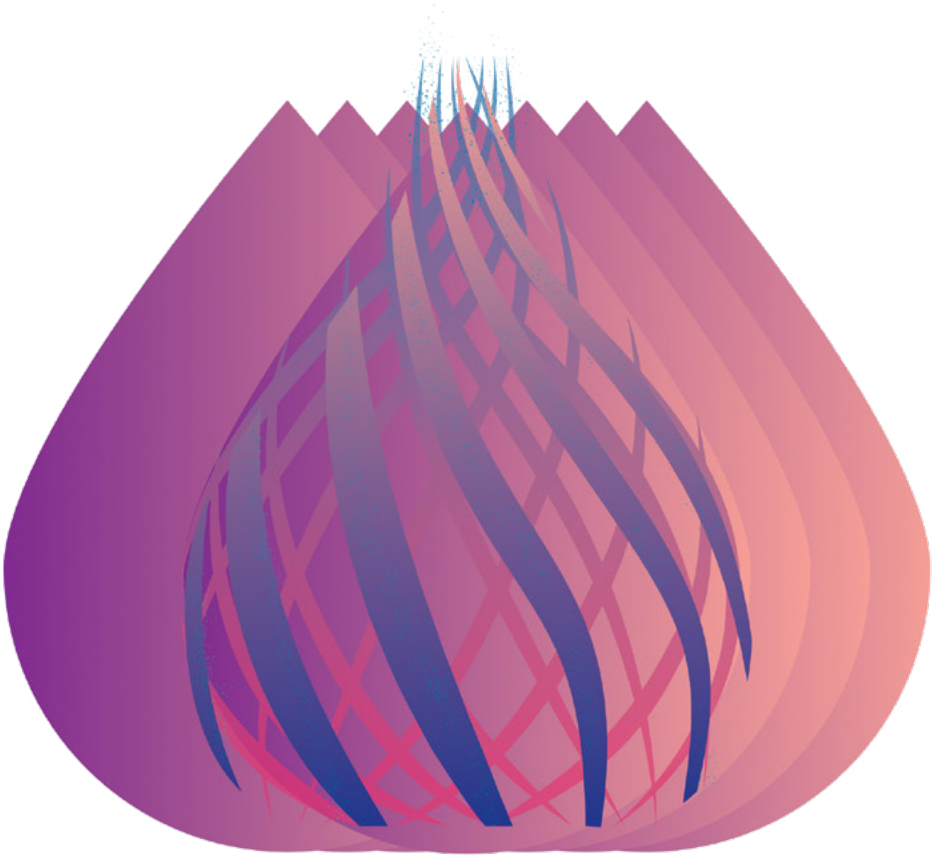

World Health Organization

Handbook for the use of digital technologies to support tuberculosis medication adherence

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ABBREVIATIONS

aDSM	active TB drug safety monitoring and management
AI	artificial intelligence
ART	antiretroviral therapy
BMGF	Bill & Melinda Gates Foundation
BMU	basic management unit (smallest administrative unit registering TB patients, e.g. district)
DOF	dose observation fraction
DOT	directly observed therapy for TB
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
ERS	European Respiratory Society
FDC	fixed-dose combination
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIPAA	Health Insurance Portability and Accountability Act
HIS	health information system
HIV	human immunodeficiency virus
HMIS	health management information system
ICT	information and communication technology/-ies
IMEI	International Mobile Equipment Identity
LED	light-emitting diode
LIS (LIMS)	laboratory information (management) system
LTBI	latent tuberculosis infection
M&E	monitoring and evaluation
MDR-TB	multidrug-resistant tuberculosis
MEMS	medication event monitoring systems
MoH	Ministry of Health
MSF	Médecins Sans Frontières
NGO	nongovernmental organization
NTP	national tuberculosis programme
PHC	primary health care
RCT	randomized controlled trial
SDG	Sustainable Development Goals
SIM card	subscriber identity module card (used to connect cell-phones, tablets and MEMS to a mobile phone network)
SMS	short message service (mobile phone texting)
SOP	standard operating procedure
SWOT	analysis of **s**trengths, **w**eaknesses, **o**pportunities, **t**hreats
TB	tuberculosis
TPP	target product profile
VOT	video-supported treatment for TB
WHO	World Health Organization

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December 2017

INTRODUCTION

Advances in mobile technologies, network coverage and Internet access have transformed the way we interact with each other in our daily life. Instant access to information and rapid sharing of news are becoming the norm in our professional, social and personal environments. These developments have created new, exciting possibilities to improve patient care by turning data into useful information for individuals and for programme management. For example, social media channels and mobile text messaging campaigns can promote and raise awareness on health and disease. Mobile phones can help community health-care workers communicate better with patients. Faster feedback from laboratories can be achieved by automating the transmission of diagnostic test results to clinicians and electronic health records. Guidelines, training material and educational content can be shared and updated more efficiently in digital format than on paper.

The various applications of digital health are relevant for major disease programmes such as those focused on tuberculosis (TB) prevention and care. They have the potential to transform the delivery of different dimensions of services, bringing the notion of patient-centred care within reach, even under very basic conditions.

In 2015 and 2017, the Global TB Programme of the World Health Organization (WHO) convened technical consultants to explore how innovative digital technologies could be integrated more systematically into the various aspects of its End TB Strategy *(1–3)*. A conceptual framework was developed, grouping different digital health products into four areas relevant to TB: patient care, surveillance and monitoring, programme management and e-learning *(4)*.

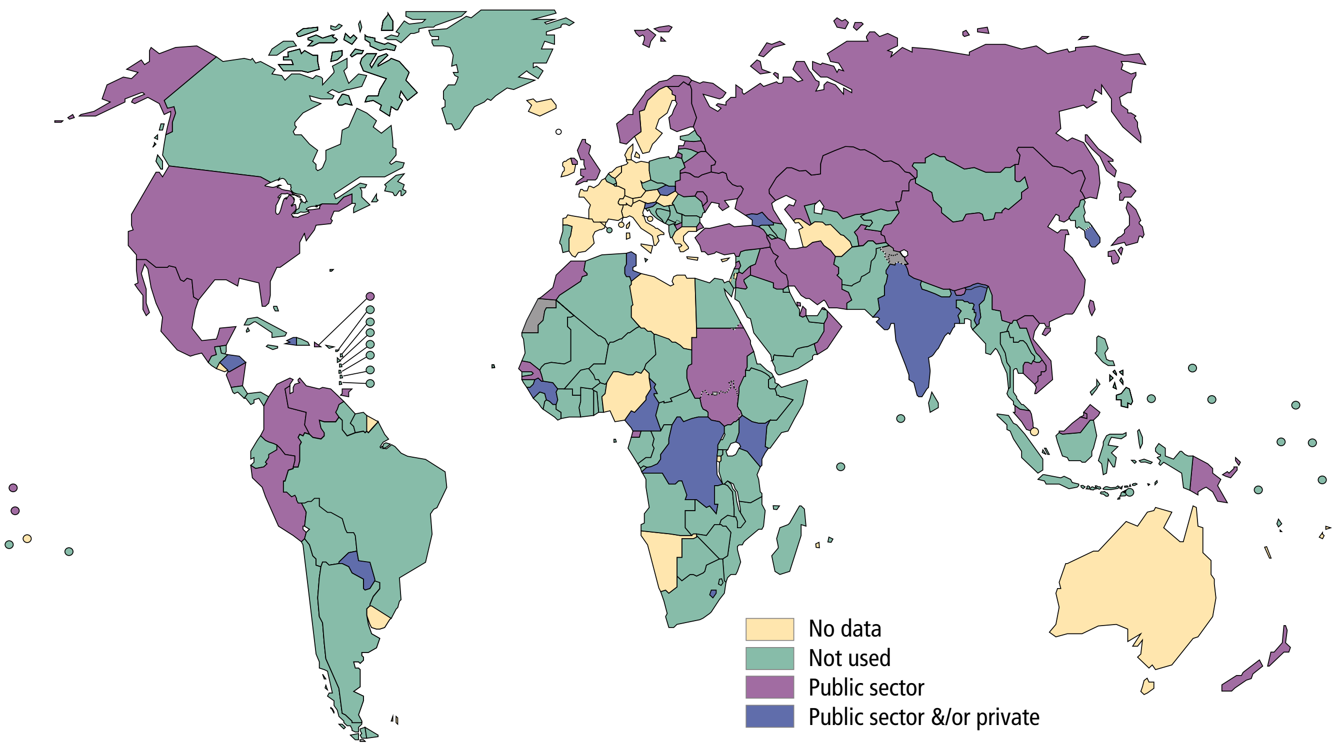
One important application of digital health in TB patient care is the support that it can lend to medication adherence. TB programmes have already been using short message service (SMS), video-supported treatment (VOT) and medication event monitoring systems (MEMS)[1] to help patients complete treatment and health-care workers to monitor both daily dosing and treatment continuity (Map 1). In April 2017, WHO released its first evidence-based recommendations for the use of digital technologies in support of the administration of TB treatment and medication adherence, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of evidence *(6)*. With the release of these guidelines, there was a surge in demand by national TB programmes for clearer instructions on how to choose the best suited interventions and implement them under the circumstances that they face in their daily efforts.

This handbook was conceived to answer to this demand. It is focused on the implementation of the most common digital health products being used in support of TB treatment adherence, and for which some evidence is already available from studies in TB treatment programmes. The instructions provided thus address primarily the "patient care" function of digital technologies for the End TB Strategy, as described in WHO's "agenda for action" *(4, 7)*. Staff of TB programmes and practitioners in both the public and private sectors who are directly involved in such efforts make up the main target audience of the handbook. The text takes a step-wise approach to help the user think systematically through the critical stages needed for successful implementation. One of the main challenges that the authors of this

1 This includes medication boxes with a special closure to record the time and date at each point it is opened and closed, or approaches such as 99DOTS requiring patients to self-report that are currently under study (5) (*see also* Chapter 2).

handbook aimed to address is the ever-changing nature of the digital health landscape as innovations are continually introduced to enhance the existing products. The implementer will need to stay abreast of developments to ensure that the best possible use is made of state-of-the-art technology as it moves forward.

Map 1. In 2016, were SMS, VOT, MEMS or other digital technologies being used to support medication adherence in TB patients? *(8)*



CHAPTER 1.
ASSESSING THE DIGITAL HEALTH LANDSCAPE

1.1 Background

Successful implementation of digital health solutions requires due consideration of the larger context of the health system and patient population in which they will operate. Just as good health care requires looking at the whole patient holistically, introducing digital innovations needs to consider the entire system into which they fit beyond the specific technology concerned. The patient needs to be positioned at the centre of an integrated process of data management to support quality care and enable informed decision-making.

Among the challenges to implementing an effective and sustainable digital health approach is the lack of guidance on evaluation of potential solutions, their purpose, and where they should be best situated within the national and subnational levels of the health system. In this section, the reader is provided with a framework to assess the key elements of an existing information system to help identify opportunities and gaps along the four critical steps of the patient pathway: care-seeking, diagnosis, treatment and follow up.[2] This allows the mapping of needs along the entire pathway to match with existing and potential digital health solutions. Although the focus of the assessment is on national TB programme activities, broadening the scope of work to include the overall health sector and other key health programmes (e.g. HIV, maternal health care and malaria) will provide insights into potential opportunities offered by other useful resources in the country. The assessment can be done by the TB programme staff or by an external agency.

A digital health assessment consists of the following sequential building blocks:

1. Country situational assessment
2. Stakeholder framework
3. Digital health activities framework
4. Gaps and needs analysis of the TB patient pathway
5. Developing a national digital health agenda

1.2 Country situational assessment

As a first step, a country situational assessment follows a standardized approach to collect key information. Components include: the country's administrative structure; prevalence and incidence of the most common diseases; health system structure, including different types of health providers and health sector-related legislation and policies; public sector medical system for the general health/primary health care (PHC) system; TB programme activities and delivery of services by administrative level, laboratory, recording and reporting processes and procedures; infrastructure for information and communication technologies (ICT), including health management information systems (HMIS), laboratory information

2 The framework described here follows the one developed recently by KNCV Tuberculosis Foundation *(9)*.

systems (LIS), interoperability between different health programmes, back-up and maintenance; and human resource capacity.

The aim of this first step is to provide basic background intelligence about the country context in which the digital health system will be implemented. National guidelines, national TB programme reports, results from local surveillance and research activities, national policies, field assessments, and interviews and focus group discussions with key stakeholders can all serve to gather the information.

Annex I details the elements that help to describe the country situation in a structured way.

1.3 Stakeholder framework

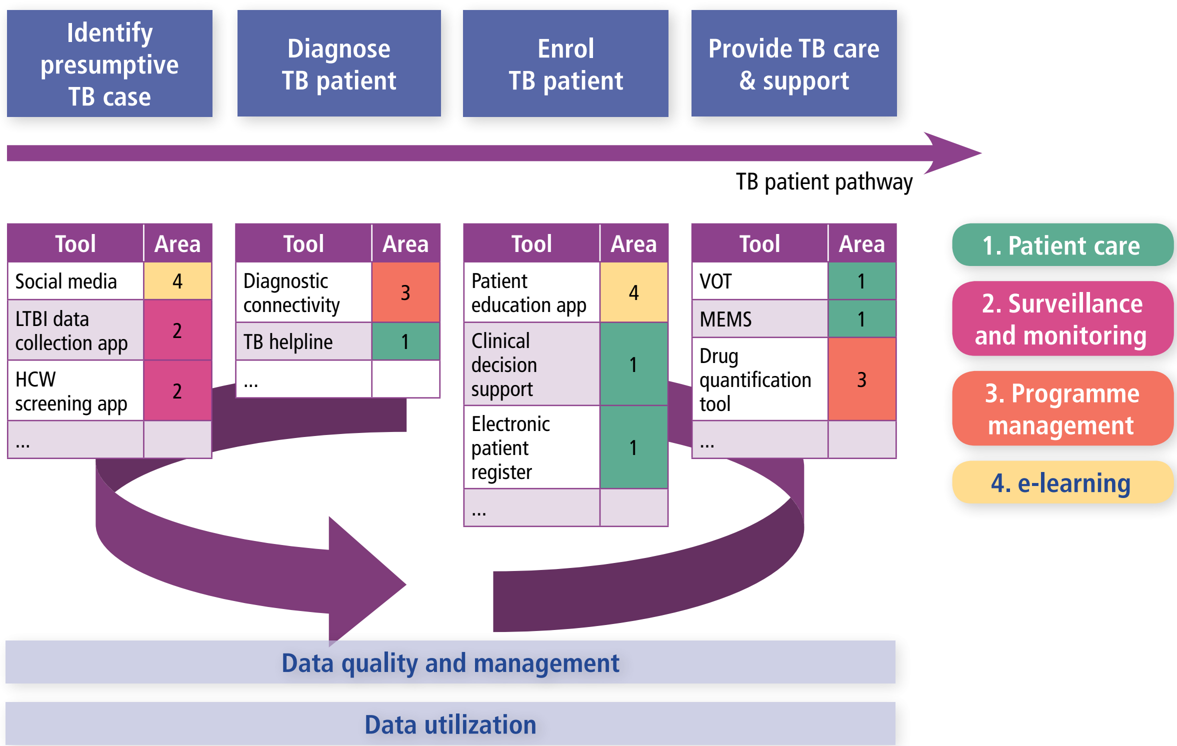
The stakeholder framework lists all relevant stakeholders, and describes their roles and contributions to digital health in the country (*see* Annex II). After completion, the stakeholder framework is used to assess where gaps exist, and if partnerships with new organizations will be beneficial to the current and/or planned activities for implementation of digital health technologies.

1.4 Digital health activities framework

Once the country situation has been described and all relevant stakeholders have been identified, the digital health activities framework can be used to show which digital health solutions are currently employed in-country, where they are being used, and to identify opportunities for implementation of new solutions. The framework also considers existing digital health solutions in other health programmes and provides a summary of previous digital health programmes, including their status, level of utilization, results achieved, and which partners and organizations have been involved. It is recommended to invite stakeholders from all relevant disease programmes when completing the framework, as other sectors might add valuable experience in applying digital technologies to common problems (e.g. data management or medication adherence).

By categorizing the different digital health solutions by the four functions identified in the WHO "agenda for action" for digital health in TB *(4)* (*colour-coded in* Fig. 1.1), one can more easily visualize if technologies are clustered in a particular area and missing elsewhere. It also illustrates how integration and interoperability between different steps in the patient pathway are addressed. It is conceivable that a number of systems could service more than one area (e.g. an electronic patient register may be helpful for both enrolment and care, and educational apps may cut across all four areas of the patient pathway). Data quality, management and utilization should be described for all implementation. An example of a digital health activities framework structured under four separate blocks in the patient pathway is shown in Fig. 1.1.

Fig. 1.1. Example of a completed digital health activities framework [adapted from a framework of the KNCV Tuberculosis Foundation *(9)*]



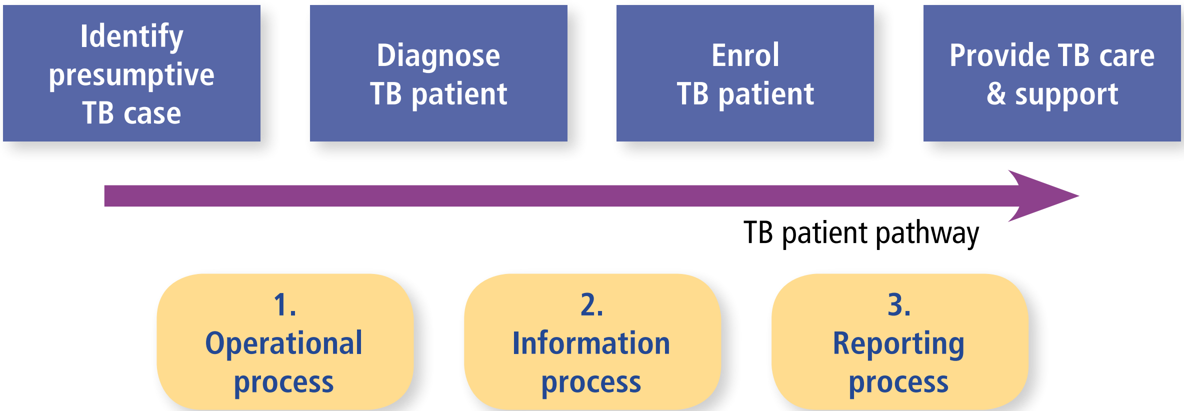
HCW: health-care worker; LIMS: laboratory information management systems; LTBI: latent tuberculosis infection; MEMS: medication event monitoring system; VOT: video-supported treatment for TB

1.5 Gaps and needs analysis of the TB patient pathway

Information collected during the country situational analysis, discussions with stakeholders and the digital health activities framework, when supplemented with observations and meetings during field visits, can then help identify gaps in the patient pathway. This gives a better profile of the weaknesses in the current system, as well as the prioritization of gaps and needs in which digital health solutions could play a role. The gaps and needs analysis can either focus on all steps in the TB patient pathway or on a specific step (e.g. "Provide TB care and support").

When developing the gap analysis, it is proposed to follow the trajectory of a typical patient along the care pathway (Fig. 1.2). This approach helps to describe systematically the quantity and quality of the data underpinning the different processes *(10)*. It also enables a more appropriate selection of sites for observational field visits and a more complete description of the pathway. First, all operational processes (e.g. laboratory investigation requests, patient referrals for treatment initiation) as well as information systems and the reporting processes (e.g. access to electronic TB registers, data collection, utilization of information) are to be observed and described during field visits. Field visits should start at the entry points into the health system where presumptive TB patients are first identified, followed by visits to TB laboratories and TB dispensaries, hospitals, or other facilities where treatment initiation and management take place.

Fig. 1.2. TB patient pathway



Second, stakeholders and programmes involved with health conditions other than TB can also be consulted to have a broader overview of the systems. It is also important to engage with the private sector, which, in many countries, treats a large proportion of TB patients and which may be distant from the national TB programme. An in-country workshop can facilitate presentation of initial observations and visualization of all processes along the TB patient pathway to in-country participants involved in providing TB care and treatment. Stakeholders from different levels, such as TB specialists, TB regional coordinators, laboratory technicians, TB nurses, nongovernmental organizations (NGOs), patient representatives and other partners should be invited.

Finally, once the digital health assessment is completed, it should provide the necessary background information to identify opportunities and approaches for successful implementation of digital health solutions. Interventions usually aim to strengthen health systems by improving their effectiveness, efficiency or their quality, and very commonly, a combination of these dimensions. This is an important point to keep in mind when assessing the role of digital technologies within the overall health service structure.

1.6 Developing a national digital health agenda

The process for establishing the agenda starts by systematically identifying country-specific "digital health questions" from the gap analysis. These questions are then rigorously and transparently prioritized before they are disseminated to all key stakeholders involved in digital health technologies. This approach differs from the more conventional expert consultation by broadening the discussion with a multidisciplinary cross-section of national actors. Following this, the digital health questions are translated into TB digital health needs. In this process, it is important that the choices made are not built around technologies that are present or preferred by particular agencies but around the needs. Creativity is important, and the needs may translate into a commissioning of solutions best adapted to the local demand. It is crucial that an unbiased process is followed to ensure that any interests are declared and conflicts mitigated transparently. The ultimate goal is that the national TB programme acquires a plan of action that is likely to provide the workers and the patients with the best possible returns on the investment made. The agenda needs to articulate clearly with other planning structures in place, such as the national TB strategic plan or any "e-health strategy" governing policies on digital health in the public sector.

CHAPTER 2.
CHOOSING THE BEST SOLUTION

2.1 Introduction

Treatment of active TB typically requires the daily administration of a combination of medicines for 6 months to 2 or more years. Likewise, the shortest treatment for latent TB infection (LTBI) lasts 3 months, although daily treatment for 6–12 months is more widely used. Both first-line and second-line TB medications often cause adverse reactions, which may negatively impact upon the patient's treatment experience, leading to interruption of treatment. People with LTBI may have no manifestations of disease and such people may therefore be particularly at risk of not adhering to the prescribed treatment.

Erratic treatment adherence – even in patients who ultimately complete their medication – has unfavourable consequences, including the protracted spread of infection, prolongation of treatment, acquisition of drug resistance, chronicity of disease and death *(11–13)*. Interventions to improve adherence have traditionally targeted the health system, the social environment and patients themselves *(14–16)*. The most widely known means of ensuring adherence has been in-person directly observed treatment (DOT), either at the health facility or the patient's home. Evidence for the effectiveness of DOT has been disputed *(17, 18)*. National tuberculosis programmes (NTPs) have struggled with various challenges in the field to ensure repeated face-to-face encounters over many months. DOT impacts substantially upon other competing activities in a patient's life, and is often considered patronizing. The current mainstream view is to consider DOT within a package of different options to support patient-centred treatment *(6)*.

In recent years, patients and health-care providers have taken advantage of the improved global access to information and communication technologies (ICT). Scalable, ubiquitous and increasingly affordable ICT is destined to keep diversifying the modalities of communication and will thus influence approaches to adherence support and monitoring. For instance, MEMS boxes do not only provide patients with a means to remember to take their medication but the dosing data that the device generates can alert the health-care provider to risky behaviour patterns in time to take action before treatment is interrupted. Action will commonly involve a physical encounter to discuss common adherence issues such as the management of symptoms, motivating the patient to complete treatment even if feeling well, guidance on proper drug usage and dosing, understanding and responding to adverse drug reactions, ensuring an uninterrupted supply of medication and scheduling clinic visits. During the same interaction, other health conditions relevant to overall outcomes, such as smoking and HIV, may also be addressed.

The integration of TB care into primary health care may present opportunities to deploy and study ICT solutions for conditions other than TB. A holistic approach that integrates digital technologies in different processes of health care is desirable *(19)*; hence the importance of a proper landscape analysis ahead of implementing a solution (*see also* Chapter 1). As various digital health products have been developed in support of various components of TB programmes, such as electronic medical records and mobile applications to educate patients and health-care workers, it is important to validate the appropriateness of these products, as well as optimize their uptake on a larger scale. Challenges are emerging for national authorities to track the many different digital initiatives mounted to improve TB prevention and care efforts, missing out on opportunities for collaboration and risking the underuse or wasteful parallel development of tools with a similar purpose.

In this section, we describe the main elements that would help implementers to choose the best possible digital solution(s) for TB treatment adherence support from the approaches that have been deployed and studied most widely in recent years, and which are most amenable to large-scale roll-out, even in settings with limited resources.

2.2 Three solutions and the associated evidence base

Data reviews ahead of a 2017 update of the WHO *Guidelines for the treatment of drug-susceptible tuberculosis and patient care* identified three digital technologies – SMS, MEMS and VOT – for which studies had been completed among TB patients and that were well positioned to support daily TB treatment on a large scale *(6, 20)*. In this section, the focus is on the relative strengths and weaknesses of these technologies in their most common form today.

2.2.1 SMS

SMS is a standard, built-in function native to all types of cellphones worldwide, and is generally inexpensive and easy to use. It is thus widely applied for communication with outpatients, either via regular, automated messages to take their medications, or by supplying information related to their health or condition (unidirectional), or by providing interaction about care (bidirectional). The potential impact of mobile phone texting in areas of public health such as smoking cessation, antiretroviral treatment and chronic diseases generated widespread interest and led to multiple studies and evidence reviews, inclusive of TB treatment more recently *(20–24)*. Although SMS-based interventions have been reported to improve medication adherence in studies of persons with non-TB conditions – particularly when used interactively *(25)* – three recent randomized controlled trials (RCTs) in different geographical settings did not show that SMS reminders improve TB treatment adherence over the standard of care *(26–28)*. These studies included a variety of DOT components in their control groups and had reasonably high levels of adherence overall. More studies on patient reminders and interactive approaches are currently under way *(29–31)*. However, research has yet to look more creatively at how SMS can influence adherence behaviour other than by reminding people to take their pills, such as by channelling cash transfers when milestones are achieved, by combining SMS reminders with other digital solutions and by targeting other points along the patient pathway *(25)*. Interactive SMS communication with patients, for instance, has the potential to triage patient care in real-time, thereby improving the quality and efficiency of patient support between in-person visits *(32)*. The popularity and affordability of SMS present a compelling case why further studies are needed to investigate its potential more exhaustively.

2.2.2 MEMS

MEMS aim to provide more patient flexibility when following up medication; to support patients with dosing and refill reminders and instructions; and to compile patient-specific dosing histories to enable counselling and differentiated care. Currently available MEMS fit into one of two categories: electronic medication boxes and sleeves to fit a blister package.

MEMS boxes consist of automated electronic devices that record and inform the health-care provider about the regularity with which a medicine container is opened. Older devices recorded usage on the container itself, but mobile telephony now allows patient reminders and alerts to the caregiver to be emitted swiftly when medicine boxes remain unopened for a day or more. The use of affordable, scalable types of MEMS medication boxes for TB patients has been studied under programmatic conditions in

China. Some studies have looked at the accuracy of MEMS dosing, the correlation between the opening of MEMS devices and actual ingestion of medication by patients *(33)*, and the acceptability of MEMS by both patients and providers *(34)*. In addition, a large (4500 patients) cluster-randomized trial showed a statistically significant effect of MEMS on adherence relative to the standard of care; however, the effect on successful treatment completion was less clear *(26)*. Another randomized trial with 3800 patients in 24 clusters will follow up with patients 6, 12 and 18 months after treatment to evaluate the impact on health outcomes of this MEMS-enabled approach, including a cost–effectiveness analysis *(35)*. Preliminary results from this study are expected in late 2018.

MEMS sleeves are a newer variant consisting of medication blister packs fitted with custom envelopes on which is printed a unique series of phone numbers that are disclosed only when the pills are expressed from their packaging. The patient is expected to dial these toll-free numbers daily in the sequence that they are revealed, thus providing the receiving end with a patient-specific dosing history that can be used to verify adherence. The main prototype of this system – 99DOTS *(5)* – is being implemented on a very large scale in different TB/HIV and drug-susceptible TB (DS-TB) treatment sites in India (e.g. in the public sector in Mumbai). The feasibility and acceptability of 99DOTS among patients and providers was the subject of small-scale evaluations primarily in Samastipur, Bihar *(36)*. An ongoing study, conducted by India's National Institute for Research in Tuberculosis, is assessing the acceptability and accuracy of 99DOTS-compiled dosing histories, and validating with random testing of urine for isoniazid in 825 patients in Mumbai and Chennai. Results are expected by mid-2018. In addition, evaluations of the impact on adherence and final outcomes of 99DOTS versus daily self-administration of fixed-dose combinations (FDCs) supplied each month will be conducted in both the private and public sectors in India. Results are expected by the end of 2018.

2.2.3 VOT

Remote video communication to deliver care can reduce the inconvenience of frequent travel for health-care visits as well as the risk of exposing other individuals to TB while still infectious, thus saving resources for both patients and the health service provider *(37, 38)*. While earlier solutions envisaged the use of landline for videophone linkage, the availability of Internet-enabled smartphones and tablet computers equipped with free and/or customised video communication software has increased options for both real-time (synchronous) and recorded (asynchronous) interactions *(39, 40)*. Two observational studies of VOT for TB treatment from high-income settings suggest that the technique can produce similar outcomes to in-person DOT *(41, 42)*. Two RCTs of VOT in London and the Republic of Moldova, recruiting about 100 and 200 TB patients, respectively, in the intervention arm, are expected to publish their findings shortly, while other studies are currently under way *(43–45)*. Given the potential benefits of VOT, studies are needed that evaluate VOT versus actual standard of care (typically self-administration of treatment) and evaluate the acceptability of VOT in different population subgroups – particularly among adolescent girls and women – and in various high-burden and resource-limited geographical settings.

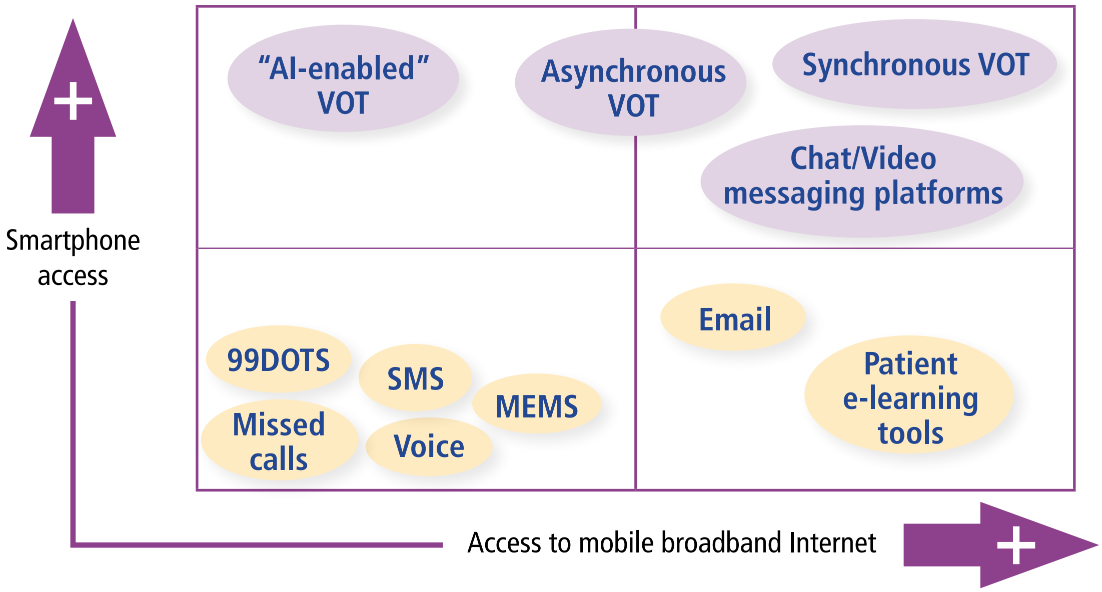
2.3 Implementing SMS, MEMS and VOT

This handbook aims to translate the findings of research and case studies on digital technologies into advice that helps implementers to adapt such solutions to the realities of the field. Trials are mounted to test whether a technology will work under controlled conditions and their impact is quantified using objective methods. However, it is not feasible for programme managers to replicate trial conditions under the usual field conditions. Health-care practitioners and patients interact in uncontrolled, real-life settings and thus need practical aids that are appropriate for and adaptable to distinct time points and environments. Adherence support technologies should be part of an integrated approach complementing the delivery of quality care. For example, it is unrealistic and undesirable for patients on a longer multidrug-resistant (MDR)-TB regimen to be placed on exclusive VOT for two years. The risk of interruption is not uniform during the treatment period or between patients. A singular solution may therefore be warranted only at particular points in the pathway. Special attention is needed when there is a change in the treatment regimen with the attendant risk of adverse reactions; when the patient questions the need to continue the prescribed treatment as symptoms disappear and she or he feels better; when the patient travels to a location remote from the usual treatment centre; or when other events overshadow the centrality of daily treatment among a patient's other routines.

The three digital products discussed have individual strengths and weaknesses, which determine their suitability for distinct circumstances, as well as the preferences of the patient and health-care workers. Based on the different characteristics of each of the adherence technologies and the patient's individual situation, multiple options might be suitable. Two external factors are critical to decisions on which products to propose: access to smartphones and to broadband Internet via mobile subscription. Fig. 2.1 maps out where different variants of the three products described in this handbook are roughly expected to be placed on an incremental, two-dimensional scale of these two factors. This matrix does not capture all possible determinants of large-scale impact (e.g. distribution of TB patient burden or user proficiency to operate the technologies), but some of them may vary in the same way as the two resources plotted in the graphic (e.g. smartphone literacy is expected to increase as these devices become more commonplace). Smartphones and tablet computers, given their advanced computing power and storage space, could be a valuable resource for multiple aspects of TB care important for continued adherence even when (mobile) broadband Internet is unavailable or erratic (e.g. recording asynchronous VOT, storage of patient medical records and patient education). Technologies such as SMS and MEMS – which can operate without mobile broadband Internet coverage – are currently the most accessible, affordable and scalable adherence approaches in resource-limited settings. Where (mobile) Internet is reliable and hardware available, solutions with more connectivity requirements can become additional options. Fig. 2.1 also plots other complementary applications that can support the three focus products of this handbook: voice and "missed calls" with the lowest phone/Internet requirements, and email and e-learning apps that require more resources.

The increasing range of technologies available to assist treatment adherence is conducive to the goal of patient-centred, differentiated care *(46, 47)*. Nonetheless, digital technologies are still to be regarded as tools that take advantage of today's powerful communication to strengthen the rapport with the patient: they are not end-to-end solutions in care. Another important consideration is that all the digital technologies discussed are premised upon the regular observation of a person's behaviour in order to follow up adherence: this poses a number of ethical issues *(47)*. The form and degree of intrusiveness differs by technology, varying from receiving a daily SMS text message to which a patient may need to reply, the automated monitoring of the opening of a medicine box, or the video observation or recording of the taking of medication. The benefits of having a more objective record of dose intake and increased opportunities to interact with patients has to be balanced with the potential downsides, such as patient perceptions of coercion, loss of individual control, a sense of being tracked and distrusted, and concerns on confidentiality. These issues need to be discussed at length with the patients, who may have very divergent views about external monitoring. Additionally, other factors to consider when determining eligibility include the ability and willingness to learn to use and manage the technology, and patients' constancy in adherence during the entire course of therapy. For instance, severe visual impairment may create difficulties for certain patients to follow the steps needed for VOT and 99DOTS without assistance and therefore another solution may be more appropriate. Longer-term acceptability has been demonstrated with weekly SMS and phone support of patients undertaking HIV treatment *(48, 49)*, although this has yet to be shown for TB treatment. Likewise, the long-term persistence of patients to call 99DOTS numbers each day or recording and sending video files daily has yet to be studied.

Fig. 2.1 Minimum requirements for adherence approaches



AI: artificial intelligence; MEMS: medication event monitoring system; VOT: video-supported treatment for TB

The major considerations that govern the selection of digital solution(s) are listed more exhaustively in Annex III *(see also (50))*. The different considerations will help the implementer think through the relative strengths and weaknesses of each option in terms of the following five domains:

1. Is there a **matching of goals** between the needs of the programme and the technology?
2. Which **functional features of medication adherence** does the technology best support (e.g. direct observation, real-time interaction, patient counselling and support, personalization of treatment regimen and dosage, patient report of adverse reactions, differentiated care)?
3. How mature is the **product development** on a range from concept stage to a full-fledged product available in differentiated variants?
4. Are **operational requirements** for the system to function realistic for the given context (e.g. feasible; affordable access to electricity, cellular networks, Internet and server; training needs; language)?
5. What **evidence** exists for the functionality, effectiveness, efficiency, quality and other aspects of the technology?

2.4 Overview of the digital solutions for adherence support

2.4.1 SMS

Objective

- SMS is used by the health-care provider and patient to communicate regularly. The exchange may be either one-way (e.g. automated SMS sent regularly to the patient) or two-way (e.g. patient responds to SMS by sending another text or by phoning).

Solution

- In most situations where SMS is employed in support of medication adherence, a standardized message is sent to the patient following a specific timeline or upon triggering by a specific event. The patient is then expected to respond to a series of actions, which may include an acknowledgement of SMS receipt.
- By its nature, SMS, even when sent and received on a daily or fairly regular basis, cannot be expected to replace an in-person clinical encounter or an observed dose. SMS reminders have been shown to not increase efficacy compared with the standard of care in different settings. Therefore, if SMS is considered for the support of TB patients on treatment, one needs to think beyond automated reminders (Box 2.1).
- In patients unable to attend in-person health visits regularly, SMS can help flag problems as they arise. For instance, the patient can use SMS for a "chat" session. If the issue is not solved, it can be triaged into a more intensive communication, using voice, video or an in-person visit.

Activities

- Prior to the start of medication, the patient and health-care worker discuss the expectations and use of SMS as an option in the treatment plan.
- The discussion needs to cover the objectives and procedures to be followed to handle the eventualities, such as anticipated delays in reply; "fall-back" options if SMS communication fails; and expectations around time of day and contact person who the patient can phone for follow-up support if this utility is not in-built into the phone application.
- There are three main options to offer SMS interventions:
  - native texting application on the mobile phone, an inbuilt feature of all cellphones, operating via subscription mobile telephony network;
  - third-party messaging software installed on smartphones – such as Facebook Messenger, WhatsApp and Viber – operating via subscription data services or wireless Internet (WiFi);
  - customized, dedicated application created specifically for TB care support. The advantages of this approach include: the ability to be modified to address programmatic needs; inclusion of additional features to the basic text message system (e.g. elaborate background information on TB and its care); protection of sensitive patient information to address confidentiality issues, which are of particular concern in health care; development of a dedicated system to manage SMS, including summary dashboards on patient history of adherence available on the health-care worker terminal; and compatibility and interoperability with an electronic patient register. The downside of this option is that the programme needs to apportion time and funds to develop, test and optimize the application ahead of use, and keep it serviced.

- Other logistical matters need to be worked out to ensure clarity. Understandably, patients usually want to know who is paying for the hardware, networks and communications. Many patients nowadays own at least a feature phone with inbuilt texting application. Some people might not own a phone or may own a SIM card but share a phone with others. The TB programme needs to cater for these different situations. In some interventions, TB programmes have lent or donated phones plus SIM cards; others have restricted their projects to the provision of a toll-free SMS or phone service on the understanding that the patient will use her/his cellphone.

Subactivities

- Additional provisions may be necessary for the following:
  - an acknowledgment of receipt of the SMS or confirmation of action taken, requiring the patient to respond actively;
  - interaction with other digital technologies in use (e.g. linking up with a MEMS, an electronic patient register or VOT);
  - integration of a patient enabler function (e.g. vouchers for transport or food basket; conditional cash transfers in reward of milestones achieved).
- If a special-built SMS product is created, it could incorporate a mechanism to collect feedback on experience of use by both the patient and the health-care provider. Some of this information could be gleaned from the "back-end" of the programme but a possibility to gather user opinion could be helpful, so long as this does not compromise on the primary purpose of the app.
- Objective data collection practices will enrich the current knowledge base about the feasibility and potential roles of SMS in care. Adherence to good practices in observational study data collection and reporting allow for experiences to be documented in a more standardized manner *(51, 52)*. Such lessons would be important for communicating widely as they could guide programmes elsewhere, and for facilitating further research.

Status and country experience

SMS interventions for TB care have been piloted in several high- and low-resource settings, and are likely to be driving many of the digital health interventions in TB care, both public and private (Map 1). However, there is as yet no known example of broad national scale up or countries with a policy for its use at this time. In countries where populations affected by TB have limited access to smartphones, Internet or network data, SMS may be the only digital option widely available. But even where Internet data services are widely available, SMS remains the only viable option for the vulnerable fringe of patients without ready access to more advanced means of communication.

In many countries, TB care is often not fully integrated into primary care, specialized care or the private sector, so there is an opportunity for TB programmes to tailor SMS and other digital interventions to the specific needs of TB care. Nonetheless, common comorbidities such as HIV infection and diabetes may require concerted action with other efforts at employing digital technologies. Provision and financing of SMS-based digital health services can either be publicly provided, or via public–private partnerships. Opportunities may also be created by other services available on the same phone that the patient uses: one such example is mBanking and mobile money (e.g. TIBU in Kenya *(53)*). In addition, TB notification and patient medical history data may also be required to link or send to facility or regional/central-level databases.

Box 2.1. "Beyond reminders": exploring the role of SMS in support of TB treatment adherence

Author

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Background

Use of digital technologies such as SMS in the treatment of HIV, TB and other conditions is based on the premise that when today's communications are used well they can improve the effectiveness, efficiency and quality of health services, and have a positive impact on population health. Worldwide, billions of mobile texts are exchanged each day, making SMS the most widely used means of data transfer. Its low cost and its ubiquity on all cellphones make it one of the likeliest means of reaching patients across income groups, including the vulnerable fraction of the population. However, three recent RCTs in Africa and Asia looking at SMS reminders to TB patients to take their daily medication failed to show improved patient-important outcomes at the end of treatment. Another RCT investigating SMS in support of LTBI treatment in Canada also showed no clinically important effect on treatment completion, although people on SMS support were less likely to present to a health facility for adverse drug reactions but more likely to report them earlier. This indicates that the digital intervention may be fulfilling unmet needs in patient information and reassurance.

Objectives

Develop, implement and scale up evidence-based interventions to help people complete TB treatment using SMS technology available on the most basic forms of cellphones in use globally.

Description

An SMS-based intervention is proposed to study if the technology can improve treatment adherence, beyond the reminder function for which it has been largely deployed up till now. The intervention is based on the principle that structured, interactive communication with patients can improve one or more dimensions of care, and the fact that SMS is ubiquitous and likely to be used. A mobile phone platform would allow multiple functions, including the registration of patients via their mobile phone numbers; regular contact with patients via SMS, prompting them to report any problems that can be followed up by the health-care provider with SMS, voice or video (if using a smartphone); scheduled messaging for clinic visits, testing, refills or other timed events. Providers can communicate with patients, complete a medical record and set alerts for shared clinical management. The provider interface employs a secure server to handle data. It can operate via SMS data packets or switch to Internet when available. The design conforms to international security standards and is built for scale, with the ability to add new clinics and programmes rapidly.

Main outcomes

Impact will be measured in relation to effectiveness (medication adherence and/or final treatment outcomes), efficiency (cost–effectiveness) or quality (quality of life and patient/provider satisfaction).

Lessons learnt

The concept builds upon the successes and failures of past SMS studies of patients treated for TB, HIV and other diseases, and RCT findings of SMS used as a means to stay in touch with people living with HIV starting ART in Kenya *(32, 59)*. It is supported by other data emerging on the utility of this approach in the management of other conditions such as problem drug use, maternal and child health, and bronchial asthma. Trials among different patient groups suggest that the bidirectional nature of an intervention is a critical determinant of adherence *(25, 60)*, and that simple reminders and one-way messaging are less likely to be effective.

The proposed concept is expected to be particularly suited for TB patients receiving integrated HIV care, care for accompanying comorbidity and treatment during pregnancy.

Expected challenges include the programmatic desire to implement in-person DOT at any sign of non-adherence. VOT and MEMS may be appropriate for some patients or during certain times in their treatment but their availability may be restricted (e.g. lack of trained persons, unavailability of hardware, broadband Internet limitations). Future generations of the product could profit from new methods being tested out to analyse large amounts of data.

Conclusions

SMS-driven patient support is worth exploring more thoroughly, given that the underlying technology offers clear advantages of simplicity, low-cost and popularity, as it is available on all mobile phones. A concept is proposed on how to test out three key functions on the patient pathway – registration, check-in and scheduling – which are important for adherence and good-quality care. The intervention would be delivered as an integrated mobile-phone application, accompanied by a strong component for the gathering of evidence for continued improvement, and to assess which dimensions of final outcome the technology is likely to influence. A target product profile (TPP) will be created outlining a concept that can cover these features.

2.4.2 MEMS

Objective

- Two types of MEMS are in common usage for TB care today (*see also* *Section 2.2.2*):
  - A **MEMS box** consists of an automated pill container that emits audible and visual alerts to remind patients to take medication or to request refills. The device can also register the patient's pattern of opening the box, providing the caregiver with an instant record of usage patterns, and allow swift action in case of non-adherence.
  - **MEMS sleeves** (as per 99DOTS prototype; *see* 99DOTS.org) where the patient is required to dial toll-free numbers daily upon removing pills from a blister package.

Solution

- In the most automated form of MEMS, the patient is provided with a battery-operated medication box which, depending on the model, transmits a signal to health-care providers either when it is opened or when it remains unopened for a given time (Box 2.2). The box is typically split into compartments for the different medications, is equipped with light-emitting diodes (LEDs) and printed dosing instructions. It emits alerts when dosing or refill is due and these signals are transmitted to the health-care provider either by direct download via universal serial bus (USB) when the patient visits the facility or over a phone network using a SIM card *(54–56)*. The charges for SIM card operation and for maintenance of the medication boxes are typically borne by the service.
- For 99DOTS, patients receive their TB medication blister packs ready fitted with the paperboard envelopes containing the toll-free numbers *(5)*. In India, the envelopes and associated ICT requirements cost less than US$ 1 per patient per month. These envelopes are also printed with

graphics and pictograms to promote proper use. The provider keeps the call-in record of the patient to monitor adherence.

- The fundamental assumption behind both forms of MEMS is that once the box or packaging is opened, the medication will be taken by the patient. One study with more than 400 TB patients in China has reported a correlation between medication monitor records of "pill in hand" and levels of rifampicin in urine samples tested at random *(33)*. The correlation between 99DOTS call-in records and ingestion of TB medication is currently being evaluated in India.

Activities

- The health provider supplies the patients with the MEMS box containing their medications or medication blister wrapped in 99DOTS envelopes.
- Both the health-care providers and the patients are trained in their use.
- Patients use the equipment as instructed on a daily basis and the health-care provider remotely monitors adherence. A desktop or mobile application with an adherence calendar for the health-care provider supports targeted counselling per patient.
- The same ICT platform may integrate the outputs from both MEMS boxes and 99DOTS (*see also* Box 2.2). This enables providers to handle data from a mix of patients on different devices and also to shift patients from one device to another without disrupting the indicator information. For instance, patients on treatment for DS-TB may be using 99DOTS and others on treatment for MDR-TB might be using a MEMS box.
- If the patient has not opened the MEMS box or called the unique 99DOTS toll-free number, the patient can be reminded by SMS or a voice call to take medication.

Subactivities

- A logistics chain must be in place to guarantee an uninterrupted supply of MEMS containers and service any technical faults that may develop.
- The 99DOTS envelopes need to be produced, delivered and fitted to the blister packs, which should be available and in use in the country. Additionally, the free phone service must be organized and kept in good working order.
- It is important to make sure that data are routinely collected on the indicators of system performance and malfunction, progression of and adherence to treatment, as judged from usage of the devices.

Status and country experience

- The State Council in China has adopted the MEMS box as part of DS-TB and MDR-TB case management for the NTP in 2016–2020. It is planned to scale up use of the device countrywide. A national tender process has been completed and deployment is expected to commence by the end of 2017. The deployment plan involves a stepped scale up in three provinces, involving about 60 000 patients over 2017–2018.
- 99DOTS is being scaled up rapidly in India for HIV-associated TB and DS-TB patients and implementation is ongoing in Myanmar.

Box 2.2. Two MEMS approaches with large-scale implementation potential in high TB-burden settings

Authors

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Background

Populous countries such as China and India bear a large proportion of the global burden of TB disease and death. In many high TB-burden countries, care services are becoming more decentralized, making it increasingly important to provide workable solutions to help patients complete their treatment. Achieving the WHO End TB Strategy targets for end-of-treatment success in both DS-TB and MDR-TB patients will require more action on treatment adherence.

MEMS boxes with special closure that records the time and date whenever the container is opened have been in use since technologies to monitor the usage of pill containers were pioneered several decades ago in an effort to improve TB medication adherence. More recently, it has become feasible to equip such devices with digital means to alert patients to prescribed treatment and inform health-care providers about usage by remote connection. Increased affordability of ICT is making it possible to mass-produce and roll-out MEMS boxes appropriate for TB at large scale even in resource-limited settings. A MEMS approach using sleeves - 99DOTS (*see also* 99DOTS.org) – is also been deployed on a large scale. The diversity and quality of evidence underpinning their use is steadily increasing through both RCT and observational study data (*see also* Sections 2.2.2 and 2.4.2 in the main text).

Objectives

Tracking the large-scale implementation of MEMS technologies in high TB-burden settings

Description

MEMS boxes and 99DOTS are being rolled out on a large scale to improve TB treatment adherence and outcomes. Customization of the technologies to the local needs is key to wider adoption. evriMED™ (www.evrimed.com) is one example of a MEMS box developed specifically for TB care in resource-limited countries through funding by the Bill & Melinda Gates Foundation (BMGF). The system can be customized to the specific needs of patients on treatment for DS-TB, MDR-TB and TB/HIV. Its prototype is also being used in trials of MEMS for TB *(35)*. One variant of the evriMED is the Easy Cure Box being used in India, which consists of a lightweight cardboard container housing a battery-operated electronic monitoring device that passively registers when the container is opened. Inside the box is a supply of TB FDC medication in blister-packs. Patients are given multiple days of medication upon refill and monitored remotely using an ICT interface. With 99DOTS, the FDC blisters are packaged in a custom envelop printed with phone numbers that are revealed each time patients takes their medication (*see also* Section 2.2.2). This approach is widely used across India.

The dosing histories generated by the two technologies enable health providers to identify good and poor adherers to provide highly effective counselling, and thus use healthcare resources more efficiently and effectively.

Main outcomes

RCT data from China have shown that MEMS boxes can improve TB treatment adherence *(26)*. China and India are deploying MEMS technologies on a vast scale for both DS-TB and MDR-TB patients. In China about 60 000 patients in three provinces are expected to be provided with MEMS boxes in the coming two years. In India, more than 50 000 patients were using 99DOTS by November 2017, and an additional 250 000 patients are expected to be enrolled in five states by early 2018. About 2000 MDR-TB patients are expected to be supported with MEMS boxes in 2017–2018.

Integrated user interfaces that can combine data from different types of MEMS are being tested in DS-TB patients in the private sector in Mumbai and Patna, and in MDR-TB patients in the public sector in Chennai.

Lessons learnt

MEMS interventions should place a minimum demand on the skills of patients and providers to operate them. Training of providers and patients on the use of the devices needs to be straightforward and supplemented by aids to enhance proper use (e.g. pictograms; *see* http://thearcadygroup.com/resources/medication-monitor-staff-training-guide_india/).

MEMS boxes and 99DOTS currently in use in India are being integrated into the national electronic notification system for TB – Nikshay system (http://nikshay.gov.in/AboutNikshay.htm). The unique (IMEI) number for the MEMS box is linked to its user's identification number on Nikshay.

The experience thus far has also demonstrated the feasibility and acceptability of integrating 99DOTS with the medication supply chain and associated treatment protocols. In situations where 99DOTS cannot be used due to the lack of regular access to a telephone or during the initial phase of treatment of MDR-TB with an injectable agent, triaging patients to the best suited MEMS variant is being explored.

Counselling is also key to the understanding of patient barriers to adherence and to take appropriate action. More automation could further help providers consolidate, monitor and act on the dosing histories. Counselling to prevent patients from interrupting treatment upon early signs of risk remains ad hoc and could be triggered via automated analysis of the dosing records.

Conclusions

As in other fields of digital health, MEMS for TB care is an area where rapid development has occurred in recent years. The technologies that run MEMS have diversified to include boxes equipped with electronic monitoring and other approaches like 99DOTS. The evidence of the impact of MEMS on adherence is accruing. MEMS technologies are currently being implemented on a very large scale in countries with the highest caseloads of TB in support of the objectives of the End TB Strategy. The experience of their use in different patient groups will be valuable for implementing the devices in other low-income and high TB-burden settings.

2.4.3 VOT

Objectives

- Video communication between patient and health caregiver, live or self-recorded, is used to emulate a physical encounter and to enhance TB medication adherence and treatment completion.

Solution

- Communication is mediated primarily through Internet-enabled smartphones or tablet computers. The use of other hardware such as desktop computers, laptops and videophones is also possible.
- Of the three digital solutions discussed in this handbook, live (i.e. synchronous) VOT is the closest approximation of a physical encounter, given that it allows both interactive visual and verbal communication. However, it has a number of requirements that may severely limit its feasibility in low-resource settings. Live VOT depends upon the availability of advanced mobile computing technology, which is often not available to many TB patients; reliable broadband Internet on the side of both the caregiver and the patient; and the flexibility of both the patient and caregiver to time their encounter when they are both available. A common workaround for some of these challenges is to use asynchronous VOT (recorded video). This limits the interactivity of live sessions, but is partly mitigated by a utility inbuilt in some applications for asynchronous VOT, allowing the patient to alert the caregiver when counselling is desired.
- With asynchronous VOT, there is a risk that dosing is not correctly verified or even intentionally falsified. This element still needs to be evaluated.
- VOT interaction is not limited to observation of TB medication being ingested. It is also meant to create an opportunity to manage associated problems (e.g. adverse drug reactions, comorbidities). As with other adherence solutions, this would limit the burden on both the patient and the health services.

Activities

- Mobile broadband Internet via 3G or 4G or wireless broadband (WiFi) is a critical requirement for synchronous VOT. Asynchronous VOT could still be managed if Internet access is erratic during the day.
- A TB programme must decide which of the three existing options to implement VOT is the best suited for their needs, by weighing the pros and cons of each option (the tool at Annex IV helps in taking such a decision):
  - video messaging platforms that are often pre-installed on mobile electronic devices (e.g. Skype, WhatsApp, Viber);
  - a proprietary, licensed, application for VOT;
  - customized, dedicated VOT application created specifically for TB care support by individual programmes (*see also (58)* for an example of this).

Subactivities

- As with the other digital technologies used in TB care and prevention, VOT is expected to develop and change at the rapid pace at which ICT evolves. Future users will be informed by an expanding evidence base on its effectiveness in TB care and prevention, and in which areas of medication adherence the solution is most suitable. Continued collection of information using descriptions of user experience, qualitative studies and – where possible – quantitative designs would help to better understand the expected enhancements that could address quality of care, patient experience and implementation practicalities in TB programmes.

Status and country experience

- VOT can currently be envisaged only in selected settings provided with Internet connectivity, usually in urban and semiurban areas. In middle-income countries such as Belarus, this could extend over much of the territory (*see also* Annex V). However, in common with social media operating on Internet, synchronous and asynchronous VOT may still be possible when patients travel across national borders (*see also* Box 2.3).
- Another limitation to global expansion of VOT is access to hardware, although forecasts suggest that smartphone penetration in developing countries will drive the global expansion of mobile telephony and will outstrip access to the Internet. Advancement of technology could thus make it possible to perform VOT even where Internet connectivity is destined to remain poor in the foreseeable future. For instance, the recognition of the individual signature of a given patient taking specific medication can now be accomplished at the level of the phone using software enhanced with artificial intelligence *(57)*. This removes the concern of transmitting video files over the Internet (broadband requirements, potential confidentiality breaches) but can still allow the health-care worker and patients to track treatment adherence (*see also* Fig. 2.1).
- Belarus expanded a VOT programme nationwide following a small pilot study in the capital in Minsk in 2016 *(58)* (*see* Annex V). By September 2017, 231 DS-TB and MDR-TB patients had been enrolled in all regions of Belarus; 97% of all video sessions were deemed to be of good quality, and no phones were lost or traded by the patients (6 phones needed repairs covered by the warranty). Final treatment outcomes have been achieved for 61 patients (96% treatment success, 2% death and 2% loss to follow up), while 170 patients were still on treatment as of September 2017. While the findings are encouraging, VOT is available only for a small minority (5%) of the total TB patients on treatment.

Box 2.3. Experience with asynchronous VOT for TB in the United States and Mexico

Author

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Background

Videoconferencing with TB patients on treatment is recommended as one of the ways to support medication adherence *(6)*. The advent of videophones, computers and Internet-enabled smartphones in the past decade has diversified the range of options for offering video-supported treatment (VOT) in both high- and low-resource settings. As synchronous VOT is limited to the time when both patients and health-care providers are available, and requires a reliable Internet connection, researchers at the University of California, San Diego, pioneered an asynchronous VOT application for smartphones, which lets patients record and exchange videos of each medication dose with their health-care provider *(61)*. This approach has since been emulated elsewhere (e.g. www.emocha.com/) and is being studied in RCTs.

Objectives

A series of studies measuring treatment observation rates (dose observation fraction [DOF] = doses observed/doses expected) were conducted through TB programmes in the U.S. and Mexico to assess the feasibility, acceptability and patient perceptions of asynchronous VOT for monitoring anti-TB treatment adherence. Participant interviews assessed sociodemographics, behavioural risk factors, VOT perceptions and out-of-pocket costs. Patient characteristics associated with DOF were examined to determine the generalizability of VOT across TB patients. The U.S. sites included four urban and two rural TB programmes; one of the two Mexico sites targeted TB/HIV-patients. All sites included TB patients aged >18 years who had >30 treatment days of TB treatment remaining.

Description

VOT uses a Health Insurance Portability and Accountability Act (HIPAA)-compliant application that patients download onto a smartphone or tablet computer and register in a web-based Client Management System accessed by TB programme staff. Following a two-week run-in period of in-person DOT to ensure that patients can tolerate their treatment regimen, patients are trained on how to record themselves swallowing each medication dose in a verifiable manner. As soon as the patient stops recording, the application encrypts the date/time-stamped video, uploads it to a secure server through cellular or WiFi networks, confirms delivery, and deletes the video from the device. When a network connection is not present, recording is still possible; the encrypted video files remain on the device and repeated upload attempts are made automatically until the video is delivered. This automated process makes it simple for the patients to operate and lowers the risks of modification, deletion or repeat sending of videos. Once delivered, TB programme staff view videos through the Client Management System to observe and document each dose taken, as well as accompanying problems such as adverse drug reactions. Patients who do not send their videos or whose recording was uninterpretable are followed up and contacted by a case manager. The system also allows SMS and emails to be sent to patients when doses are due and after scheduled doses are missed. The Client Management System includes a treatment adherence record that can be printed or sent to electronic medical records.

Main outcomes

By 2016, 378 U.S. and 30 Mexican TB patients used VOT for 5.5 months on average (range: 1–13); age range was 18–87 years, approximately half had less than a high school education, and over two thirds owned a smartphone *(39)*. Mean DOF range was 81–96% across sites, and was comparable or higher than that of patients exclusively using in-person DOT. The only predictors of higher DOF were longer duration and ease of VOT use, fewer problems using VOT and foreign birth, indicating good generalizability of VOT across TB patients. The majority of patients reported that VOT was preferred over DOT, "very easy to use", more confidential than DOT, and they would recommend it to other TB patients. TB programme staff reported that VOT was feasible, took less time per patient and cost less than DOT. No differences were observed between urban and rural or U.S. and Mexico sites.

Lessons learnt

VOT enabled TB programme staff to quickly identify patients who had missed doses and provide support needed to ensure high adherence. Most TB programme staff could manage twice as many patients with VOT compared with community-based DOT, reducing staff and transportation costs, while patient satisfaction with their care remained high. While TB programmes only conducted DOT during business hours, asynchronous VOT made it possible to observe patients on weekends, holidays and after hours, as well as during travel. Thus, there were fewer self-administered doses that would have had to be made up resulting in earlier treatment completion. Increased autonomy through VOT also allowed patients to take medications closer to meals and bedtime, potentially reducing adverse drug reactions. While many patients possessed their own smartphone, loaning phones to patients without one is realistic, given that only 13% of loaned smartphones were lost, stolen or broken during the studies.

Conclusions

VOT is a feasible intervention to support TB medication adherence even in situations where Internet is only erratically available. Observations from higher-income settings where DOT is used regularly showed higher patient preference, reduced patient and provider workload, and lower programme costs, implying that VOT may replace in-person visits for at least part of the treatment period. More studies under different programmatic conditions (e.g. comparing VOT with self-administered treatment *(62)* or other digital technologies) would be helpful to inform prospective users.

CHAPTER 3. IMPLEMENTING A DIGITAL TECHNOLOGY FOR TB MEDICATION ADHERENCE

3.1 Introduction

Once a digital solution for medication adherence is selected, the implementation phase can begin. This chapter breaks down the general steps towards implementation, discusses practical programmatic considerations during this phase, suggests resources for further information, cites real-world experiences from deployment of digital technology solutions that support medication adherence, and points the reader to other resources for more in-depth information.

3.2 The general implementation phases

The previous chapters outline the process for conducting a landscape assessment on digital health, current evidence and use of SMS, MEMS and VOT, and how to choose between these technologies, given the specific conditions and needs of the programme. While the considerations for implementation in different settings vary, some programmatic issues recur as the most important enabling factors or barriers to implementation.

This chapter describes a step-wise approach to implementation based on four distinct phases:

- Planning (needs assessment, solution selection)
- Development/adaptation (configuration, implementation)
- Roll-out (piloting the project, training, scale up)
- Maintenance (monitoring and evaluation, project evolution and sustainability).

These four steps can form the basis of a costed plan. It is expected that the implementation of digital technologies for TB medication adherence will be an iterative, constantly evolving process due to the complexity of health and telecommunications systems, as well as progression of in-country infrastructure (Fig. 3.1). Project planning thus needs to be flexible in order to adapt to the fluctuations throughout the duration of the multiyear project.

3.3 Planning

A comprehensive *action plan* is developed to summarize the major project components and to help reach agreement among stakeholders on project aims[3]. The action plan needs to include the following elements:

a. ***System description.*** Describe the system objectives in full detail, including functional requirements (i.e. what the system aims to accomplish) and non-functional requirements (i.e. overall system

3 Various approaches to project management have been developed that can assist in planning. The PRINCE2 approach uses a Project Initiation Document *(63)*. The planning document for information systems proposed by PATH includes an example Work Plan in Annex 10 of *(64)*.

characteristics). The purpose of a system description is to form an understanding among all project stakeholders on project goals, objectives and scope, including where possible, what the system will *not* do. Different solutions target distinct aspects of TB medication adherence (e.g. monitoring dosage and/or ingestion events, patient education, communication with provider), so clarity on system objectives is essential to address health system targets along the patient pathway.

b. ***Concept note.*** Draw up a document that describes the main challenges to be addressed and presents the main justifications for the proposed digital solution. The note needs to describe how the proposed technologies will interact with or complement other solutions that are envisaged to promote adherence, or the "strategic fit" *(7)*[4]. For example, if MEMS is proposed, the concept note needs to outline how it will articulate with other activities with converging aims, such as simplification of treatment algorithms in national guidelines, staff sensitization and training, introduction of FDCs and patient enablers.

c. ***Roles and responsibilities.*** Identify all stakeholders and personnel participating in system development, piloting, launch and maintenance. This should include government agencies involved in TB prevention and care, such as the staff of the NTP and the Ministry of Health, private health-care providers as well as funding agencies supporting the project. Ethics clearance may be needed ahead of implementation and the national body responsible for bioethics is best consulted early *(47)*. For instance, certain interventions may pose novel problems on confidentiality, which are unfamiliar to the NTP (e.g. exchange of personal video recordings over the cloud). End-users of a system should also be defined both on the provider as well as the patient level, and engaged at all stages of implementation (*see also* Section 3.3.1). Oversight of the project would best be conducted by a steering committee. Clear hierarchies for decision-making should be established, particularly in anticipation of approval for major changes to the project plan.

d. ***Personnel.*** Describe all human resources needed for the project, including long-term employees as well as temporary contractors such as software developers, educators for training and technicians performing maintenance. Include in the description the duration and level of engagement for each of these groups during the project. Programmatic personnel such as project managers and staff should have clearly defined responsibilities such as administrative support, data entry, data management, analysis and reporting.

e. ***Financial.*** Develop short-term and long-term plans to cover costs throughout all phases of implementation. When the project is funded by multiple sources, ensure that all costs are covered across the various budgets. It may also be important to provide some leeway to account for currency fluctuations and inflation. Include contingencies, for example, to cover potential additional costs if implementation is delayed. Financial requirements will vary depending on the solution, the setting and other factors, but many key items need to be detailed (*see* Annex VI). The total cost of ownership of the project should be estimated across all phases of implementation, accounting for both recurrent and fixed costs. Long-term funding of the project needs to be identified to improve the chances of sustainability. This may need to be formalized through a memorandum of understanding with an agency willing to commit to this engagement. An approach that carefully factors in integrated actions that facilitate the common objectives is more likely to be sustainable in the long run and to attract domestic or external funding.

f. ***Project activities and timeline.*** List step-by-step details of all project activities, including elements such as key personnel involved, duration (i.e. start and end dates), anticipated milestones and major project deliverables. Attention should be given to training all system users, including technical and administrative staff, as well as health providers and patients. Scale-up phases should also be

4 The template used since 2012 by the Global Fund for its funding proposals can be adapted for this purpose *(65)*.

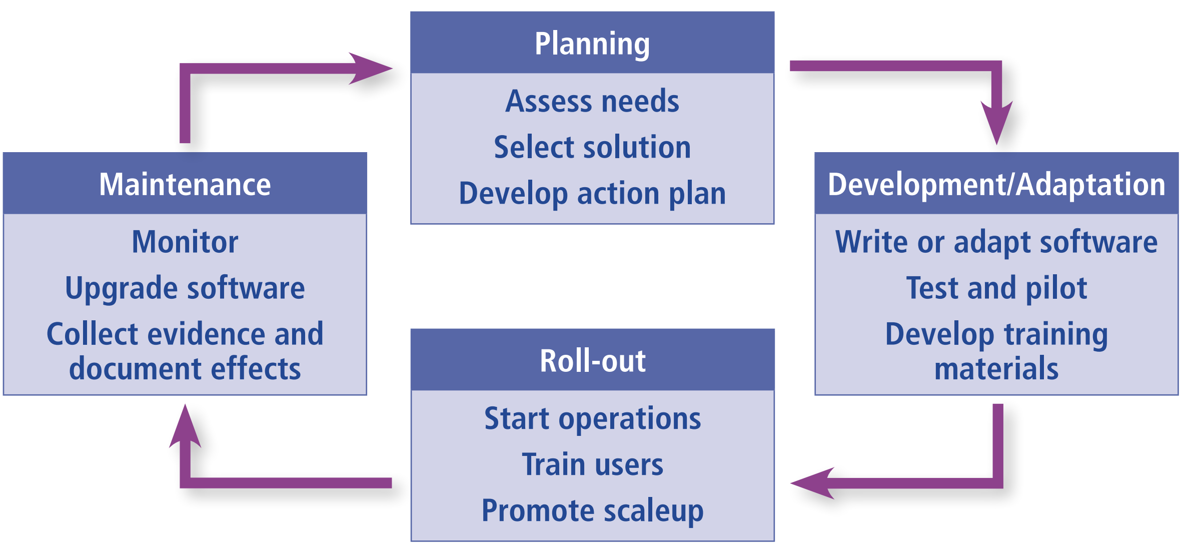
stipulated; for example, the expansion from pilot sites to regional and ultimately national scale. More details should be provided for the first year of the project, and broader five-year activities can be included to describe roll-out and maintenance efforts (*see* Annex V). Describe how the project will interact or overlap with existing paper-based or digital solutions, including (if applicable) plans for transitioning entirely to a digital system. Add guidance on whether any data should be concurrently recorded electronically and via paper, keeping in mind that any parallel systems/duplicate documentation would need to be tailed off over time to reduce workload and increase investment in the novel intervention. Timelines can be usefully plotted on a Gantt chart, with major milestones along a realistic calendar.

g. ***Technical document.*** A technical document that describes in more detail the features of the digital adherence solution helps to guide implementation and is particularly important to develop if locally built software is commissioned. This document could be in a TPP format *(7)*, with a description of the main product parameters in terms of requirements (connectivity, electricity, speed, devices, software, mobile network), anticipated lifetime and data management policies (encryption, data security, confidentiality, transmission, sharing, storage, server location, retention). An explanation on how the technology fits within the existing digital ecosystem should also be included. This document could be annexed to the implementation plan and together these are then used to gather stakeholder opinions, seek ethics clearance and so on.

h. ***Outcomes.*** Provide a description of anticipated outcomes or results. During the initial stages of the project, indicators will largely be process-oriented, while indicators for measuring the impact of the programme on health outcomes and TB programme efforts will need to be included in long-term assessments (*see* Annex VII). Additionally, impact indicators need to be identified to facilitate future research and generate evidence for impact on medication adherence and resource use. Choosing relevant, measurable outcomes can benefit policy development, given that current recommendations for the use of digital technologies in delivery of and adherence to TB treatment are conditional and based on estimates of effect, which are of very low certainty *(6, 66)*.

i. ***SWOT analysis.*** Include a SWOT (**s**trengths, **w**eaknesses, **o**pportunities and **t**hreats) analysis for the current digital health activities related to TB.

Fig. 3.1. The four-step cyclical implementation process used by Management Sciences for Health [adapted from Fig. 4.1 of *(67)*]



3.3.1 Lessons learned from recent experiences

- ***Stakeholder engagement.*** Meet with stakeholders early in the project development process to involve them in the planning process. Project involvement will vary, so initial clarification of different roles is important for project implementation. Stakeholders should include patients, health-care providers, government representatives from national laboratories, pharmacies and the Ministry of Health, technical/ICT staff and project staff. Conducting key informant interviews and focus group discussions among patients and health-care providers are among the general approaches to assess the eventual feasibility, acceptability and perceptions of a technology. Another approach is to hold a national workshop if the programme is intended to be rolled out nationwide. There may be a national authority responsible for a government digital or e-health strategy. Conformity of the adherence solutions to this framework is important *(68)*, and discussions need to encompass potential barriers to implementation related to infrastructure, patient-level factors, social environment and health-care services *(69)*. Early engagement will result in getting the most out of stakeholder commitment and involvement.
  - *Example #1 – VOT focus groups in San Diego and Tijuana in 2009 (70)*. Five groups of TB patients recently completing in-person DOT, and four groups of health-care providers participated in focus groups to evaluate the feasibility and acceptability of VOT. Facilitators described VOT, explained the parameters and constraints of the specific solution (e.g. only health-care providers could view the recordings), and a semi-structured interview guide was used to elicit feedback. Overall, both groups identified many potential benefits to VOT, felt reasonably confident in their ability to use a system if provided with adequate training, and indicated high levels of acceptability of such a programme. Recommendations on technical components to increase adherence as well as site-specific concerns such as network coverage were also acknowledged during the focus groups.
  - *Example #2 – Digital health in Kazakhstan*. A digital health workshop of stakeholders was conducted in Kazakhstan in May 2017. Attendees were split into four different groups to represent each step of the patient pathway (*see* Fig. 1.1). Groups were asked to list substeps, identify expected difficulties and provide some suggestions for improvement using digital technologies. Participants reviewed existing digital health technologies, conducted a needs assessment along the TB patient pathway, and discussed the opportunities for and feasibility of implementing digital health solutions. Digital health technologies for diagnostic connectivity, surveillance and monitoring, and treatment adherence technologies were highlighted.
- ***Collaboration.*** Other digital health systems may have been deployed in the same setting, and engagement with the developers and users of these systems may lead to opportunities for resource-

Box 3.1 Resources – collaboration

- mHealth Compendium Database. In: mHealthKnowledge [online database] (http://www.mhealthknowledge.org/resources/mhealth-compendium-database, accessed 2 December 2017).
- mHealth Working Group Inventory of Projects. In: Global Digital Health Network [website] (https://www.mhealthworkinggroup.org/projects/mhealth-working-group-inventory-projects, accessed 2 December 2017).
- Partners working on e/mHealth for TB. In: World Health Organization [website] (http://www.who.int/tb/areas-of-work/digital-health/partners/en/, accessed 2 December 2017).
- Global Digital Health Network [website] (https://knowledge-gateway.org/globaldigitalhealthnetwork).
- From principles to practice: implementing the principles for digital development. In: Principles for Digital Development [website] (http://digitalprinciples.org/from-principle-to-practice/, accessed 2 December 2017).

sharing, or in gaining feedback from lessons learned. Reaching out to other agencies and groups working on digital health solutions for TB or other health conditions could provide opportunities for learning lessons from previous or existing projects (*see also* Box 3.1).

- ***Project management.*** Hire an experienced project manager and decide on a formal approach to the project. Various certification programmes exist in project management such as PRINCE2, ITIL and PMP, but other project management resources should be consulted and are beyond the scope of this document (*see also* Box 3.2).
- ***Budgeting.*** Various budgeting templates are available and can be adapted to the project requirements (*see also* Annex VI). If the project is approved, changes may need to be made to the funding proposals to align them with the national TB strategic plan *(71)*, and the external donors to the TB programmes engaged to invest in digital technologies. Additional consideration must be given to these budgetary factors on the project timeline, as securing and disbursing funds may take a year or longer (*see also* Box 3.2).
- ***SOPs.*** Develop detailed standard operating procedures (SOPs) for patient enrolment, patient consent, data collection, data quality assurance, reporting and other project components as needed. Track version numbers and dates of revision of SOPs, and ensure that all documents are up to date prior to roll-out of the system to account for changes during development and adaptation. Have clear change-management procedures in place prior to launch, and note which stakeholders should be involved in which activities (*see also* Box 3.3).
- ***Training.*** Develop a plan for acquiring the training materials that will be required, how they will be developed and disseminated, what strategies may be used (e.g. train-the-trainer process), required software and hardware user manuals, technical documentation (e.g. data dictionaries) and maintenance manuals. These training materials will also serve as resource guides for future project staff. All training content needs to be translated or adapted to the local context.

Box 3.2 Resource – Project management and budgeting

- PRINCE2 project management *(63)*.
- Total Cost of Ownership Model for CommCare or other mobile health solutions. In: Dimagi [website] (http://sites.dimagi.com/totalcostownership, accessed 2 December 2017).

Box 3.3 Checklist of key SOP elements

- Unique title
- Author
- Version number
- Dates of revision
- Dates of approval
- Responsibility
- Purpose
- Definitions equipment/materials
- Procedure (i.e. step-by-step instructions)
- Appendices/Related documents

Checklist of SOPs to develop

- Staff training
- Participant recruitment
- Patient enrolment
- Patient consent
- Participant training
- Study/monitoring visits
- Data collection/entry
- Data management and security
- Quality assurance
- Reporting
- Maintenance
- Troubleshooting

- *Example – aDSM training package (72).* A training package developed by WHO and technical partners focuses on active drug safety monitoring and management (aDSM), including adverse event reporting.
- *Example – MEMS user guide (73).* A user manual on a MEMS device (evriMED) targeting TB health providers in China. The guide provides information on product components, key features, steps of use, battery replacement, set-up and data collection, among other topics.

- ***Transition.*** Depending on the long-term goals of the project, a plan may be required for handing over the project to a national agency or third party. A clear exit strategy should be devised, with capacity-building to prepare for the transition. If equipment needs to be returned at the conclusion of the project, document the plans to facilitate this.

3.4 Development

During this stage of the project, software will be developed and tested, and there are many different approaches to this process. Regular milestones during system development should be established for when to bring in users to solicit feedback and test the technology. This will help to confirm that the technology is fulfilling its objectives, and that it is appropriate, intuitive and user-friendly. A communication process between system users and technical developers should be established to translate feedback into needs and/or technical adjustments (*see also* Box 3.4). It is important to engage with experts in digital health who are abreast of the state of the science in the technology in order to provide the best possible advice on the product to invest in. The pace with which technology advances is at times breathtaking, meaning that the next generation of a product piloted today may be on the market when the original product is scheduled for roll-out. Project piloting will also be impacted by the scope, timeline and plans for scale up. Additional factors such as geographical reach, complexity of the programme, and availability of personnel and funding will also need due consideration.

Box 3.4 Resource – development

- WHO/ExpandNet. Beginning with the end in mind: Planning pilot projects and other programmatic research for successful scaling up. Geneva: WHO; 2011 (http://www.expandnet.net/PDFs/ExpandNet-WHO%20-%20Beginning%20with%20the%20end%20in%20mind%20-%202011.pdf, accessed 2 December 2017).

Training materials produced in the planning stage should now be implemented for all users (staff, patients, district health officers, NTP staff and all others). Technical components such as software usage as well as administrative components should be covered during training, with all staff reviewing relevant materials to understand data entry, data management and data interpretation. Key data management topics (*see* Annex VIII) should be reviewed and incorporated into training materials. During training courses in the pilot phase, materials and approaches (e.g. presentations, in-person training, mentoring, and continued support and/or feedback) should be tested and improved prior to roll-out. By the time scale up is to start, all training materials should be finalized and compliant to ensure consistency.

- *Example 1 – MEMS brochure for EASY CURE Box (74).* A simple brochure was developed for EASY CURE Box, a medication monitor in India designed to send alerts to the patient on medication dosing and refills. The brochure lists important information for health providers and patients, including the purpose of the monitor, its benefits, instructions on usage, adherence calendar, follow-up procedures when doses are missed, patient registration on the system, labelling the pills according to regimen, health staff responsibilities and troubleshooting.

- *Example 2 – 99DOTS ART staff brochure (75).* A guide targeting TB care coordinators, staff nurses, counsellors, medical officers, pharmacists and data managers. The folded brochure includes general information on the 99DOTS system, its potential benefits, how the system works, information for patients, and specific roles and responsibilities of staff using the system.

3.5 Roll-out

Once roll-out starts, implementation must be tracked to ensure that any barriers are tackled early on. This also includes planning for responsive technical support to fix issues, and sufficient budgeting for customization after the introduction phase. Preparation for the introduction of the technology is a critical step, particularly discussion with the end-users to make sure that they understand the change and embrace it as something positive that will help them in their work. Lack of "buy-in" is a threat to the success of the programme, and if it happens the intervention needs to be re-discussed with the stakeholders. Semi-structured interviews can also be conducted at this stage, and they will generate feedback from users following actual hands-on experience, versus interviews conducted during project planning.

- *Example – WelTel SMS pilot study in LTBI patients in British Columbia (76).* Following a pilot study, a researcher conducted semi-structured interviews with five patients and the clinician coordinating the programme. Feedback gained from the clinician included reduced time in detecting adverse events, and an increased ability to support patients and reduce the social stigma of TB through regular communication. Useful administrative feedback on workload (e.g. initial increase in paperwork and time at the clinic) and technical difficulties was also provided. Patients expressed an increased feeling of support, and felt the solution was convenient. Some barriers to uptake were identified, including a lack of willingness to learn how to text and problems with network coverage. Suggestions included messages for appointment reminders.
- *Example – Formal usability study of evriMED device in China.* In anticipation of a broader scale up of the evriMED technology in China, a formal usability study was conducted in two counties. The study, involving 50 patients and 10 providers, was designed to formally evaluate acceptance by patients and providers of both this new technology and of this approach to TB care management. Patients and providers used the device for a month and then were systematically evaluated (via semi-structured interviews) to obtain general feedback and to qualitatively and quantitatively assess the feasibility and acceptance of the technology/approach. Based on this study, product design was slightly modified and additional training was provided to staff regarding the use of dosing information in patient counselling. The results were published recently *(34)*.

Consideration and monitoring of staff attitudes and sensitivities must take place throughout roll-out. Continuous monitoring helps to learn how the adherence technology needs to change or improve when technology does not fit the needs of the intended end-users. Potential barriers to successful implementation can include staff-level challenges such as:

- changes in workflow and staff hierarchy;
- shifts in workplace culture due to new ways of working;
- perceptions of being replaced as a result of redundancies created through digital system functions, leading to lower staff morale;
- managing expectations of both project leadership as well as those responsible for monitoring and surveillance;
- added burden of training new staff because of high turnover;

- shifts in skills required to perform job functions, particularly with technical abilities, leading to under- or overqualified staff.

Clear communication and reinforcement of project goals should be undertaken to keep staff engaged. Each staff member should understand why the new technology is needed, what changes are being made to workflow, what their specific responsibilities are, what steps will be taken and when, and what mechanisms exist to allow feedback or support for troubleshooting.

3.6 Maintenance

3.6.1 Introduction

Once roll-out is over, project maintenance begins. Activities during this phase include training, system updates, reporting, supervision, monitoring and evaluation. These steps are crucial to ensuring project success, and although the bulk of activities will happen prior to roll-out, continued maintenance is required to keep the project moving. The project may also need to adapt to changing regulatory, ethics and reporting requirements, and to the background digital technology landscape.

One of the most significant areas of focus during maintenance is technical upgrades and troubleshooting. There may be bugs that need to be fixed in software, or updates needed for improvement based on feedback post roll-out. Mobile smartphone apps may require repeated upgrades throughout the project, meaning that staff may need to travel to have their cellphone serviced, unless the process can be completed "over the air". If the software has not been developed in-house, licenses and/or contract renewal fees may be required. Beyond computers and phones, other hardware equipment may also need maintenance, including servers, printers, routers and chargers.

An issues-tracking log is one logistical tool that may be helpful to maintain, at least at central level. Annex IX provides an example of how such a sheet would document technical changes, allowing staff to track requests and changes that have been implemented. This includes updates to fix bugs as well as system upgrades. If approvals are needed, these would also need to be tracked. The log is typically developed and adapted with the technical staff prior to implementation to include all necessary elements. A virtual copy of the log (e.g. Google worksheet) could allow several users in different locations to access and edit the information.

3.6.2 Risks

One critical component of the maintenance phase is dealing with project risks. These risks can be mitigated through careful identification of various risk scenarios, determining their level of impact (low to worst-case scenario) and planning actionable steps in response. Common risks include lack of leadership/oversight, poor or inconsistent management, misunderstanding or confusion related to project development, failures during deployment due to project changes, and operational restrictions due to lack of long-term project sustainability or termination of external financing *(64)*[5]. In developing strategies to address risks, four main approaches can be taken: avoidance of risk in project development, transference of risk, mitigating but not eliminating risk, and accepting risk consequences. Risks may also fluctuate in severity and likelihood at different phases of the project.[6]

5 For specific risks to VOT products, *see* TPP online supplement section 1.1.9 *(7)*. The same issues could apply to other digital technologies employed for TB medication adherence support.

6 *See* Table 8.1 from *(64)* as an example that could be adapted.

3.6.3 Evolution

Be aware of which changes may drastically impact the scope of the project. If NTP or national requirements cannot be folded into routine updates, a new implementation cycle may be required, starting with drafting a new action plan. For example, a digital solution targeting medication adherence in patients with LTBI might be later expanded to patients with active TB.

3.6.4 Monitoring and evaluation

Monitoring and evaluation will track project progress during piloting and roll-out of a product to identify problems requiring maintenance, and eventually to demonstrate the impact of the solution on medication adherence and other health-related outcomes[7]. A "virtuous" cycle of monitoring and quality improvement is proposed to ensure that the product continues to remain relevant to the programme priorities, and to also seize opportunities presented by novelties in technology (Fig. 3.1). The different elements for monitoring are important to list and develop into a data flowchart, such as data inputs, quality assurance, feedback loops to users, indicators, outputs and reports. Data collection in medication adherence must account for varying schedules of patients on different treatment regimens, and at different stages of treatment.

Indicators selected should be process-oriented, evaluating the performance of the system during roll-out and maintenance, and impact-oriented, evaluating the impact of the solution on treatment adherence and health outcomes, as well as programmatic targets (*see* Annex VIII; Box 3.5). Indicators should be adapted to match country circumstances and the target audience.

Box 3.5 Resource – M&E

- Monitoring and evaluating digital health interventions: a practical guide to conducting research and assessment. Geneva: WHO; 2016 (http://apps.who.int/iris/bitstream/10665/252183/1/9789241511766-eng.pdf, accessed 2 December 2017).

7 For specific determinants of success that can be used to develop indicators for medication adherence, *see* TPP online supplement section 1.1.8 *(7)*.

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ANNEX I. ELEMENTS OF COUNTRY SITUATIONAL ASSESSMENT ON DIGITAL HEALTH FOR TB

(adapted from digital health assessment framework developed by the KNCV Tuberculosis Foundation *(9)*)

Domain	Description of different elements
Country background	Describe the relevant demographic, political (administrative divisions) and socioeconomic characteristics of the country, including language(s) spoken and literacy levels.
Health system background	Describe the incidence and prevalence of TB and other relevant health conditions (e.g. HIV/AIDS, diabetes, smoking). Describe the regional and national health-care system – structure, levels, coverage, resources, providers (e.g.% public/private), health-care expenditure overview, sources of funding, insurance, distribution of services, etc. Describe major disease programmes that exist in the country and how they are organized. **National health data collection** Describe what disease data are captured by the Ministry of Health (MoH), how these are captured and what data platform the country uses (e.g. DHIS2, paper-based). **HIS infrastructure** Describe the existing and planned health information system (HIS) infrastructure. Is any project under development, recently tried or planned for implementation? **Sharing of health and disease information** Describe if, what and how information is shared between different disease programmes or between different MoH institutes (e.g. national body responsible for drug safety).
Digital Health-related strategies, regulations and policy	**e-health policy** Is there a national strategy for development of electronic systems in the public sector? Describe guiding principles, main topics and priorities for the country and programmes (e.g. data usage agreements, patient confidentiality). **MoH/NTP ICT activities and strategy** If there is an e-health strategy, does the MoH have a focal point devoted to it? Describe the role of digital health in the national agenda/national policy – what role, if any, how much of a priority, etc. Include: • decision-makers/oversight of digital health related to design, adoption, implementation; • specific objectives and proposed activities for digital health. **Unique identifier** Can the health services access a single, unique, personal identifier for *all* patients – adults, children, non-residents, prisoners, etc. – at the point of care (e.g. databased social security number, ID card, fingerprint identification, health-care smartcard)? Or do they rely on an identifier created for a particular health-care episode (e.g. basic management unit [BMU] TB register number)? Describe any guidelines related to uniquely identifying persons or personal information. **Data security/exchange** Describe guidelines that are in place to ensure data security, patient privacy and standards that enable data exchange (e.g. HL7).

Domain	Description of different elements
Tuberculosis background	**National TB statistics** Describe the disease burden context, geographical areas with the highest burden, rural/urban comparison, DR-TB prevalence, mortality registration, etc. **TB programme structure** Describe the structure of the TB programme, including relevant policies (particularly on diagnostic algorithm, treatment and medication management), and level of integration with other services and with the private sector. **TB treatment services** Describe the available TB services per administrative level, including private providers, if existing. **TB laboratory network** Describe what diagnostics are in place, where they are located, how samples are transported or patients travel, if a laboratory information system (LIS) or diagnostic connectivity software is implemented, how results are communicated and what is the turnaround-time. Also include private facilities if existing. **Supportive systems** Describe supportive systems that are in place and how they are organized, such as supply chain management. **Patient management** Describe patient management systems that are used for TB (e.g. paper-based or electronic health records systems), including those for patient support and education.
TB recording and reporting	**TB monitoring and surveillance** Describe TB surveillance programmes – organization, integration of services, strategic goals, case notification rate, etc. **Recording and reporting processes** Describe what forms and reports are used at different levels, which data and indicators are recorded, at which level data are processed and analysed, and if and what feedback is provided to lower levels.
Technology infrastructure	Describe the national technical environment (network/use coverage in public and private sectors, mobile phone infrastructure and accessibility, Internet accessibility, costs, mobile money and electricity). Describe the technical environment of the MoH/NTP, e.g. availability of data repository, servers, etc. Describe technical infrastructure at different administrative levels/organizational units (hospitals, health centres, etc.), including personal computers, local area networks, Internet connectivity, power.
Technology literacy and Human Resources	Describe the technology literacy of the general community, health-care workers and patients. Also describe the availability of dedicated staff such as data managers, ICT officers (including roles and responsibilities) per administrative level.

ANNEX II. EXAMPLE OF STAKEHOLDER FRAMEWORK FOR DIGITAL HEALTH AND TB

(adapted from digital health assessment framework developed by the KNCV Tuberculosis Foundation *(9)*

Area	Stakeholder	Description	Contribution to Digital Health *(supporting, opposing, neutral)*[8]	Role
Governmental bodies	NTP			
	HIV programme/ department			
	Ministry of Health			
	Ministry/Department of ICT/HMIS			
	Primary health care programme/services			
	Pharmacy services			
	Other: Specify			
In-country development community (NGOs, Foundations, etc.)	e.g. Local NGO			
	e.g. Local WHO			
	e.g. Local United States Agency for International Development (USAID)			
	Other: Specify			
	Other: Specify			
Health Facilities (National, non-public)	e.g. Mission facilities (religion-based)			
	e.g. Private facilities			
	e.g. NGO facilities			
	e.g. Workplace facilities			

8 Include an estimation of level of influence – see power cube in *(77)*.

Area	Stakeholder	Description	Contribution to Digital Health *(supporting, opposing, neutral)*[8]	Role
Health Facilities (National, non-public) *continued*	e.g. Large hospitals			
	e.g. Pharmacy			
	e.g. Laboratories			
	Add stakeholder			
Insurance	e.g. Public insurance department			
	e.g. Private insurance company			
	Add stakeholder			
Professional associations	e.g. Health care (doctor, nurses)			
	e.g. Pharmacy associations			
	Add stakeholder			
Funders and Investors	e.g. Global Fund			
	e.g. Local funder			
	e.g. Banks			
	Add stakeholder			
Other international partners	WHO, MSF, TB Alliance, etc.			
ICT companies/ vendors	e.g. ICT infrastructure/ hardware			
	e.g. Software development			
	Phone network companies			
	Internet companies			

ANNEX III. MAJOR CONSIDERATIONS FOR CHOOSING A DIGITAL ADHERENCE SOLUTION

Score different technologies (e.g. 1→3) against each domain and then add the scores down the columns.

Domains	SMS	MEMS	VOT
Domain 1: Goals of TB programme and the technology 1. Does the technology have specific health outcome goals? 2. Does the technology have clear, measurable health system targets (or activities)? 3. Does the technology align with the WHO and/or country policy to enhance TB programme performance *(4)*? 4. Has the role of the technology already been defined, e.g. NTP already committed to adopting it, commercial interest, model for public–private collaboration? 5. Does the technology decrease travel time and associated expenditure? 6. Does the technology accommodate patients who are travelling or in situations with uncertain communication coverage? 7. Does the technology allow for monitoring outside regular clinic hours (weekends, holidays, evenings)? 8. Is the technology meant to streamline scheduling of health visits for the care provider and patient?			
Domain 2: Functional features of the technology 1. Does the technology accommodate personalized medication regimens and dosages? 2. Does the technology provide a graphic or other easy instruction to the patient about the proper regimen? 3. Does the technology prompt the patient (audible or visual reminders) to take the medication or to refill as needed? 4. Does the user prefer any particular technology? 5. Does the technology allow the patient to ask questions prior to medication intake? 6. Does the technology allow the patient to self-report adverse reactions or other feedback on treatment? 7. How do the available options rank between them in terms of real-time interaction between the patient and caregiver? 8. How do the available options rank between them in terms of verification that the correct dosages have been received? 9. Does the technology register patient history of adherence? 10. Is the technology easy to adjust in case the patient is travelling or there are changes in visit schedules?			

Domains	SMS	MEMS	VOT
Domain 3: Development status 1. Has the technology already been successfully piloted in the country or elsewhere? 2. Has the technology been validated under a diverse and/or similar set of conditions? (i.e. geographical, sociocultural, institutional characteristics) 3. Is the technology available for immediate deployment (an "out-of-the-box" solution)? 4. Does the technology require relatively minimal training of patients and providers to function correctly? 5. Does the technology have language restrictions?			
Domain 4: Operational requirements 1. Does the technology require daily coverage of telephone/Internet network to function? 2. Does the technology require a stable electricity source? 3. Can the data be stored on a secure server? 4. Is the technology license-free (e.g. open source)? 5. Are testing protocols freely available for adaptation? 6. Does the technology have clear technical specifications? 7. Can the technology be integrated with other electronic systems? 8. Is the technology "ready" for the next generation of digital devices? 9. How do technical requirements compare with other options? 10. How do the initial costs rank between different options? 11. Can programmatic implementation be accurately costed? 12. Does the technology incur costs on the patient?			
Domain 5: Evidence of effectiveness, efficiency and quality 1. Functionality: does the technology work as intended? 2. Efficacy: does the technology have a demonstrable effect on health targets in a controlled setting (i.e. RCT evidence)? 3. Effectiveness: does the technology have a demonstrable effect in an uncontrolled setting (i.e. observational studies in a real world)? 4. Efficiency: does the technology reduce costs for the same outcomes? (or improve outcomes with same costs?) 5. Quality: is the technology likely to improve or reduce the qualitative aspects of care (e.g. patient information and reassurance, satisfaction, unmet needs in managing adverse drug reactions, depersonalizing the encounter)? 6. Acceptability: is the technology considered acceptable? 7. Interpersonal: what is the expected effect of the technology on stigma associated with TB?			
Sum of scores			

ANNEX IV. COMPARISON TABLE OF DIFFERENT VOT OPTIONS

Dimension	Third-party video messaging platform *(e.g. Facebook Messenger, Skype, Viber, WhatsApp)*	A proprietary, licensed, VOT application *(e.g. SureAdhere, EMOCHA (78, 79))*	Customized VOT application created by a local provider *(e.g. Belarus example (58))*
Dedicated/customizable for a TB encounter	No	Yes	Yes
Development costs for user	No	Only for adaptation	Yes
Fees for use of software (apart from data charges)	No	Licence charges	No (may be part of development costs)
User ownership	No	Authorized to use	User-defined[9]
Established mechanism of updates and debugging (including support team)	Yes	Possible	Possible
Global network of users	+++	+	–
Patient-level adherence data available	No	Yes	Yes
Easy to install and use on different machines (e.g. no retraining)	+++	++	++
Security of data when stored and transmitted	Encryption is the rule	Defined by developer	User-defined
Interoperability with other data systems used in TB care (e.g. electronic patient register)	No	Requires adaptation to the base software, using the application programming interface (API)	User-defined
Are recorded videos saved on patient device?	Yes	No	User-defined
Additional functionalities		Sending reminders per text message	

9 If software ownership is not transferred as part of the development contract, an escrow may be negotiated to cover for situations where the developer ceases work (*see* page 42 of *(67)*).

ANNEX V. PROGRAMMATIC IMPLEMENTATION OF VOT IN BELARUS

Example of a 5-year timeline[10]

Objective(s). To develop and implement a national VOT programme in Belarus in support of treatment adherence and supervision during the ambulatory phase of treatment, and to improve TB treatment outcomes

Phase 1. Planning (Year 1 – 2015)

- *Conduct a feasibility assessment* – conducted by WHO in January 2015 with support of the European Respiratory Society (ERS)
- *Engage stakeholders to provide input on solution* – WHO survey of public views on priority areas in early 2015, WHO/ERS joint technical consultation to develop detailed technical TPP for VOT in February 2015
- *Develop a costed project proposal* – developed by the Global Fund in February 2015
- *Establish a working group to provide oversight and guidance* – established by the Ministry of Health of Belarus in February 2015
- *Draft detailed technical specifications* – drafted by local Belarusian company "BelPromProject" for VOT app in May 2015
- *Secure in-country ethics committee approval for pilot project* – secured through Ministry of Health in September 2015

Phase 2. Development/adaptation (Year 2 – 2016)

- *Finalize the software* – development finalized by BelPromProject in January 2016
- *Link solution to current national digital health systems* – "VOT module" added to the Ministry of Health of Belarus' national electronic tuberculosis patient registers in February 2016
- *Train staff* – trained dispensary nurses in January 2016
- *Distribute hardware and train patients* – distributed smartphones and trained patients in January 2016

Phase 3. Roll-out (Years 2 & 3 – 2016-2017)

- *Initiate patient enrolment* – initiated single-site preliminary pilot in Minsk in January and February 2016
- *Monitoring and evaluation of pilot study results* – monitoring by NTP, Ministry of Health of Belarus from January to October 2016
- *Publication of preliminary results* – pilot findings published in European Respiratory Journal in March 2017 *(58)*

Phase 4. Maintenance/scale up (Years 2–5 – late 2016–2019)

- *Expansion of solution nationwide* – expansion to all seven country regions with planned recruitment of 450 patients (150/year) with Belarus Red Cross and the Global Fund from October 2016 to 2019; 231 patients from all regions of the country were on VOT by 1 September 2017

10 Adapted from Box 4.1 *(67)*

ANNEX VI. SAMPLE BUDGET TEMPLATE TO ADAPT FOR USE IN PROJECT PROPOSALS ON DIGITAL SOLUTIONS FOR TB[11]

Budgeting category	Year 0 (pre-launch)	Year 1	Year 2	Year 3	Year 4	Year 5
1. Governance						
Meetings (technical working groups, stakeholder input, end-user focus groups)						
Administrative support (needs assessment, agenda development)						
2. Management						
Overall project management (project manager staff, field staff, stakeholder involvement, travel time, work hours)						
Research, monitoring and evaluation (data collection, surveying, travel costs for site visits)						
3. Design/development						
Development (programming, customization)						
Software and interfaces						
Content, standards and localization (SOP development, national manuals)						
4. Deployment						
Hardware (mobile phones, chargers, SIM cards & registration, modems, servers, computer equipment, replacement units)						
Deployment (hosting fees, web access)						
Training (initial and refresher)						

11 Adapted from PATH's mHealth mobile messaging toolkit, Appendix E: total cost of ownership budget matrix. Copyright © 2014, PATH *(80)*.

Budgeting category	Year 0 (pre-launch)	Year 1	Year 2	Year 3	Year 4	Year 5
5. Operations						
Data and communication services (voice and data plan)						
Server management and hosting						
Administration and call centre support (office Internet, electricity, water, rent, supplies, building safety)						
Technical support, hardware insurance, replacements						
Total						

ANNEX VII. PROPOSED INDICATORS TO MONITOR THE PERFORMANCE OF DIGITAL SOLUTIONS FOR TB TREATMENT ADHERENCE[12]

System performance
• Proportion of evaluated system functionalities performing properly, needing adjustment, or with software bugs/ system errors requiring fixing • Proportion of medication adherence system users trained and active out of target number of users, including both health-care providers and patients • Number of months of delay in implementing medication adherence solution • User-friendliness and operator satisfaction questionnaire rating using Likert scale (for both health provider and patient) • Quarterly or annual cost of medication adherence system implementation and maintenance per TB patient entered in the system • Cumulative annual or monthly downtime of central server (for web-based systems)
System coverage
• Proportion of health facilities nationwide where the solution has been implemented by end of each quarter or project year • Proportion of health facilities where solution has been implemented with at least one person trained in using the system by end of each quarter or project year
Registration & treatment
• Number of TB patients registered in the digital health technology and reporting system by end of each quarter or project year • Proportion of TB patients on treatment registered in the digital health technology and reporting system out of all TB patients on treatment by end of each quarter or project year • Number of MDR-TB patients registered in the digital health technology and reporting system by end of each quarter or project year • Proportion of MDR-TB patients on treatment registered in the digital health technology and reporting system out of all MDR-TB patients on treatment by end of each quarter or project year • Proportion of TB or DR-TB patients whose outcomes are being recorded in the system out of all patients in the system by end of each quarter or project year
Drug supply management
• Proportion of actual drug consumption versus project consumption • Number of sites with supplies of anti-TB medication stock, as well as number of months of stock available at specific time points • Average waiting time between ordering a drug and receiving the drug

12 Adapted from Table 4.1 of *(67)*. These indicators are meant to assess the implementation of an intervention and not its impact on effectiveness, efficiency or quality, for which additional variables would need to be collected on patient-level adherence and final outcomes among people who receive the intervention and, ideally, those who do not.

ANNEX VIII. PROPOSED TOPICS FOR TRAINING ON DATA MANAGEMENT OF TB MEDICATION ADHERENCE[13]

- Procedures to collect and validate TB medication adherence data;
- Procedures for data aggregation and synchronization to server;
- Procedures for data export and/or download;
- Procedures for generating monitoring reports on progress and routine reports on TB medication adherence (i.e. weekly, monthly, quarterly, yearly);
- Procedures for transfer of TB patient information from local to national level;
- Reporting on data management, and monitoring and evaluation activities to the NTP;
- Managing and using standardized indicator definitions;
- Procedures for compliance with data security and confidentiality policies, including data encryption and storage;
- Preparing and maintaining data files for research, including removing personal identifiers;
- Maintaining the database and ensuring that back-up procedures are implemented for data recovery (for staff at the national level, if relevant).

13 Adapted from Box 4.2 of *(67)*

ANNEX IX. ISSUES TRACKING LOG

Sample of a standardized way of collecting feedback on a software under development

Status	Priority	Issue description	Requested by	Request date	Approval status	Action to be taken	Impact	Anticipated resolution date	Notes	Actual resolution date
Open	Low	EXAMPLE: Additional information needs to be included on a quarterly medication adherence report.	Project staff	01/01/2017	N/A	EXAMPLE: Technical staff to add the fields to the report.	EXAMPLE: Reporting delayed	31/01/2017	EXAMPLE: NTP consulted and agreed on new date to submit reports	15/02/2017
In progress	Medium	EXAMPLE: An error message is displayed after data are entered into a certain form.	Clinical staff		Pending approval	EXAMPLE: Technical staff to identify and resolve the error.	EXAMPLE: Data collection delays		EXAMPLE: Update to clinical system to be performed by technical person consulted through field visits.	
Closed	High	EXAMPLE: Content language needs updating to reflect local terminology.	Patient feedback		Approved	EXAMPLE: Project staff to review system content, update materials, obtain approval, and provide technical staff with revised materials. Patients to be called and informed of changes.	EXAMPLE: Project delays		EXAMPLE: Local translators consulted to determine appropriate language.	
	Critical	EXAMPLE: Indicators need to be updated to reflect standard definitions.	NTP		Not approved	EXAMPLE: Project staff to meet with the NTP to revise definitions, then provide technical staff with revised materials.	EXAMPLE: Project delays		EXAMPLE: Project outcomes revised, approved.	

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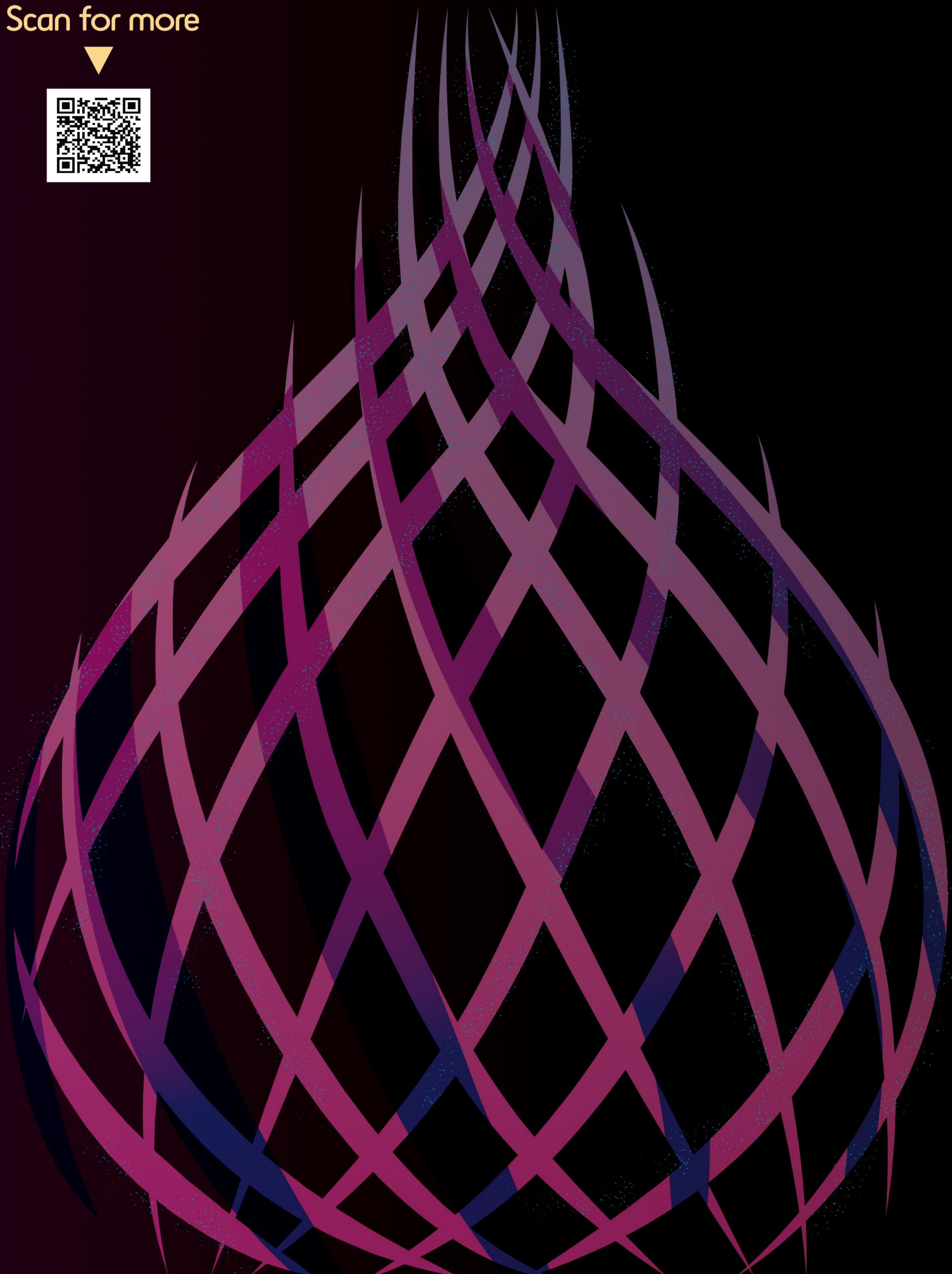

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