Studies to inform the development and practical rollout of a digital adherence intervention, Video-Observed Therapy (VOT)

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Doctoral thesis

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Declaration

I, Fatmatta B. R. Wurie confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been indicated in the thesis

Abstract

BACKGROUND: Prior to the COVID-19 pandemic, globally, tuberculosis (TB) was the leading cause of death from a single infectious agent. It is an important example of a curable condition which has well-documented treatment adherence challenges. WHO recommends the use of video-observed therapy (VOT) as a flexible alternative to DOT (Directly Observed Treatment). There is limited evidence of VOT's acceptability and how it may enable patients to engage with their treatment to elicit optimal adherence outcomes. This PhD thesis aims to improve understanding of patient groups who may benefit most from VOT.

METHODS: Drawing upon a narrative literature review, this PhD thesis includes: a) a study to identify factors that predict non-completion of TB treatment through a retrospective cohort analysis of cases with TB notified to the Enhanced TB Surveillance System in England, Wales and Northern Ireland between 2010 and 2017; b) a study comparing VOT to in-person DOT to examine the factors which affect the levels of engagement with DOT and VOT and whether these affect the level of treatment observation achieved in DOT and VOT groups through a secondary analysis of the UK DOT/VOT trial dataset using descriptive analysis and logistic regression; c) a qualitative study exploring the lived experiences and perspectives of DOT and VOT users in two settings, the UK and Republic of Moldova using semi-structured interviews with 16 UK DOT/VOT trial participants and 22 Moldovan DOT/VOT trial participants. Themes were mapped onto the Capability Opportunity Motivation Behaviour (COM-B) model, Theoretical Domains Framework (TDF) and Behaviour Change Wheel (BCW) to identify how the VOT and DOT functions, strategies and its policy categories elicit treatment adherence outcomes to support decision-making on commissioning of DOT and VOT interventions.

RESULTS: Recent migration to the UK (0 -1 years from entry to the UK to TB notification), multidrug resistance, increasing social complexity and a previous TB diagnosis were significantly associated with non-completion of TB treatment. Higher levels of initial engagement with VOT (90% initially engaged) rather than DOT (49% initially engaged) were observed amongst all patient groups. Amongst those who initially engaged with either DOT or VOT, patients with TB on VOT had improved TB

treatment adherence compared those on DOT. Women were less likely to adhere and those with a history of being lost to follow-up were also less likely to adhere. The COM-B model and TDF provided explanatory frameworks highlighting how VOT acted on key behaviour change domains and utilised key strategies to facilitate adherence behaviour change. VOT facilitated patient-provider interactions served as a prompt/reminder to address forgetfulness through regular personalised messages from VOT observers, building rapport and habit-forming practices. VOT was a flexible, time- and cost-saving alternative to DOT and supported patients with split dosing or negotiated timing of dosing to manage side effects and pill burden. VOT also served as an incentive through the provision of a smartphone and data plan, free domestic calls, text messages and internet access linking patients to providers, banking and social support services. In turn these 'capability and 'opportunity' components of the model enhanced 'motivation' by supporting patients to re-gain autonomy, self-responsibility and establish regular dosing. There were mixed views on privacy with participants expressing concerns on how video clips would be used, shared and may compromise confidentiality and increase stigma.

The Behaviour Change Wheel identified seven key functions ('active ingredients') of VOT: Enablement (increasing means/reducing barriers to increase capability), Education (increasing knowledge or understanding), Persuasion (using communication to induce positive or negative feelings or stimulate action), Training (imparting skills), Incentivisation (creating expectation of reward), Restriction (using rules to reduce opportunity to engage in target behaviour) and Environmental restructuring (changing the physical or social context).

While participants on DOT felt cared for, they had doubts about their personal necessity for treatment, found DOT invasive and stigmatising, time-consuming and costly. At a health system level, DOT was resource-intensive and batch collections of medicines made it difficult to prove fidelity.

CONCLUSION: VOT promotes engagement and adherence to TB treatment in all groups at risk of non-adherence, which suggest it is a more acceptable approach to TB treatment observation compared to DOT. VOT can be universally applied to all patient groups in need of adherence support, including inclusion health groups (those with a current or history of homelessness, imprisonment, drug misuse and current alcohol misuse, vulnerable migrant groups (asylum seekers and refugees), in

low TB incidence settings. DOT is an acceptable intervention to some groups with multiple needs (participants who were aged over 55, had a prison history, a history of homelessness (more than 5 years ago) and those with current alcohol problems). The evidence from this research could be used to develop a personalised decision support tool to support clinicians to offer VOT to groups based on risk of poor adherence and quantitative and qualitative assessment of acceptability and engagement.

Use of the e-Health Implementation Toolkit (e-HIT) supports the national and practical roll-out of VOT to all patient groups in need of adherence support, including those with social complexity. In the era of COVID-19 and acceleration of the use of digital innovations, monitoring the roll-out of VOT should also involve engagement with patients on privacy and confidentiality issues. Engagement with the TB workforce is needed to examine staff attitudes to support learning on what adaptations could be made to VOT and to inform their needs and health system readiness, strengthen health protection and global health security. Further engagement with healthcare professionals to secure their buy-in, address their concerns and to minimise “technology fatigue” is needed. VOT has shown that it improves treatment adherence and while trials are yet to provide convincing evidence to data that it enhances final outcomes, the technology itself does have the potential to reduce treatment-related costs at a patient and health service level. In 2020 WHO proposed VOT as one of the options to support adherence in its target product profiles for TB preventative treatment. Further real-world programmatic evidence on how VOT works and health system cost-effectiveness should continue to be conducted under different conditions of care, including in different geographical settings, patient sub-groups and at different stages of treatment.

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Impact statement

General overview

Tuberculosis (TB) is the leading killer from a single infectious agent, after COVID-19. TB can be treated with six months of antibiotic pills according to a prescribed approach. For some people with multi-drug resistant TB (MDR-TB) it requires up to 24 months of complex treatment.

It is challenging for patients to stick to their prescribed TB treatment approach due to its complexity, the length of treatment and side effects. The personal circumstances that people with TB experience may also make completing TB treatment difficult, particularly if they have complex social circumstances. The consequences of not sticking to the prescribed TB treatment regimen can lead to patients not recovering from TB, remaining infectious for longer periods of time, spreading it to other people and the risk of developing drug-resistant TB.

In the UK, DOT is recommended for people who have a history of missing doses, those with MDR-TB, HIV, had previously had TB and for those who have social complexity including people who experience homelessness and rough sleeping, drug misuse, prisoners and those with mental health problems. There is mixed evidence

on whether DOT is effective in helping people to take their TB treatment regularly and recover from TB. It is also expensive, inconvenient and stigmatising for patients.

Research has shown that VOT is a more effective and cost-effective alternative to DOT. The underlying factors that influence whether people stay on the treatment are complex and patients require additional support. Further work is needed to identify groups who need support and the parts of VOT that can influence the identified patient groups' motivation and ability to stay on their treatment. A better understanding of how VOT could be tailored to patient groups will help people stay on their treatment and reduce waste and inefficiencies in the healthcare system.

Research

This research study shows recent migrants, those with multidrug resistance, increasing social complexity and a previous TB diagnosis were unable to complete their TB treatment. 90% of people on VOT initially engaged compared to 49% of DOT patients. Amongst those who initially engaged with either DOT or VOT, patients on VOT were more likely to stay on their TB treatment compared to those on DOT. When describing people's experiences of VOT and DOT in the UK and Moldova, application of the Behaviour Change Wheel demonstrated how VOT's functions ('active ingredients') targeted the COM-B model components and used key behaviour change strategies to elicit improved adherence outcomes at an individual level. VOT was a flexible, time- and cost-saving alternative to DOT. It helped patients re-gain their independence and motivated them to stay on their treatment. Regular messages from the VOT programme support team reminded them to take their treatment, provided comfort and support and helped them to build a routine. VOT also helped people to split their doses to manage their side effects. The free smartphones and data plans were an added incentive. There were mixed views on whether VOT provided privacy and there were concerns on how video clips would be used and shared. While participants on DOT felt cared for, they had doubts about whether the treatment was necessary and they found DOT invasive and stigmatising, time-consuming and costly. For healthcare providers it was resource intensive and batch collections administered made it difficult to prove patients were taking their treatment.

Practice and policy

WHO now recommends VOT as a suitable alternative to DOT and is recommended by NHS England. A national VOT service for TB has been established in England. This research demonstrates the individual effects of VOT in promoting adherence TB treatment in all groups at risk of non-adherence to TB treatment. The higher levels of initial engagement and experiences of VOT suggest it is a more acceptable approach to TB treatment observation compared to DOT by providing a more holistic approach to TB treatment supervision, upholding autonomy and minimising the deleterious effects of social and economic disadvantage on poor TB treatment adherence. Findings also suggest DOT may support groups with more multiple and complex needs and these groups will require more intensive measures to support their adherence through specialist integrated care services. The evidence from this research could be used to develop a personalised decision support tool to support clinicians to offer VOT to groups based on risk of poor adherence and quantitative and qualitative assessment of acceptability and engagement.

Use of the e-Health Implementation Toolkit (e-HIT) supports the national and practical roll-out of VOT to all patient groups in need of adherence support, including those with social complexity. Monitoring the roll-out of VOT should also involve engagement with patients on privacy and confidentiality issues. Further engagement with healthcare professionals to secure their buy-in, address their concerns and to minimise “technology fatigue” is needed. VOT has shown that it improves treatment adherence and while trials are yet to provide convincing evidence to data that it enhances final outcomes, the technology itself does have the potential to reduce treatment-related costs at a patient and health service level. In 2020 WHO proposed VOT as one of the options to support adherence in its target product profiles for TB preventative treatment. Further real-world programmatic evidence on how VOT works and health system cost-effectiveness should continue to be conducted under different conditions of care, including in different geographical settings, patient sub-groups and at different stages of treatment.

PhD structure

This PhD was primarily informed by two case studies:

1. NIHR-funded TB Reach DOT / VOT trial in the UK
2. RSTMH-funded qualitative study embedded in an existing Global Fund and UNDP- and Global Fund -funded DOT / VOT trial in Moldova

Figure 1 below shows an overview of the PhD thesis components

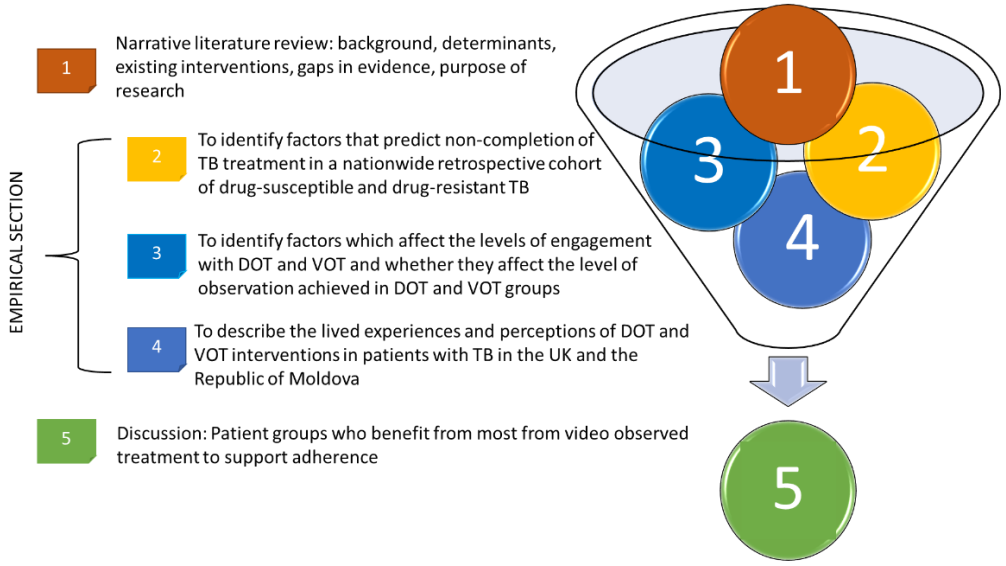


Figure 1: overview of PhD thesis components

Chapter 1: Narrative literature review, background and justification for research

This chapter will provide an overview of treatment adherence definitions, approaches for its assessment and will be followed by an assessment of adherence and treatment observation in the context of tuberculosis (TB) care. Whilst an overview of the relevant models and theories that have been used to examine adherence behaviour will be provided, emphasis will be placed on two similar theoretical models, the Perceptions and Practicalities Approach (PAPA), which was recommended by NICE Medicines Adherence guidelines CG76 to address individual-level factors affecting non-adherence (NICE; 2009) and the Capability Opportunity Motivation Behaviour (COM-B) model, which is the 'hub' of the Behaviour Change Wheel (Michie, van Stralen, and West 2011).

1.1. Adherence definitions

Adherence is defined as "the extent to which a person's history of therapeutic drug-taking coincides with the prescribed regimen." (2003) Adherence is a vital component of the self-management process by patients and their interaction with medication for managing acute and long-term chronic conditions to bring about successful outcomes in patient care by providing quality of care and preventing increased healthcare use from conditions amenable to timely and appropriate treatment.

There are multiple definitions of adherence in the pharmacological and behavioural medicine evidence base, which have been consolidated into a quantifiable taxonomy of adherence. As part of a consensus exercise coordinated by the European Society

of Patient Adherence, Compliance and Persistence (ESPACOMP), the taxonomy was launched (Vrijens et al. 2012). It is recognised as the only globally accepted taxonomy for adherence, which describe three key components, namely initiation, implementation and discontinuation:

- *Initiation* of the treatment: when the patient takes the first dose of a prescribed medication
- *Implementation* of the dosing regimen: defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken during the period of persistence (i.e. the time period between initiation and discontinuation)
- *Discontinuation:* marks the end of therapy, when the next dose to be taken is omitted and no more doses are taken thereafter

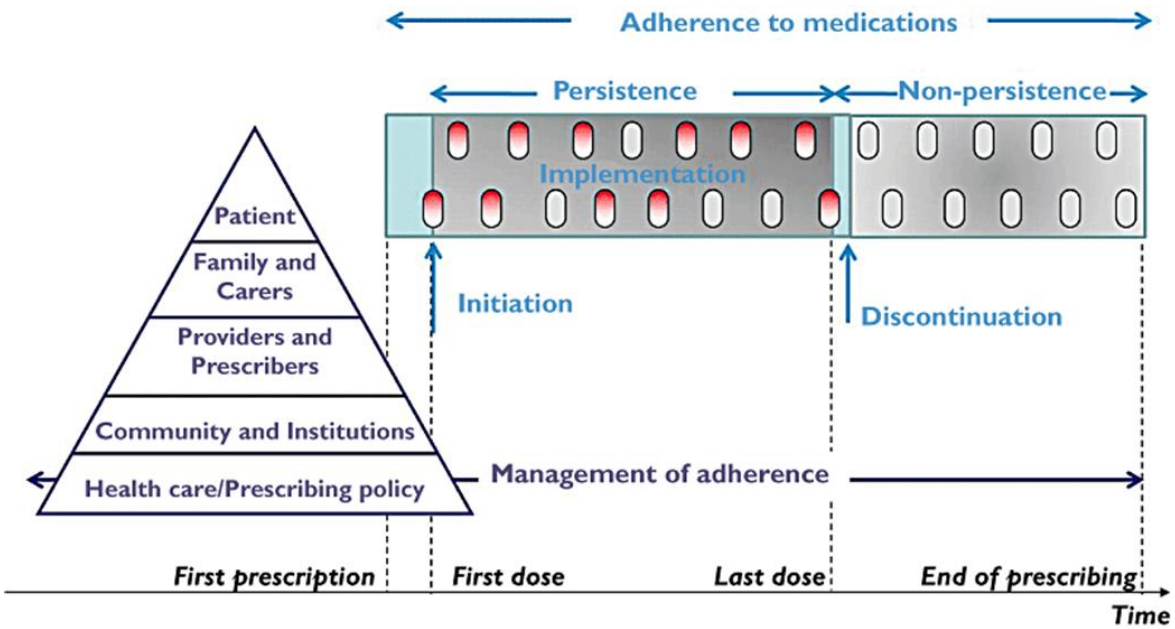


Figure 2: Illustration of the different components of adherence to treatment. Source: Vrijens *et al* 2012

As such, non-adherence can occur through late or non-initiation of the prescribed treatment, sub-optimal implementation of the dosing regimen or early discontinuation of the prescribed treatment. The former U.S. Surgeon General C. Everett Koop had articulated: “Drugs don’t work in patients who don’t take them” (Blaschke et al. 2012). Early work exploring the importance of adherence has estimated that 30-50% of people do not take their treatment as prescribed. WHO reports that overall, approximately 50% of medication for long-term conditions are not taken as prescribed, with even higher rates in low income settings (WHO; 2003).

WHO also reports that non-adherence is an important moderator of health system effectiveness (WHO; 2003). An NHS England report in 2015 has estimated approximately £300 million of prescribed medicines are wasted each year, some of which can be attributed to intentional and non-intentional adherence to treatment (Hazell B and Robson R 2015). Based on this, if adherence rates are low this will not translate into maximal health-related impact (Burnier 2006) (Cutler and Everett 2010) and will lead to significant losses in healthcare spending (Bender and Rand 2004; Sokol et al. 2005; WHO; 2003).

1.2 Tuberculosis treatment regimens and challenges

TB infection occurs when a person inhales bio-aerosols containing *Mycobacterium tuberculosis* (*M.tuberculosis*) that reach the alveoli of the lungs. These *M.tuberculosis* are ingested by alveolar macrophages; the majority of these bacilli are destroyed or inhibited. A small number may multiply intracellularly and are released when the macrophages die. If alive, these bacilli may spread through lymphatic channels or through the bloodstream to more distant tissues and organs

(including areas of the body in which TB disease is most likely to develop: regional lymph nodes, apex of the lung, kidneys, brain, and bone) (Centers for Disease Control and Prevention (CDC)).

TB is a curable disease after following the time-limited ‘short-course’ of anti-tuberculosis treatment, which lends itself to the taxonomy of adherence cited by (Vrijens et al. 2012). The standardised oral regimen for drug-susceptible TB lasts for 6 months starts with four drugs, designated as ‘first line’ (isoniazid, rifampicin, pyrazinamide and ethambutol) administered during the 2-month initiation phase, followed by two drugs (isoniazid and rifampicin) during the 4-month continuation phase (WHO; 2017).

In 2022 WHO recommended use of a shorter 4-month regimen composed of rifapentine, isoniazid, pyrazinamide, and moxifloxacin and another 4-month regimen for treatment of children with non-severe TB. The standard 6-month regimen remains as the alternative option for the treatment of drug susceptible pulmonary tuberculosis (WHO 2022).

It has been postulated that mycobacteria are so hard to kill with antibiotics because dormant cells exist even in patients with active disease and these cells are far less susceptible to antibiotics than metabolically active bacteria (Connolly, Edelstein, and Ramakrishnan 2007). However, it has since been suggested that mycobacterial cells divided asymmetrically, creating a tapestry of cell types with widely different sizes and growth rates (Kupferschmidt 2011).

The side effects of treatment include: unexplained loss of appetite, nausea or vomiting, jaundice (yellowing of skin or eyes), persistent tingling, numbness, or burning of hands or feet, persistent weakness, fatigue, fever, or abdominal

tenderness, easy bruising or bleeding or blurred vision or changed vision may occur. Patients taking rifampicin or rifapentine will notice an orange discoloration of their urine and possibly other body fluids, which is a normal occurrence and clinicians are advised to inform their patient this will happen ((CDC)).

Isoniazid-resistant TB refers to *Mycobacterium tuberculosis* strains in which resistance to isoniazid and susceptibility to rifampicin has been confirmed in vitro.

A shorter MDR-TB regimen refers to a course of treatment for MDR/RR-TB lasting 9–12 months, which is largely standardized, and whose composition and duration follows closely the one for which there is documented evidence from different settings.

Longer MDR-TB regimens are those used for the treatment of MDR / rifampicin-resistant (RR-TB). These last 18 months or more and may be standardized or individualized. These regimens are usually designed to include a minimum number of second-line TB medicines considered to be effective based on patient history or drug-resistance patterns.

The Guideline Development Group tasked with updating the WHO consolidated guidance for drug-resistant TB (WHO 2019) assessed the individual contribution to patient outcomes of medicines used in longer MDR-TB regimens using evidence considered for the update. Following a thorough assessment of the relative benefits and harms, recommendations were made for each medicine and they were classified into three groups. See Table 1 below.

Table 1 Grouping of medicines recommended for use in longer MDR-TB regimens

Group and steps	Medicine
Group A: Include all three medicines	• levofloxacin OR moxifloxacin • bedaquiline • linezolid
Group B: Add one or both medicines	• cycloserine • terizidone
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	• ethambutol • delamanid • pyrazinamide • imipenem–cilastatin OR meropenem • amikacin (OR streptomycin) • ethionamide OR prothionamide • p-aminosalicylic acid

The policy recommendations on the treatment and the care for patients with drug-resistant TB (WHO 2019) are as follows:

1. Regimens for isoniazid-resistant tuberculosis:

- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.

- In patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen

2. The composition of longer MDR-TB regimens:

- In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment after bedaquiline is stopped.
- If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.
- Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.
- Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Bedaquiline should be included in longer MDR-TB regimens for patients aged 18 years or more. Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.
- Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.

- Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens.
- Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Amikacin may be included in the treatment of MDR/RR-TB patients aged 18 years or more on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.
- Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.
- p-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible.
- Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens.

3. The duration of longer MDR-TB regimens:

- In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.
- In MDR/RR-TB patients on longer regimens, a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy.
- In MDR/RR-TB patients on longer regimens that contain amikacin or streptomycin, an intensive phase of 6–7 months is suggested for most patients; the duration may be modified according to the patient's response to therapy.

4. Use of the standardized, shorter MDR-TB regimen

- In MDR/RR-TB patients who have not been previously treated for more than 1 month with second line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens.

The use of streptomycin and other injectable agents has also been associated with increased serious adverse events.

1.3 Tuberculosis and non-adherence: an epidemiological perspective

TB is an important example with well-publicised and longstanding treatment adherence challenges due to the inherent complexity of regimens, the duration of treatment and modest tolerability of anti-microbial drugs. Barriers to adherence

include side effect management, pill burden, denial of TB diagnosis, depression/fatalism, fear, stigmatisation and unintentional non-adherence (forgetting and/or difficulties in understanding dosing in combination and frequency) and early improvement of symptoms. The long duration, complexity of TB treatment regimens and socio-economic difficulties can make it difficult for patients to complete treatment as prescribed (Kaona et al. 2004; Horsburgh, Barry, and Lange 2015; Munro, Lewin, Smith, et al. 2007; D'Ambrosio et al. 2014; Kik et al. 2009; Story et al. 2007; Dara et al. 2012; Falzon et al. 2016). In the context of TB, poor adherence is cited as the primary reason for sub-optimal clinical benefit (WHO; 2003) and leads to poorer clinical outcomes, the development of drug resistance, increased duration of infectivity and consequent onward transmission of infection (Hirpa et al. 2013; Moonan et al. 2011; Munro, Lewin, Smith, et al. 2007; Weis et al. 1994; Ormerod and Prescott 1991; Mitchison 1998; Pablos-Mendez et al. 1997). Given this, the first pillar of the End TB Strategy of the World Health Organization (WHO)—Integrated, Patient Centred Care and Prevention—calls for “treatment of all people with tuberculosis including drug-resistant tuberculosis; and patient support” (WHO; 2015b).

Prior to the SARS-CoV-2 global pandemic, TB was the leading cause of mortality from a single infectious agent worldwide and remains a pervasive global public health problem with an estimated 10 million incident cases and 558,000 multi-drug resistant cases in 2017 (WHO; 2019).

England has a TB incidence of 8.3 per 100,000 population was reported in 2018 (PHE; 2019) (ECDC; and WHOEurope; 2019) (Figure 3 and Figure 4). Despite an approximate 44% decline in the number of people with TB from 8,280 in 2011 to

4,655 in 2018 low incidence settings, it remains has one of the highest TB rates of Western Europe (Figure 4).

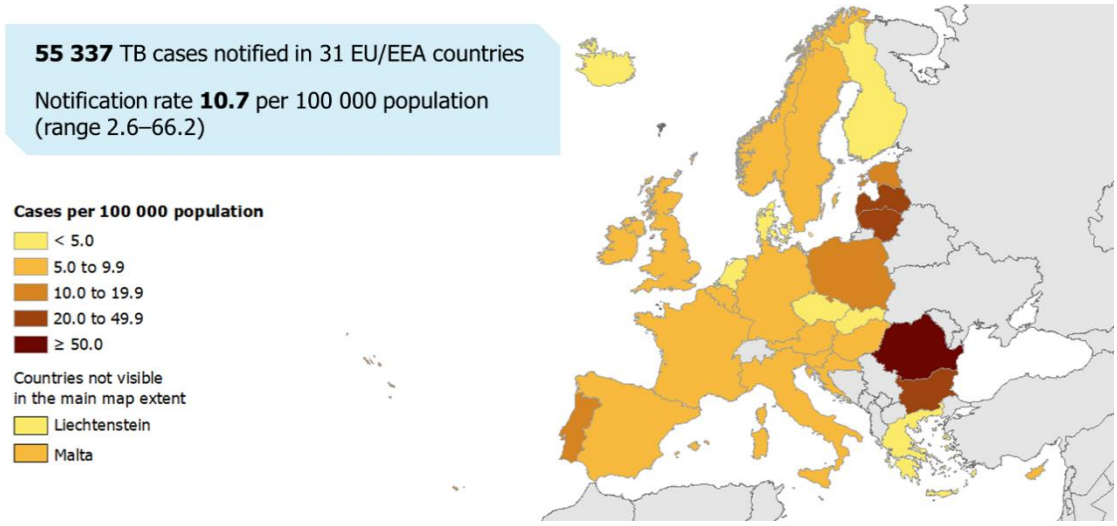


Figure 3: Tuberculosis surveillance and monitoring in Europe 2019–2017 data
Source: ECDC/WHO (2019)

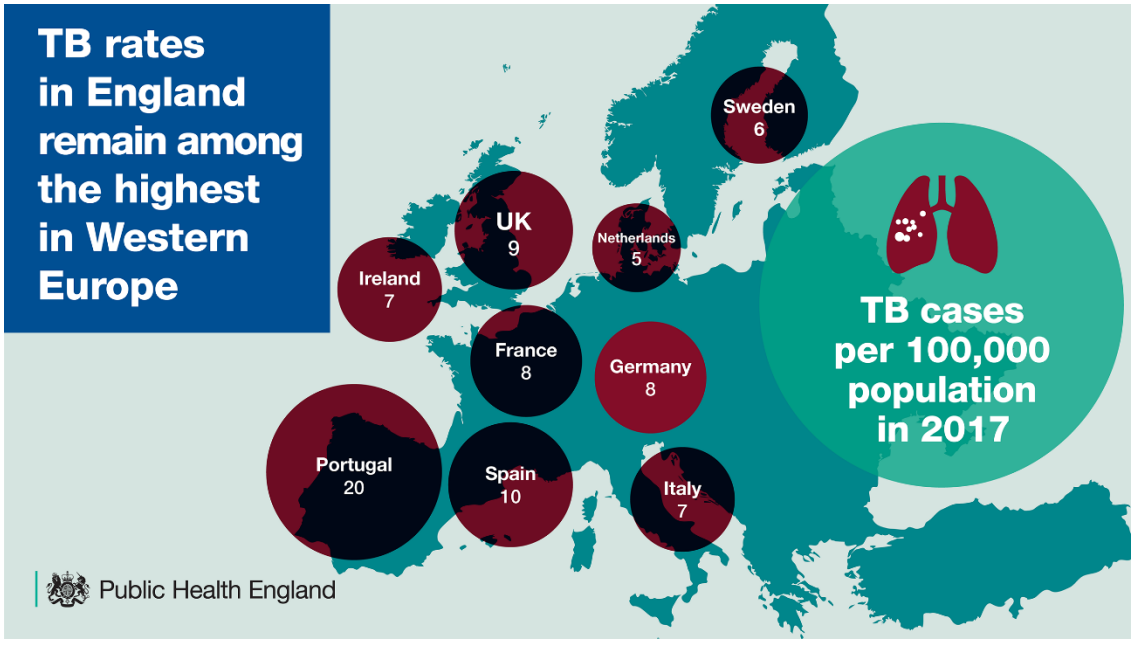


Figure 4: TB rates in Western Europe per 100,000 population in 2017 Source: Public Health England (2019) (PHE; 2019)

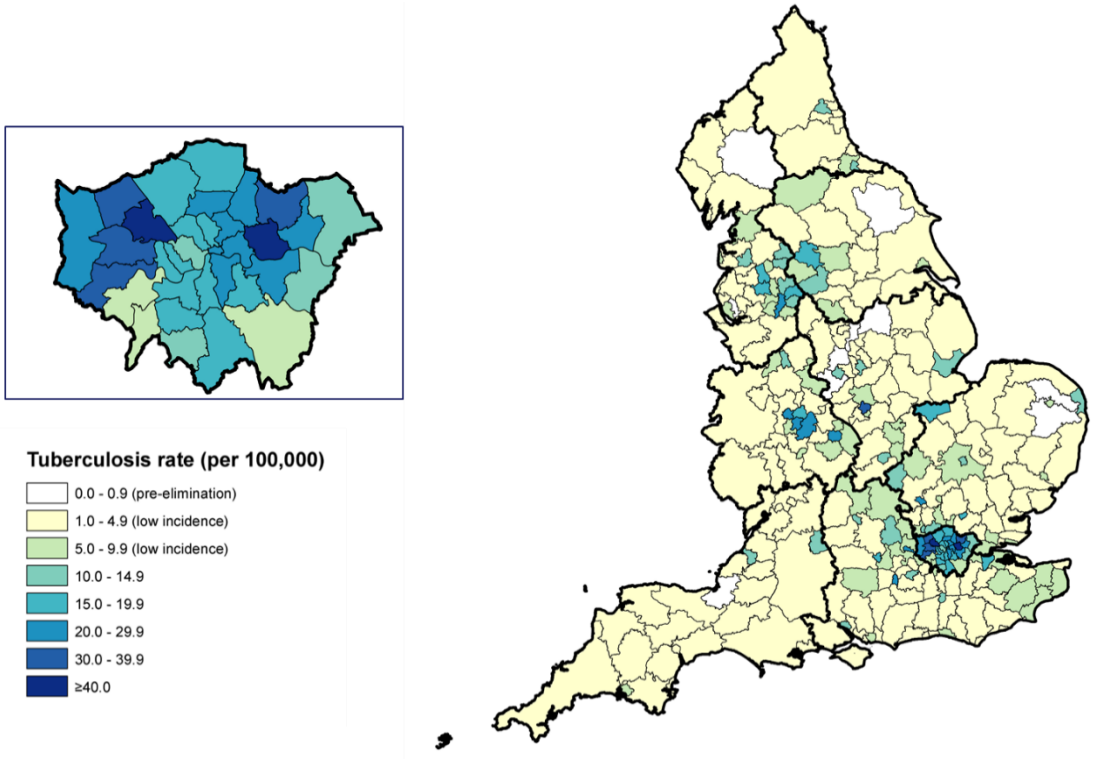


Figure 5: Source: Public Health England (2019) TB rates per 100,000 population in England by local authority districts 2016-2018 (PHE; 2019)

In low TB incidence settings like England, TB is concentrated in big cities, particularly London (Figure 5) (Story et al. 2007; van Hest et al. 2014) and disproportionately affects inclusion health groups (current or history of homelessness, a prison history, drug misuse and current alcohol misuse) and some with a current or history of mental health needs and some migrant groups (including those with unclear legal status, asylum seekers, undocumented migrants and those in immigration detention centres (van Hest et al. 2014; Story et al. 2007). In England, amongst people diagnosed with TB who were aged 15 years or older, the proportion of cases with at least one of these risk factors has increased from 9.8% in 2014 to 13.3% in 2018 (PHE; 2019). These groups are more likely to have pulmonary TB,

drug-resistant disease, have very poor treatment outcomes and are more likely to die, compared to those who do not have these social risk factors.

Poor treatment adherence increases in inclusion health populations. Amongst inclusion health groups many of these barriers to adherence may originate from their multiple and complex needs which involve co-occurring mental ill health and drug misuse problems borne from a lifetime of social disadvantage (Story et al. 2007), early-life poverty and adverse childhood experiences and trauma (Fitzpatrick, Bramley, and Johnsen 2012) (Luchenski et al. 2018). According to Public Health England's TB report published in 2019 (PHE; 2019) TB treatment completion was lower in cases with drug-susceptible TB and with at least one social risk factor (79%; 418/531) compared to cases without any social risk factors (89.1%, 3,399/3,816) (PHE; 2019). Cases with TB and with a social risk factor were more three-time more likely to be lost to follow-up (9.2%; 49/531) compared to those who did not (3.1%; 118/ 3,816) (PHE; 2019). Those with multidrug-resistant TB and a social risk factor were also less likely to complete treatment compared to those with no social risk factor (69.2%; 9/13), compared with 72.5%; 29/40) (PHE; 2019). Cases with TB were also more likely to die (6.2%, 33/531) compared to people without a social risk factor (4%, 153/3,816) (PHE; 2019).

1.4 Directly-observed treatment for tuberculosis control

TB control has been underpinned by an extensive evolution in the adoption of WHO managerial policies from the 1980s in response to the HIV epidemic leading to a sharp increase in TB notifications predominantly in Africa and the collapse of the former Soviet Union and its consequent decline in socioeconomic conditions and

health services. Poverty, malnutrition and overcrowding in industrialised countries was on the rise promoting TB transmission and TB reactivation. As such, the global TB incidence reached an estimated eight million and three million deaths in 1990 (Sudre, Ten Dam, and Kochi 1992; Kochi 1991) and prompted the response of revised managerial responses. In 1991 to focus country-level efforts, a new strategic

Box 1: The 5 elements of DOTS:

1. Political commitment with increased and sustained financing
2. Case detection through quality-assured bacteriology
3. Standardized treatment with supervision and patient support
4. An effective drug supply and management system
5. Monitoring and evaluation system and impact

response to TB control, known as Directly-Observed Therapy, Short-course (DOTS) emphasising specialised managerial functions (Box 1) was introduced by WHO in response to the 44th World Health Assembly targets for the year 2000: curing 85% of new infectious cases detected and detecting 70% of cases (WHO 1991). With particular emphasis on early case detection and to uphold the importance of strict adherence to TB treatment, DOT (Directly-Observed Treatment) became the international standard for TB control introduced by WHO in the early 1990s ("An expanded DOTS framework for effective tuberculosis Control: stop TB communicable diseases"). DOT is a well-established method to ensure treatment adherence. It involves TB patients receiving treatment under direct supervision and observation by a healthcare worker, pharmacist or trained-lay worker. DOT can be delivered in a wide range of settings, including clinic or health facility-based settings, it can be home-based or DOT can be administered by family members or through unsupervised self-administered treatment.

DOT emerged as a result of work by Wallace Fox in Madras in India in the early 1940s and 1950s around the time of the introduction of chemotherapy, which changed TB treatment so long-term hospitalisation was no longer needed. Fox concluded that while which oral medications to use were important, it was less important than adherence of self-administered treatment over the long term (Bayer and Wilkinson 1995). The historical context which underpins the debate on 'universal DOT' versus 'selective DOT' and their ethical, legal and constitutional perspectives emerged in New York City in the early 1990s is an important example of public health decision-making to tackle rising drug resistance and reactivation.

The CDC had recommended DOT "be considered for all patients because of the difficulty in predicting which ones will adhere to a prescribed regimen" ('Initial therapy for tuberculosis in the era of multidrug resistance. Recommendations of the Advisory Council for the Elimination of Tuberculosis' 1993). One case put forward in favour of 'universal DOT' by Iseman, Cohn & Sbarbaro (Iseman, Cohn, and Sbarbaro 1993) stated:

"We believe it is time for entirely intermittent directly observed treatment programs…to be used for all patients. Some will argue that it will be impossible to treat every patient with directly observed therapy and that many people with tuberculosis do comply with treatment and would be offended by having to submit to direct observation while they swallow medications. Unfortunately, the literature is replete with studies demonstrating…that professionals are not able to distinguish the compliant from the noncompliant in advance." (Iseman, Cohn, and Sbarbaro 1993)

Opposition to universal DOT was made on the grounds of resource scarcity and an unethical breach of patient autonomy and a violation of constitutional requirements by Dubler *et al* (Dubler NN et al. 1992):

"The fact that all start their post-hospitalization treatment under a common program of supervision should help to reduce the stigma of treatment and create an effective public health plan for the control of TB. Such an approach will also limit the extent to

which initial treatment decisions violate the principle of justice which seeks to preclude acts of invidious discrimination." (Dubler NN et al. 1992)

Presently, the National Institute for Health and Clinical Excellence (NICE) in England recommend DOT as a treatment administration option for MDR-TB and for high-risk groups where their complex social circumstances may impede them from adhering to TB treatment (NICE; 2016).

There is however mixed evidence of the effectiveness of DOT. Early work has reported DOT has brought about substantial improvements in treatment outcomes by increasing medication adherence by reducing drug resistance, transmission and relapse (Chaulk et al. 1995; Wilkinson 1994; Westaway, Conradie, and Remmers 1991; Frieden and Sbarbaro 2007; Weis et al. 1994). These improvements have also been reported in inclusion health groups, such as refugees and those with a history of homelessness and drug misuse problems (Schluger et al. 1995; Sukrakanchana-Trikham et al. 1992). DOT has also been reported to have increased cure rates by 18% and decreased treatment default rates by 46% in a meta-analysis of only RCTs (Muller et al. 2018). Conversely a meta-analysis of self-administered treatment versus DOT effect showed that DOT had no difference on microbiological cure and relapse of acquired drug resistance (Pasipanodya and Gumbo 2013) (Figure 6) and may be indicative of poorly implemented DOT approaches (Benbaba et al. 2016). For example, clinic-based DOT introduces social and economic constraints on patients, such as loss of income, the direct and indirect costs of accessing TB treatment, loss of privacy, autonomy and time by missing work to regularly travel to attend clinic and be observed taking treatment as part of DOT appointments. DOT approaches also negatively impact health systems by assuming that all patients recommended for DOT require uniform monitoring throughout the treatment duration,

which imposes additional costs and burden of treatment supervision on healthcare practitioners, as opposed to stratifying patients by complexity and appropriately allocate DOT resources to these more complex patients. As such, community DOT approaches may not be adhered to in practice (Wynne et al. 2014; Lei et al. 2016; Hou et al. 2012; Benbaba et al. 2016). Another major limitation attached to DOT is the fidelity of treatment observed amongst patients supported by DOT, or the extent to which a clinic provider's compliance with DOT guidance can be validated and it is possible to be conclusive that a patient is complying with the treatment regimen, where positive outcomes are reported in a few cases.

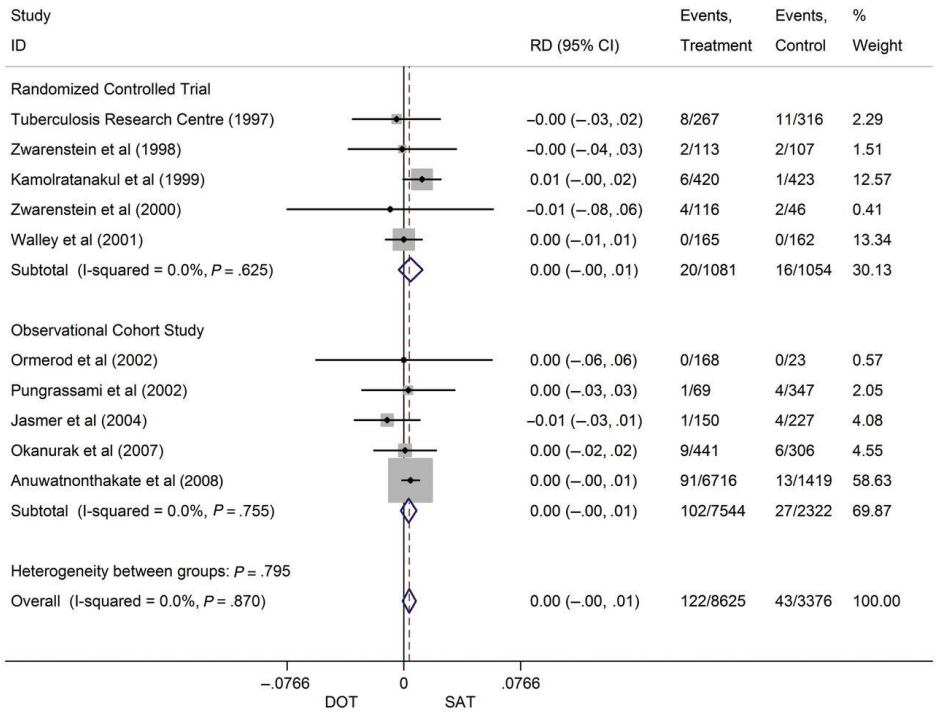


Figure 6: Pooled risk differences for microbiologic failure in patients on directly observed therapy compared to self-administered therapy. Source: Pasipanodya J & Gumbo T; 2013

1.5 Other adherence interventions

There are a range of other adherence interventions that include social support such as material support (for example food, financial incentives, transport fees), psychological support, tracers such as home visits or digital health communication (for example SMS, telephone calls), medication monitors (Liu et al. 2015), which track each dose dispensed and staff education.

As part of a systematic review of systematic reviews by (Collin et al. 2019) found there was insufficient evidence to show adherence interventions had a direct effect on the reduction in incidence of active TB in low incidence countries. A Cochrane systematic review (Lutge et al. 2015) found material incentives and enablers provided a short-term positive effect on clinic attendances, for those with drug misuse problems, homeless and recently-released prisoners but there was insufficient evidence that such incentives improved long-term adherence to TB treatment. These methods capitalise on modifying a patient's environment or behaviour or through the provision of incentives by rewarding healthy behaviour through cash or vouchers or indirectly through removing economic barriers to provide access to a particular service, which the patient may otherwise have had to pay for, such as transport to a health facility (enablers). Similarly, a Cochrane review by Karumbi and Garner (Karumbi and Garner 2015) concluded that there was insufficient evidence overall to either support or discount the effectiveness of DOT in terms of TB treatment completion or cure, with two out of 11 included studies in high-income countries (USA and Australia). In a systematic review by M'Imunya and Volmink (M'Imunya J, Kredo, and Volmink 2012) assessing patient education and counselling for promoting adherence to TB treatment, three trials reported LTBI

completion rates amongst children in Spain, adolescents in the USA and prisoners in in the USA yet did not measure progression to TB disease.

Van de Berg and colleagues (van de Berg et al. 2018) highlighted that there were a small number of studies measuring quantitative outcomes and a large variation in interventions applied, outcomes measured and the study populations among these studies could not be quantitatively synthesized and analysed. Given this, there is insufficient data to provide recommendations on effective patient support in low incidence countries.

The WHO TB treatment guidelines (WHO; 2017), for which a systematic review was conducted showed TB treatment outcomes improve with the use of adherence interventions such as patient education and counselling, material support, psychological support interventions, reminders and tracers, and digital health technologies (Alipanah et al. 2018). DOT provided by trained health workers in the community is associated with better treatment outcomes than DOT provided by family members or untrained lay workers. DOT provided in the community is associated with better treatment outcomes than clinic-based DOT. TB patients living with HIV have significantly better outcomes when treated with DOT as opposed to self-administered treatment.

1.6 Digital adherence technologies

Significant shifts in advancements in information and communication technology have taken place, largely brought about through the expansion of mobile phone technology and its access globally. The application of mobile technology (including short message service (SMS) for reminders, geographic positioning system (GPS)

for patient tracing, telemedicine for remote monitoring and video-DOT in healthcare and health promotion (historically termed as ‘m-health’) has made it possible for citizen participation in health priorities, delivery and engagement in their care (Fottrell 2015) (Denkinger et al. 2013). Its application has extended to support the control and management of treatment adherence, smoking cessation, weight loss, diet and physical activity and disease management (i.e. adherence to HIV treatment) (Bricker et al. 2014; Kosmala-Anderson et al. 2014; Mann et al. 2013; Steinberg et al. 2013; Lee and Valerius 2020). M-health pilot studies assessing the feasibility and acceptability have broadly found that technology has not served as a barrier in remote and low and middle-income settings and the promise of their large-scale application to address long-standing health issues have provided opportunities to promote behaviour change and promote better health. However, it became apparent that the success of m-health interventions was predicated on context and the relationships between citizens, innovations and health systems (Douglas 2012; Hall et al. 2014; UCL Institute for Global Health 27-28 Jan 2015). The shift towards an era of “technological solutionism” also needed to be accompanied by robust evaluation through the application of a public health lens and through variation in study design and health outcomes definitions, supported through interdisciplinary partnerships (Fottrell 2015).

M-health as an initiative was exciting – its applicability is far-reaching and particularly promising for TB control in terms of patient education and information dissemination, treatment adherence, monitoring diagnosis and disease surveillance to enhance and support TB service needs (The m-health alliance and STOP TB partnership 2012). It was no surprise that private and private-public partnerships sought to capitalise on the explosion of mobile phone use to improve accessibility and quality of care, with

devices reaching 90% of the world's population (Denkinger et al. 2013).The Denkinger *et al* (Denkinger et al. 2013) review highlights the absence of rigorous studies evaluating the different applications and implementation strategies necessary to establish the evidence base that serves to inform policy, commissioning cycles and service planning reviews.

Dayer and colleagues (Dayer et al. 2013) discussed the potential for smartphone medication adherence applications (adherence apps) to improve medication non-adherence for acute and chronic conditions and evaluated features of adherence apps across operating systems. Findings suggested adherence apps are inexpensive, scalable, accessible to anyone with smartphones and highlighted the need for research to determine whether and how effectively apps can improve adherence and therapeutic outcomes in acute and chronic conditions (Dayer et al. 2013).

The feasibility, acceptability, reliability and cost-effectiveness of videophone observation as an alternative to DOT to TB treatment adherence has been demonstrated in pilot studies (Wade et al. 2012; DeMaio et al. 2001; Hoffman et al. 2010; Krueger et al. 2010) ,with one showing high rates of adherence and large cost savings for patients and staff (Krueger et al. 2010). A mixed methods evaluation comparing home videophone to a drive-around service found videophone observation (Wade et al. 2012) offered an approach to achieve high rates of observation and was cost-effective, yet many limitations were observed, including that it did not improve the number of observations missed due to patient absence or refusal. Home videophone service was an acceptable intervention with participants describing a high degree of convenience and flexibility and enabling communication with providers and the development of rapport with them.

Beyond TB, videophone technology has also been applied to other diseases including HIV (Skrajner et al. 2009; Manby et al. 2022), Hepatitis C (Mohsen et al. 2019; Adje et al. 2022), asthma (Shields et al. 2018), dementia (Czaja et al. 2013; Boman et al. 2014), oncology (Laila et al. 2008; Stern et al. 2012), diabetes (Verhoeven et al. 2010), for end-of-life care (Parker Oliver et al. 2010; Demiris et al. 2012) and for elderly groups (Mochizuki-Kawai et al. 2008).

The expansion of smartphone use, its adaptation to address health challenges and building evidence base has led to the development of a series of digital adherence technologies (DATs) (Figure 7). These include phone-based and smartphone-based technologies, pill boxes and ingestible sensors, all of which provide the potential to offer transformative approaches to healthcare delivery by facilitating a patient-centred approach to monitoring adherence (Cross A , Kumar M , and P 2015; Garfein, Collins, Munoz, et al. 2015; Pai, Subbaraman, and Daftary 2017; Belknap et al. 2013). Whilst WHO have published a handbook providing guidance for their use of DATs for TB care (WHO 2018) following their deployment in a number of different settings, more robust evidence supporting their use is needed to better understand how the acceptability, clinical effectiveness and cost-effectiveness of DAT approaches can impact patients' treatment outcomes and support health systems.

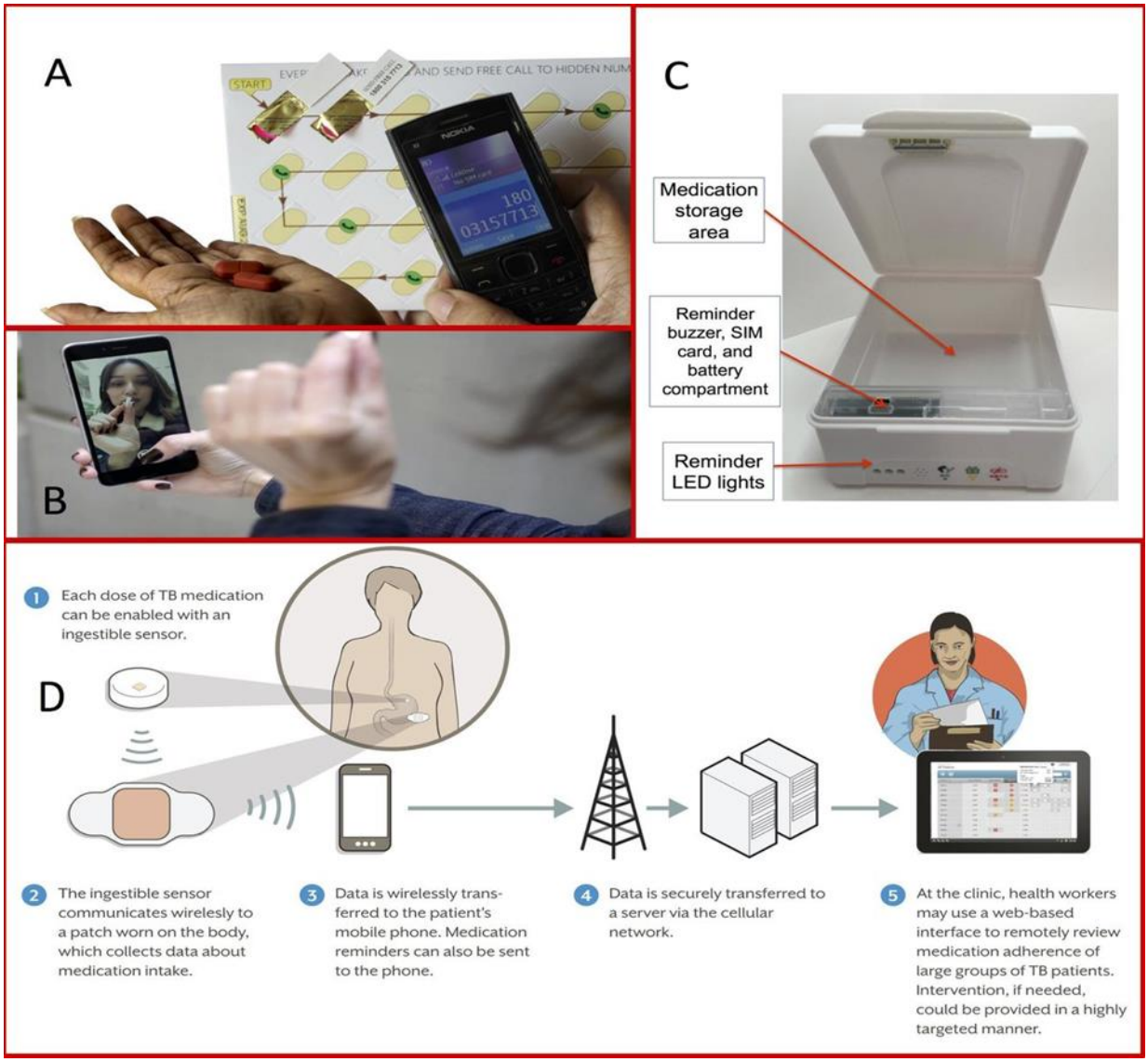


Figure 7: Digital adherence technologies being used in research and clinical care: (A) 99DOTS, a feature phone-based adherence technology (Everwell Health Solutions); (B) SureAdherence, a video DOT strategy (SureAdherence Mobile Technologies); (C) evriMED, a digital pillbox (Wisepill Technologies); (D) an ingestible sensor–based adherence monitoring approach (Source: Belknap et al.) DOT, directly observed therapy; LED, light-emitting diode; SIM, subscriber identification module; TB, tuberculosis. Source: Subbaraman et al; 2018

1.7 Virtually-observed treatment

My PhD thesis focuses on video-observation, which is referred to as virtually or video observed treatment, video DOT or vDOT (VOT) (Story et al. 2020; Story et al. 2016a) (Krueger et al. 2010) and represents the technological alternative to DOT

(2015a). With VOT, patients record themselves taking their medication and send their video clips remotely via a secure internet server to a trained healthcare professional. In accordance with a protocol, VOT enables healthcare professionals to watch their patients take their medication remotely negating the need for patients to travel to clinic or health facilities to be observed taking treatment, address concerns and provide advice and support. Patients who are supported through VOT first receive face-to-face instructions from the healthcare professional who will monitor their videos and conduct the follow-up observations. Patients subsequently submit their video clips automatically as soon as the phone is connected to a cellular data network (data plan provided with phone) or a wireless network, report side effects and ask questions on the videos. Alongside receiving support via VOT, patients visit clinics to collect medication, to submit samples to the laboratory for assessment of response to treatment (Story et al. 2020).

Standard DOT practice involves a trained health professional, or responsible lay person supported by a trained health professional, who provides the prescribed medication and observes the patient swallowing every dose (or for some schedules observing doses during weekdays with self-administered therapy at weekends). Organised by the tuberculosis clinic, DOT is delivered according to usual practice, including: a) clinic based; b) community based working with a responsible professional such as a hostel worker or pharmacist; c) through a DOT worker outreaching DOT (NICE; 2016).

The WHO treatment guidelines (WHO; 2017) recommend VOT as a suitable alternative to in-person DOT if the resources for its use are available.

A recent review by Garfein and Doshi (Garfein and Doshi 2019) outlines the evidence on effectiveness, feasibility, efficacy and costs of synchronous (live) and

asynchronous (recorded) VOT via smartphones, tablets or computers. This review highlights the importance of VOT as a tool to monitor and achieve patient adherence by demonstrating its comparability to or higher than in-person DOT and offers a cheaper alternative to in-person DOT.

Asynchronous VOT has successfully been used in London since 2007 (Story et al. 2016b) and findings from a recent trial in London have been favourable (Story et al. 2019). Findings from a total of 226 patients were enrolled; 112 randomised to VOT and 114 to DOT show at least 80% of scheduled observed doses were completed (the primary outcome measure) was greater for VOT than DOT (70% vs 31%; adjusted odds ratio 5.45; 95% confidence interval 3.10 to 9.68; $p<0.001$). Fifty-eight percent had a history of homelessness, imprisonment, drug use, alcohol problems or mental health problems. It was estimated that six months of daily VOT cost £1,645 ($2,118) per patient compared to £5,700 ($7,340) for five-times per week DOT or £3,420 ($4,403) for three-times per week DOT. The full trial protocol details are reported: International Standard Randomized Controlled Trial Number Registry (study ISRCTN26184967, DOI 10.1186/ISRCTN26184967). Findings from the trial are reported in the Appendix.

1.8 Theoretical models and TB adherence behaviour

Whilst Munro and colleagues (Munro, Lewin, Swart, et al. 2007) reviewed theoretical perspectives from which to frame HIV/AIDS and TB, there is still limited evidence of theory-driven behaviour change interventions best improve adherence to treatment for short-term curable conditions like TB, which may be distinct from that of lifelong conditions like HIV.

Adherence to TB treatment is crucial to achieve positive treatment outcomes for the affected individual, minimise risk of developing drug-resistant disease and wider public health benefit. Yet there is inherent complexity in the development of adherence-promoting interventions (Nieuwlaat et al. 2014).

These findings demonstrate the need for further research designing and evaluating interventions that account for the interplay of intersecting determinants of poor adherence which may vary within and between individuals over the course of treatment.

There are numerous determinants of adherence that exist at an intrinsic level (internal to the patient) and extrinsic level (external to the patient, such as environmental or health system-related factors) (Jones et al. 2021) (Horne et al. 2005) (Horne et al. 2019). There can be intra-person and inter-person variation in the relative importance of these determinants over time and across prescribed treatments.

With respect to TB, social risk factors such as homelessness, imprisonment, and alcohol or drug misuse determinants are commonly found to be associated with non-adherence (Jones et al. 2021; Anderson et al. 2016; Story et al. 2007), without integrative or approaches to better understand patient experience, an understanding of how social complexity contributes to disproportionality in TB treatment outcomes will be lacking. Clinical and socio-demographic factors are largely non-modifiable within the realms of applied health research and will require substantial structural and policy changes. Health system and psychosocial factors were less commonly evaluated (Jones et al. 2021). The lack of exploration of health system and psychosocial factors that may influence non-adherence to TB treatment in the published evidence base provides a limited understanding of the contextual drivers

that underpin adherence behaviour, which may serve as potential targets for intervention design.

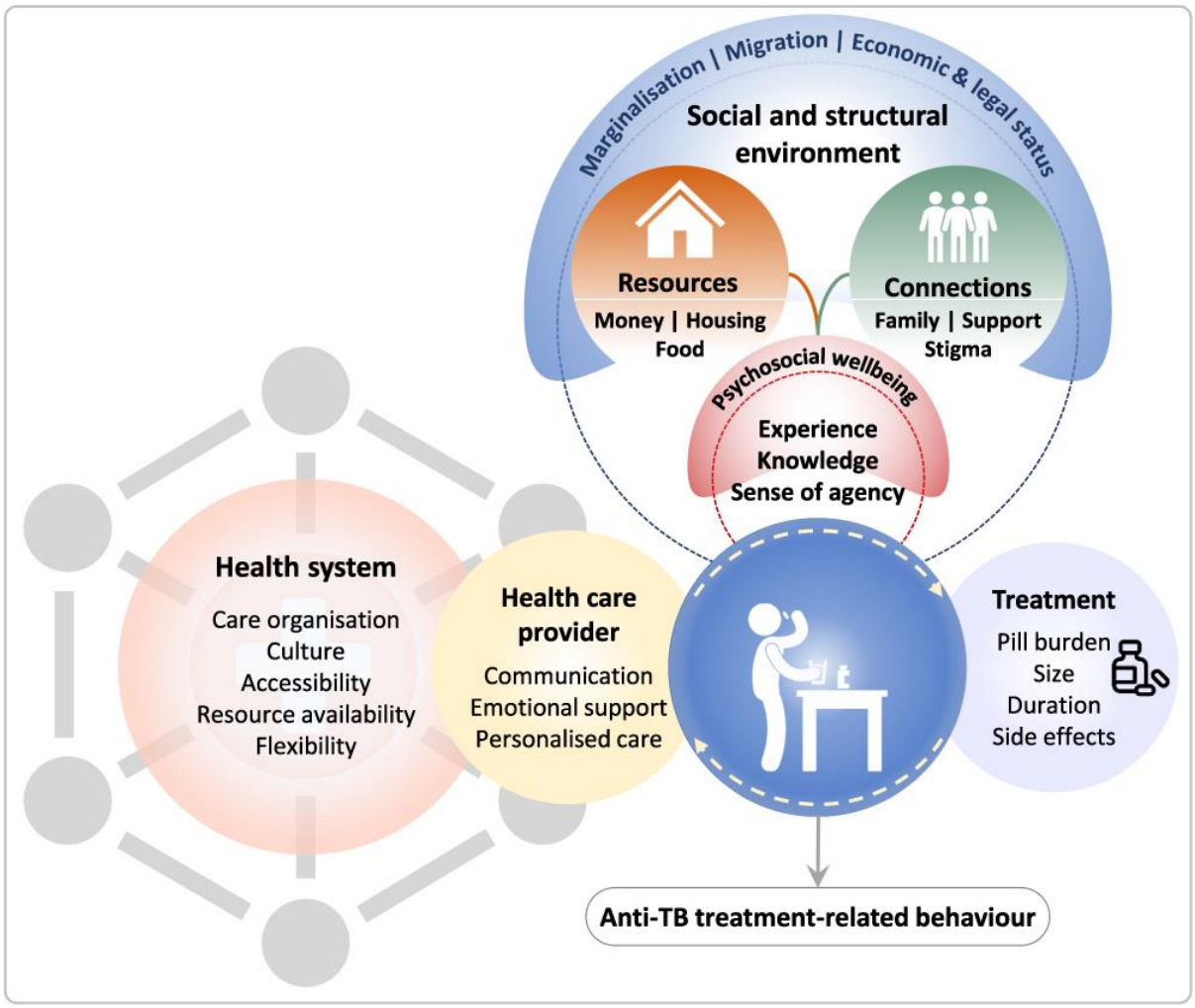


Figure 8: A socio-ecological model of the factors affecting adherence to anti-tuberculosis treatment (Source: (Kielmann K 2019))

Many factors that affect an individual's ability to access and remain on their TB treatment are beyond the control of an individual (Munro, Lewin, Smith, et al. 2007). However, the clinical concepts that explain adherence pay little regard to patient experiences and encounters with their treatment without an assessment of the broader and contextual drivers that affect individuals' motivation and ability to remain on treatment. Arakelyan *et al* (Arakelyan et al. 2021) have critically synthesised

qualitative evidence of the mechanisms through which socio-ecological factors influence the experience of being on TB treatment in high-income low incidence settings. These were classified into five domains: treatment-related, personal, social, health system and structural (Figure 8). These domains are characterised as follows:

- Treatment-related: individuals' responses to the number of tablets, complexity of regimens, duration of treatment and its side-effects, and potential interactions between TB and other medication (Craig and Zumla 2015; Curtis et al. 1994; Shiratani 2019; Gerrish, Naisby, and Ismail 2013; Searle, Park, and Littleton 2007; Moffatt, Mayan, and Long 2013; Macdonald, Rigillo, and Brassard 2010).
- Personal: how being on treatment fitted into their daily lives, sense of agency and control, health and treatment-related knowledge, experience of having treatment and being on treatment
    - Sense of agency, autonomy and control: struggles to preserve autonomy, regain control of life, and a compromised sense of self-efficacy were linked to behaviour. Forgetfulness was blamed for missed doses, and reports of patients strategically "forgotten" doses to help them regain control of their lives or return to a normal life (Kawatsu et al. 2018; Marra et al. 2004; Konradsen et al. 2014; Sagbakken, Bjune, and Frich 2012).
    - Lay knowledge, beliefs and perception of TB and TB treatment: Misconceptions, incorrect or lay knowledge, and ethno-medical beliefs regarding TB causes, transmission, and treatment outcomes were reported to negatively impact TB treatment-related behaviour via diagnostic delays, loss-to-follow-up after sputum tests, and patients not

returning for outpatient follow-up visits. Lay causes of TB included religious ideas, poisoning, cigarette and alcohol use, unsanitary conditions, poor nutrition, wearing wet clothes, colds, coughs, contact with a person with TB, and overworking, which in some scenarios led to a misinterpretation of initial symptoms (Curtis et al. 1994; Grace and Chenhall 2007; Searle, Park, and Littleton 2007; Wannheden et al. 2013; Nnoaham et al. 2006; Gibson et al. 2005; Zuñiga et al. 2014; Yamada et al. 1999).

- Physical Experience of TB and Comorbidities: Disease chronicity and a possibility of recurrence, comorbidities (HIV, diabetes), and associated general physical weakness influenced the illness experience of being on TB treatment, which, in turn affected non-adherence to treatment. Co-infection with HIV can compound patients' health issues (for example, weight loss, cough) and increase social stigmatisation (Curtis et al. 1994; Pujol-Cruells and Vilaplana 2019; Shiratani 2019; Searle, Park, and Littleton 2007; Nnoaham et al. 2006).
- Substance misuse: For people with TB who used drugs, drug use for example, crack cocaine, heroin) was often prioritised over treatment (Craig and Zumla 2015; Curtis et al. 1994; Searle, Park, and Littleton 2007; Marra et al. 2004).
- Psychosocial factors: Anxiety and worries about the consequences of having TB as well as being on treatment, self-stigmatization, and resulting social isolation and loneliness compromised health-seeking behaviour (Shiratani 2019; Gerrish, Naisby, and Ismail 2013; Searle, Park, and Littleton 2007; Nnoaham et al. 2006; Gibson et al. 2005;

Sagbakken, Bjune, and Frich 2012; Zuñiga et al. 2014; Yamada et al. 1999; van der Oest et al. 2005).

- Social: these included social and cultural norms, values, relationships, and networks that were reported to impact positively or negatively on the experience of TB treatment including adherence behaviour.
    - Social and community life: Social roles and daily lives including interactions with family, friends, peers, and other social networks affected (and in turn were affected by) the experience of having TB and being on TB treatment. Disruptive effects of treatment on daily life. (Pujol-Cruells and Vilaplana 2019; Moffatt, Mayan, and Long 2013; Macdonald, Rigillo, and Brassard 2010; Marra et al. 2004; Gibson et al. 2005; Konradsen et al. 2014).
    - Social support / lack of support: this was most pronounced in migrants, people who used drugs and ethnic minority groups. For many groups living in urban areas without family support exacerbated social isolation (Craig and Zumla 2015; Pujol-Cruells and Vilaplana 2019; Gerrish, Naisby, and Ismail 2013; Moffatt, Mayan, and Long 2013; Macdonald, Rigillo, and Brassard 2010; Marra et al. 2004).
    - Stigma: negative impact of TB-related social stigma on individual treatment-seeking behaviour was reported. For some migrants, stigma related to TB was marked and could result in exclusion of the individual from family and social networks (Craig and Zumla 2015; Gerrish, Naisby, and Ismail 2013; Konradsen et al. 2014; Yamada et al. 1999).
- Health system-related: patients' access to and use of health services, the organization of care and treatment regimens, perceived quality of care, and

relationships with healthcare professionals, including communication and support.

    - Access to TB-related knowledge and care: knowledge and health-seeking related to TB may be poorer among migrant groups and linked these to limited availability and accessibility of information, particularly in languages other than English. Documented delays in diagnosis or early misdiagnosis by frontline health services, with subsequent delays in treatment and frustration and anger for patients. This was worsened by being social exclusion, economic disadvantage or having a “chaotic” lifestyle, which affected individuals’ ability to afford to attend for care, not registered with primary care or were reluctant to seek care (Curtis et al. 1994; van der Oest et al. 2005; Craig, Joly, and Zumla 2014).
    - Organisation of care: poor understanding of the necessity of treatment contributed to collective negative experiences of healthcare in marginalised groups (Moffatt, Mayan, and Long 2013; Macdonald, Rigillo, and Brassard 2010; Komarnisky et al. 2016).
    - Interactions and communication with healthcare professionals: power imbalance inherent in the patient–provider relationship, noting the rigidity of treatment regimens, which gave greater power to healthcare professionals who could threaten patients by referring to policy enforcement (Curtis et al. 1994; van der Oest et al. 2005; Gibson et al. 2005; Wieland et al. 2012; Nnoaham et al. 2006; Sagbakken, Bjune, and Frich 2012).
- Structural: social and political mechanisms that generate and reinforce social class divisions, placing individuals within hierarchies of power, prestige, and

access to resources and how these affect patients' access to TB care and TB treatment adherence behaviour.

- Policies and funding: broader policy and financial environment negatively affecting availability of support services for people taking TB treatment, particularly for socio-economically deprived individuals (Craig and Zumla 2015; Curtis et al. 1994; Grace and Chenhall 2007).
- Legal status of migrants and refugees: migrants faced language barriers and barriers to employment that in turn affected health literacy and health-seeking behaviour. Fear of deportation or expulsion from the country resulted in mistrust of the health system, which negatively affected treatment-seeking behaviour, and also discouraged individuals' ability to voice an opinion on their treatment experience (Pujol-Cruells and Vilaplana 2019; Wannheden et al. 2013; Sagbakken, Bjune, and Frich 2012; Zuñiga et al. 2014; Yamada et al. 1999; Kulane, Ahlberg, and Berggren 2010).
- Socio-economic marginality: Homelessness, loss of employment, and associated financial difficulties affected TB patients' ability to access treatment and adhere to treatment. TB patients who lost their work due to TB experienced subsequent financial difficulties, but lacked confidence to look for employment opportunities because of fears of being stigmatized or marginalized by potential employers or colleagues (Kielmann et al. 2018; Curtis et al. 1994; Gerrish, Naisby, and Ismail 2013; Marra et al. 2004).
- Experience of violence: impact of past experiences of segregation, violence, torture, or physical or sexual abuse on current health-seeking

behaviour, including treatment-related behaviours (Moffatt, Mayan, and Long 2013; Marra et al. 2004; Komarnisky et al. 2016).

While treatment-related and personal characteristics were directly related to TB treatment-related behaviour, it also highlighted that individuals' motivation and ability to take TB treatment were embedded in a complex interplay of structural, health system-related factors and social relationships (Arakelyan et al. 2021). Figure 8 provides a useful framework through which to view patients' lives and challenges to adherence to TB treatment, as viewed through a socio-ecological model. This socio-ecological model highlights the challenges for person-centred intervention design if modifiable factors are to be accounted for in order to target poor adherence behaviour. Figure 9 presents a conceptualisation of the key behaviours to target and the mechanisms by which interventions are designed to prompt behaviour change.

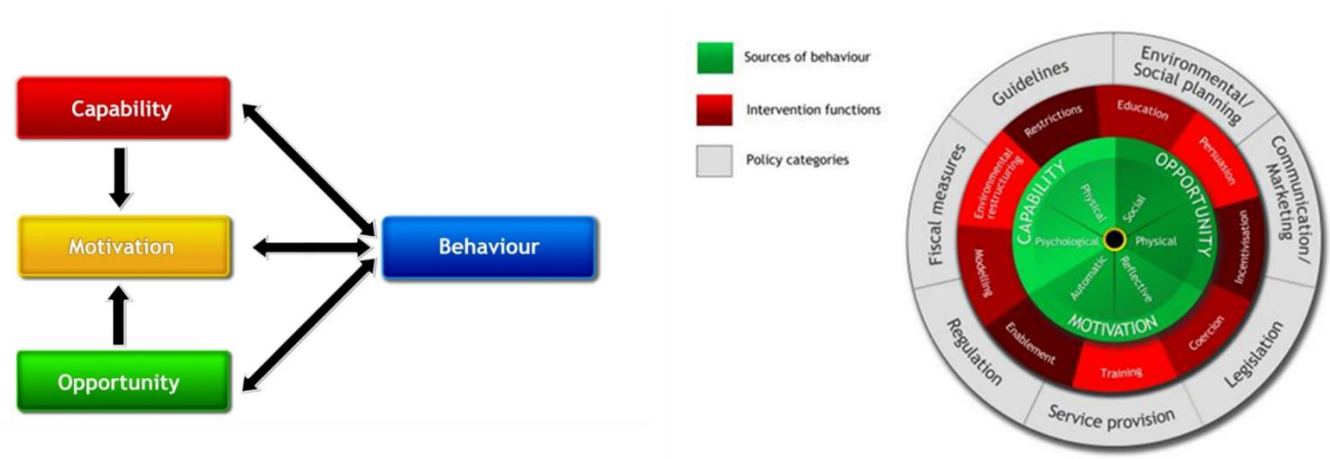


Figure 9: The COM-B model and the Behaviour Change Wheel. Source: (Michie, van Stralen, and West 2011)

The COM-B model is a comprehensive and solution-focused framework, which has been applied to understand adherence behaviour (Jackson, Eliasson, and Weinman 2014) has three components: Capability, Opportunity and Motivation.

1. Capability: consists of psychological and physical capability. Psychological capability deals with the cognitive ability of patients. Physical capability relates to patients' ability to modify their lifestyle
2. Opportunity: consists of physical and social sub-components. Physical opportunity relates to the cost of treatment, packaging, physical appearance, access to treatment and health services, regime complexity, patient-doctor communication and the social support provided to patients. Social opportunity relates to the stigma attached to the disease and the cultural beliefs that affect adherence.
3. Motivation: relates to the reflective and automatic factors affecting a patients' motivation. The reflective factor includes patients' perception of their illness, their belief about the treatment and the outcome. Automatic motivation relates to stimuli, mood or patients' state of mind.

The COM-B model forms the 'hub' of the Behaviour Change Wheel (BCW) (Michie, van Stralen, and West 2011), which is surrounded by nine intervention functions aimed at addressing deficits in one or more of these conditions; around this are placed seven categories of policy that could enable those interventions to occur. Application of the BCW starts with the basic question: *'what conditions internal to individuals and in their social and physical environment need to be in place for a specified behavioural target to be achieved*' (Michie, van Stralen, and West 2011). The BCW serves as a useful tool to enable users to design and select interventions and policies according to an analysis of the nature of the behaviour, the mechanisms

that need to be changed in order to bring about behaviour change, and the interventions and policies required to change those mechanisms (Michie, van Stralen, and West 2011).

The Theoretical Domains Framework (TDF) of behaviour change (Michie et al. 2005) simplifies and integrates 33 theories and 128 key theoretical constructs related to behaviour change into a single framework. Theoretical constructs are grouped into 14 domains by Michie *et al* (Cane, O'Connor, and Michie 2012), which encompass individual, social and environmental factors, with most relating to individual motivation and capability factors (Atkins et al. 2017). Skills can be sub-categorised into cognitive and interpersonal, and physical factors (Table 2).

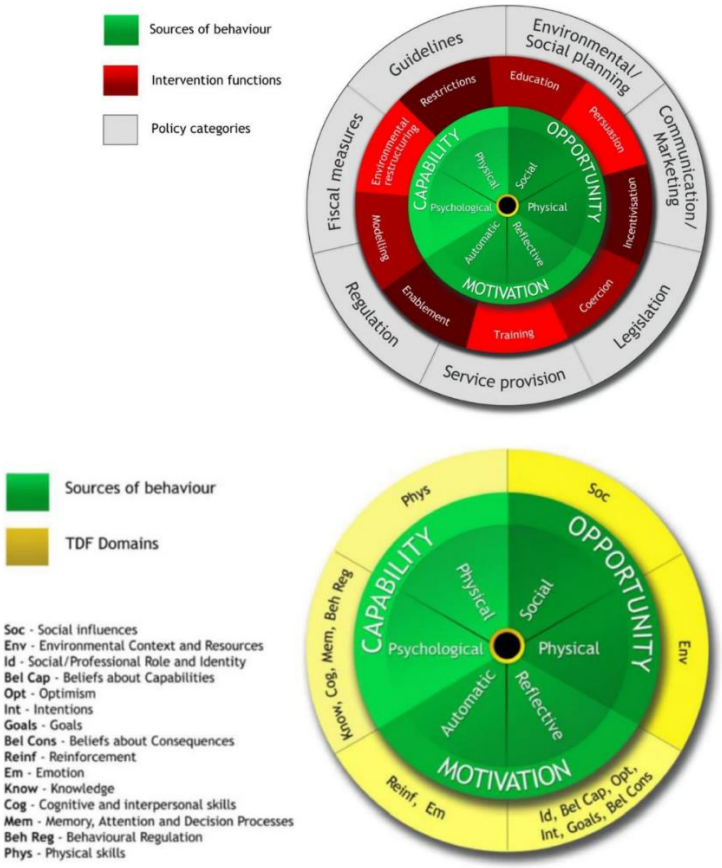


Figure 10: The Behaviour Change Wheel (BCW) (above) and the relationship with the Theoretical Domains Framework (TDF)

Table 2: Theoretical Domains Framework (TDF) of behaviour change domains and definitions

COM-B		TDF domain	Definition
Capability	Psychological	Knowledge	An awareness of the existence of something.
		Skills: cognitive and interpersonal	An ability or proficiency acquired through practice.
		Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives.
		Behavioural regulation	Anything aimed at managing or changing objectively observed or measured actions.
	Physical	Skills: physical	An ability or proficiency acquired through practice.
Opportunity	Social	Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings or behaviours.
	Physical	Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behaviour.
Motivation	Reflexive	Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an

COM-B		TDF domain	Definition
			individual in a social or work setting.
		Beliefs about capabilities	Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put to constructive use.
		Optimism	The confidence that things will happen for the best or that desired goals will be attained.
		Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way.
		Goals	Mental representations of outcomes or end states that an individual wants to achieve.
		Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation.
	Automatic	Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus.
		Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual

COM-B		TDF domain	Definition
			attempts to deal with a personally significant matter or event.

The Perceptions and Practicalities Approach (PAPA) (Horne et al. 2005) outlines that non-adherence can both be un-intentional and intentional (as shown by two overlapping circles in Figure 11) and is determined by overlapping conscious processes, such as decisions on whether or how to take the medicine and unconscious processes, including the effect of environmental cues and unconscious habits. For example, simply forgetting to take the medications, difficulty in understanding instructions, poor recall and the inability to pay for the medicines are barriers beyond the control of an individual and constitute un-intentional non-adherence. Conversely, intentional non-adherence occurs when an individual decides not to follow treatment recommendations.

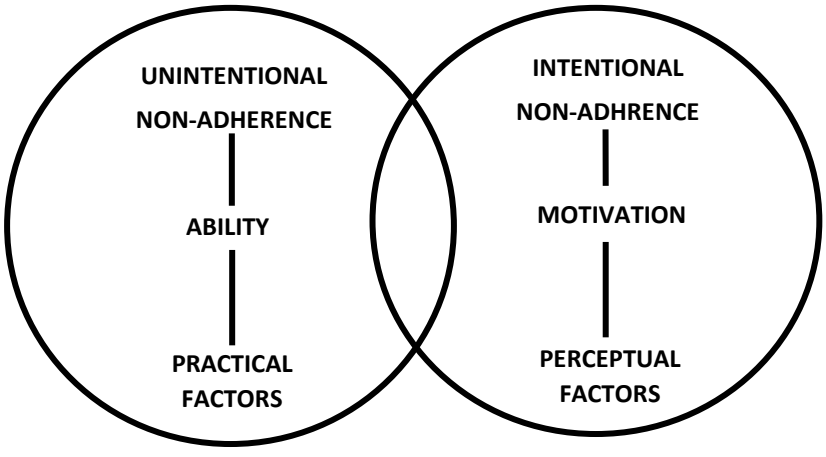


Figure 11: A conceptual map of the Perceptions and Practicalities Approach (PAPA) (Horne 2001; Horne et al. 2005)

The PAPA approach recognises that adherence and non-adherence behaviour can vary and is best understood by appreciating the affected individual's encounter with the specific treatment from the basic premise that two key attributes that are considered essential for adherence: motivation and ability. It presumes that, although a wide variety of intrinsic factors (e.g. depression and anxiety) and extrinsic factors (e.g. environmental opportunities and constraints) are relevant, their effect on adherence is likely to manifest through enhanced or reduced motivation and/or ability.

The NICE Medicines Adherence Guidelines (NICE; 2009) upholds the PAPA approach and recommends that support should be tailored to meet the needs of the individual by addressing both the perceptual and practical factors. These guidelines also acknowledge that perceptual and practical dimensions of adherence are influenced by social, cultural, economic and healthcare system contexts.

Adherence to prescribed medicines links non-adherence to *necessity beliefs*, specifically perceptions on personal need for treatment and this is relative to how concerned they are about the adverse consequences of taking that medicine (*concerns*). This has given rise to the 'Necessity-Concerns Framework (NCF)' (Horne et al. 2013) (Figure 12), which emphasises the role of patients' attitudes and decisions about their treatment. In terms of adherence to treatment, the NCF predicts that adherence will be associated with a stronger perception for the necessity for treatment and fewer concerns about adverse consequences.

A deeper understanding of a patient's necessity beliefs and their concerns about their prescribed treatment is central to how healthcare professionals can support patients in making informed decisions about their treatment and provide support to patients in adhering to prescribed regimens.

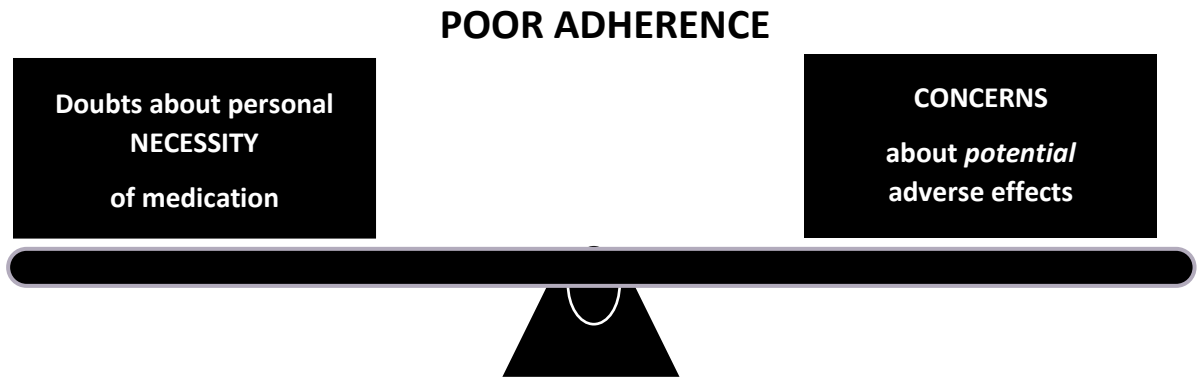


Figure 12: A depiction of the Necessity-Concerns Framework (Horne et al. 2013)

Horne and colleagues (Horne et al. 2009) have previously postulated the existence of a symbiotic relationship between the Necessity-Concerns Framework (NCF) and Leventhal's Common-Sense Model of self-regulation (CSM) (Leventhal, Leventhal, and Contrada 1998; Leventhal, Diefenbach, and Leventhal 1992) in explaining variations in treatment uptake and adherence. The CSM provides a framework to allow us to understand the *process* by which treatment perceptions influence adherence, and how the *content* of illness representations relates to these treatment representations. In addition, treatment perceptions and the NCF can be used to extend understanding of the CSM in relation to treatment adherence. Figure 13 shows how the Necessity Concerns Framework can be incorporated into Leventhal's CSM, producing an extended model (e-CSM).

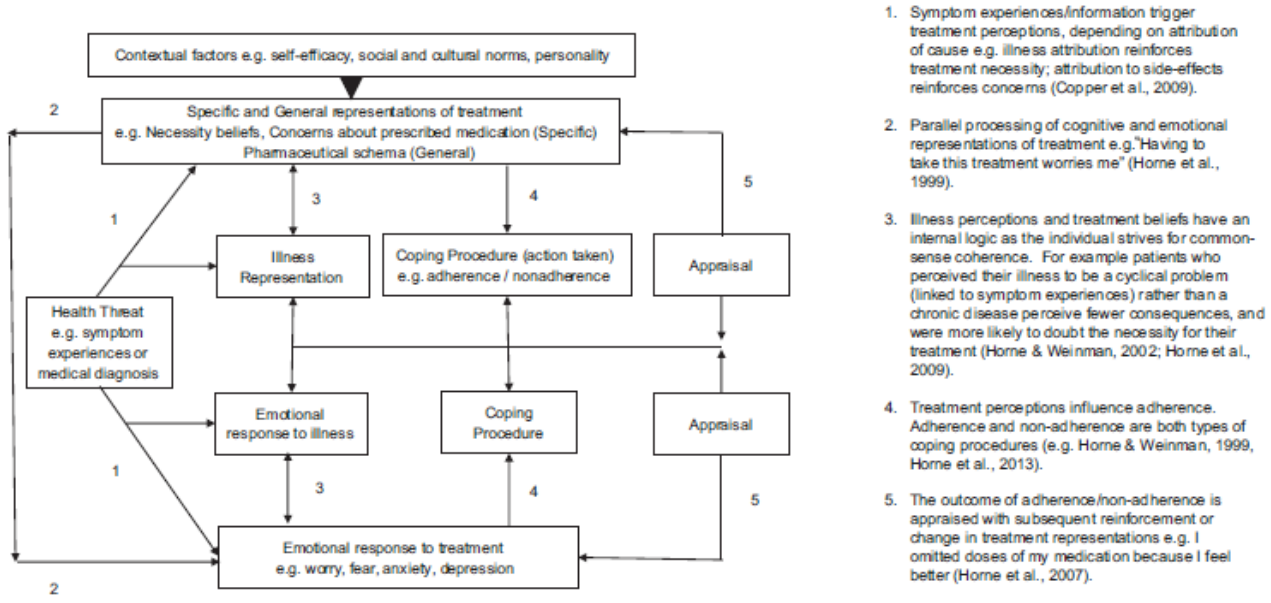


Figure 13: Treatment representations extending Levanthal's Common-Sense Model of Self-regulation (e-CSM). Source: Horne R et al; 2019

Figure 14 below provides a revised broad depiction of how PAPA can be extended to incorporate the NCF and e-CSM.

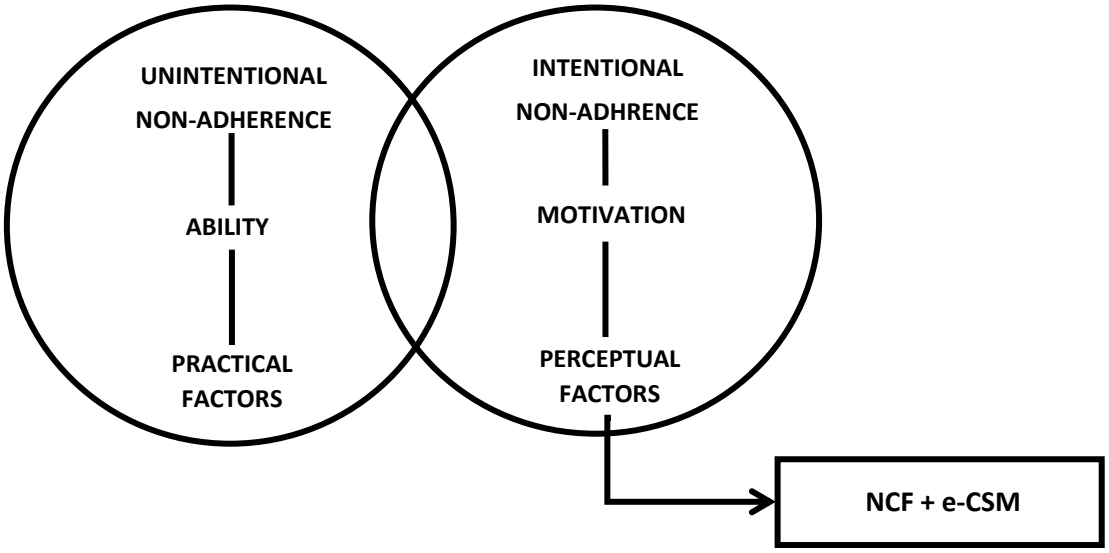


Figure 14: Extended PAPA model to include the NCF and e-CSM

1.9 Purpose of study

Under the auspices of the End TB Strategy, adherence intervention design and evaluation should explicitly target modifiable social and behavioural determinants of adherence, thereby supporting high-risk groups in accessing and engaging with patient-centred care.

Evidence supports the use of VOT as a feasible, effective and cost-effective case management tool to support monitoring of TB treatment adherence. Evidence included in this PhD thesis demonstrates that the underlying determinants of non-adherence to treatment are complex and operate at multiple levels and patients need additional support, such as encouragement through family and healthcare worker support, social support, a 'friendly' regimen that adequately balances dosing frequency with complexity to manage adverse events and incentives. To avoid replicating the 'paternalistic' aspects of DOT, the effective implementation of VOT into clinical strategies requires further work to understand how the functional components or 'active ingredients' of VOT may target the known perceptual and practical determinants of non-adherence to TB treatment and encounters high-risk patient groups face in accessing and engaging with care to elicit optimal adherence levels. I will use the PAPA framework, COM-B model and the Behaviour Change Wheel as theoretical frameworks to do this in order to support decision making on who VOT may be beneficial for and under what circumstances it be commissioned.

In 2015, I was employed as a Study Coordinator on the NIHR-funded trial assessing the effectiveness of VOT in supporting treatment adherence amongst patients with TB. My role was to lead on the qualitative aspects and collect patient satisfaction and health-related quality of life data. Given that our UK team was the first in the world to

evaluate VOT through a RCT and because we were advising a number of different international teams on its evaluation in their settings, I decided to build a doctoral research study around VOT to help better understand how it could be tailored to patient groups in those who benefit thereby reducing poor adherence and minimising inefficiencies. Furthermore my PhD thesis will contribute to an evolving understanding of how to build sustainable and inclusive strategies and address crucial knowledge gaps in understanding how VOT can facilitate healthcare access, equity and outcomes for different groups. For example, a patient-centred approach to TB treatment using a package of adherence interventions tailored to patients' needs and values may lead to improved TB treatment outcomes. The optimal package of adherence interventions to implement may vary by setting, resources, and the local epidemiology of TB (e.g. prevalence of comorbidities, including HIV coinfection), among other factors.

1.10 Research questions and methods

Using a series of studies, this doctoral research study aims to improve understanding of patient groups who may benefit most from VOT. To inform VOT's practical rollout, I will use a variety of methods to inform public health decision-making and healthcare planning to understand people's experiences of VOT in the UK and different settings and to draw conclusions on whether VOT should be universally available or on a selective basis, triaging patients depending on which groups both engage with and achieve optimal adherence levels to facilitate individualised or differentiated care to DOT or VOT.

At a population level, identifying patient groups who require adherence support will determine whether existing national guidance remains consistent with patient need and understand the proportion of patients who may benefit from VOT. This warrants an empirical analysis of a national TB surveillance dataset in England. This will also help to better understand factors that influence poor adherence in low incidence settings. Chapter 2 will identify factors that predict non-completion of TB treatment in a nationwide retrospective cohort of drug-susceptible and –resistant TB from 2010 to 2017.

Verifying true treatment adherence is dependent on the level of engagement achieved with DATs. In the context of initial engagement with VOT (for example the first video call with a patient when expected treatment doses are observed by a healthcare professional or 'VOT observer') represents an important aspect of adherence, the initiation phase. Over-reporting of adherence, for example through self-reporting via SMS text messages or phone calls without being observed taking the expected doses can limit the accuracy of measuring adherence. Conversely, patients who do not submit video clips because of travel commitments or high mobility, but nevertheless take their pills, can lead to under-reporting of adherence. Chapter 3 will examine the factors which affect the levels of engagement with DOT and VOT and whether this affects the level of observation achieved in DOT and VOT groups. Comparing assessments of levels of engagement and observation achieved with adherence in VOT and DOT will provide important insights into triaging patients depending on which groups both engage with and achieve optimal adherence levels to facilitate individualised or differentiated care to DOT or VOT for each of these approaches.

To build upon this and to understand how VOT and DOT support adherence in people's lives, Chapter 4 will explore the lived experiences and perceptions of DOT and VOT interventions in patients with TB in two settings: the UK (high income, low prevalence of TB) and the Republic of Moldova (middle-income, high prevalence of TB). This will identify the mechanisms by which DOT and VOT work in people's lives and the challenges encountered when these interventions are instigated.

The specific research questions, objectives and their contributions to the overall thesis are presented in Figure 1 and Table 3 below.

Table 3: Research study questions, objectives and methodology

Chapter	Research question	Objective	Relevance	Methodology
2	What patient groups do not complete TB treatment	To identify factors that predict non-completion of TB treatment in a nationwide retrospective cohort of drug-susceptible and –resistant TB from 2010 to 2017	To identify patient groups who do not complete TB treatment and need additional support	A retrospective cohort analysis of cases with TB notified to the Enhanced TB Surveillance System in England, Wales and Northern Ireland between 2010 and 2017. Multivariable logistic regression models were built to identify socio-demographic and clinical factors associated with non-completion

Chapter	Research question	Objective	Relevance	Methodology
				of TB treatment.
3	Which patient groups engage with VOT	To examine the factors which affect the levels of engagement with DOT and VOT and whether affects the level of observation achieved in DOT and VOT groups	A quantitative assessment of the level of engagement will serve as a measure of acceptability and a proxy measure of accuracy in measuring true adherence in groups supported by DOT and VOT	A secondary analysis of the UK DOT/VOT trial dataset using descriptive analysis and logistic regression to determine: a) adherence amongst patients randomised to DOT and VOT b) risk factors for the level of initial engagement in both allocated groups c) adherence amongst patients who initially engage with DOT and VOT
4	How does DOT and VOT support adherence in people's lives	To describe the lived experiences and perceptions of DOT and VOT interventions in patients with TB in the UK and the Republic of Moldova	A qualitative assessment of acceptability of DOT and VOT and will identify the mechanisms by which DOT and VOT work and the challenges encountered	Semi-structured interviews with 16 UK DOT/VOT trial participants and 22 Moldovan DOT/VOT trial participants A thematic analysis was used to analyse

Chapter	Research question	Objective	Relevance	Methodology
				data f to understand how the different VOT approaches compared to DOT and were perceived by patients in both settings, how they fitted into patients' lives and how they may or may not have supported them in taking prescribed doses regularly.

1.11 Candidate's role in the thesis

My approach to the PhD has been informed by a range of research roles I have held over the course of my career as a public health scientist. Whilst employed as a Senior Scientist in the Public Health England TB Unit, I conducted an empirical study analysis of the ETS TB surveillance dataset. I was employed as a Study Coordinator as part of the NIHR-funded TB Reach VOT trial through collecting data on patient satisfaction and health-related quality of life and conducted concurrent qualitative interviews with trial participants embedded in the randomised controlled trial and co-designed interview topic guides. I was also responsible for interview transcription and analysis for this thesis. I secured a small grant from the Royal Society of Tropical Medicine and Hygiene (RSTMH) for a qualitative study embedded in an existing VOT trial in Moldova. As the grant-holder for the RSTMH-funded study I was responsible for all aspects of the integrity and conduct of the study, its oversight,

obtaining ethical approval, data sharing agreements with research partners, qualitative interview data collection, translation and transcription and analysis. As part of my field trip to Moldova I was able to liaise with UNDP personnel and polyclinic staff to understand the TB patient pathway and health system.

I have strengthened my knowledge of adherence behaviour theories through my Research Assistant post as part of Professor Rob Horne's NIHR-funded SUPA programme, which aimed to evaluate a behavioural intervention to support adherence to HIV treatment. I supported the development of scoping reviews for the NIHR-commissioned IMPACT study, which aims to develop a manualised intervention to support adherence to treatment for TB. Concurrently I have drawn policy insights on patient-centred care from my role as a Senior Scientist at Public Health England supporting the strengthening of national TB programmes across EU and EEA member states through development of a TB Strategy Toolkit, in close collaboration with WHO Europe and ECDC. Through my substantive role as Migrant Health Evidence and Delivery Lead & Inclusion Health Programme Manager, I have developed evidence-informed guidance for healthcare professionals to address the health needs of migrant patients. I have also been involved in applying policy responses to national guidance development for providers of settings for inclusion health groups during the COVID-19 pandemic and sharing lessons learnt to inform the strategic vision and operational processes for the emerging Health Equity directorate of the new UK Health Security Agency.

My supervisors Professor Andrew Hayward and Professor Rob Horne have both provided feedback on conceptualisation, study designs, conduct and interpretation of findings. Professor Hayward provided tuition fee sponsorship and guidance on epidemiological approaches and expertise on health and social care needs of

inclusion health groups in the UK. Professor Horne has served as a line manager for both the NIHR-funded SUPA and NIHR-funded IMPACT study and introduced me to theoretical frameworks to represent adherence behaviour and the contribution of the PAPA framework to the NICE Medicines Adherence Guidelines.

Chapter 2: Factors associated with non-completion of TB treatment: a retrospective study in England, Wales and Northern Ireland, 2010 to 2017

2.1 Abstract

Objective: to identify factors that predict non-completion of TB treatment in a nationwide retrospective cohort of drug-susceptible and drug-resistant TB from 2010 to 2017

Methods: I conducted a retrospective study of cases with TB notified to the Enhanced TB Surveillance System in England, Wales and Northern Ireland between 2010 and 2017. I defined non-completion of TB treatment as cases with TB who were lost to follow-up, stopped TB treatment, still on treatment and were not evaluated (either transferred out or where the treatment outcome was unknown) by the end of the TB notification period. Multivariable logistic regression was used to identify socio-demographic and clinical factors associated with non-completion of TB treatment.

Results: Between 2010 and 2017, 59,602 cases with TB were notified in England. Wales and Northern Ireland, of which 14.6% (8,710/59,602) did not complete TB treatment. Being male (aOR: 1.20; 95% CI: 1.14 - 1.26), in the 15-44 age group (aOR: 1.70; 95% CI: 1.43 - 2.02) ≥45 age group (aOR: 3.55; 95% CI: 2.99 - 4.22), recent migration to the UK (0 -1 years since entry to UK to TB notification: aOR: 2.46 (95% CI: 2.25 - 2.69); 2-5 years since entry to UK to TB notification: aOR: 1.35 (95% CI: 1.23 - 1.48), a previous TB diagnosis (aOR: 1.42; 95% CI: 1.30 - 1.55), increasing social complexity (for four social risk factors: aOR: 2.73; 95% CI: 1.78 - 4.18) and multidrug resistance (aOR: 4.07; 95% CI: 3.36 - 4.94) were significantly associated with non-completion of TB treatment in the multivariable model.

Conclusion: At a population level there are challenges in supporting TB treatment adherence. Some inclusion health groups and those with multidrug-resistant disease need additional support.

2.2 Introduction

Despite an approximate 44% decline in numbers and rates of people with TB from a peak of 8,280 in 2011 to 4,655 in England in 2018, there remains a need to address the needs of inclusion health groups with social risk factors (homelessness, drug misuse, prison history or alcohol misuse problems). Amongst those with drug-susceptible TB, treatment completion is lower in people with at least one social risk factor (78.7%; 418/531) compared those without a social risk factor (89.1%; 3,399/3,816).

In low incidence settings like the UK, targeted approaches to tackle TB in inclusion health groups alongside wider system efforts to improve treatment, prevent resistance and implement new technologies are needed (Lönnroth K et al; ERJ 2015). Such efforts need to mitigate destabilising socio-structural factors and loss to follow-up due to negative TB treatment experiences (excessive travel time to clinic, lost earnings or employment, adverse side effects) to facilitate close and regular contact with healthcare workers to motivate and support patients to adhere to treatment.

Identifying patients at risk of non-completion of TB treatment will determine whether existing NICE guidance remains consistent with patient need and understand the proportion of patients who may benefit from VOT.

2.3 Objective

To identify factors that predict non-completion of TB treatment in a nationwide retrospective cohort of drug-susceptible and drug-resistant TB from 2010 to 2017

2.4 Methods

Study population:

Cases with TB are reported as statutory notifications to Public Health England through the Enhanced TB Surveillance (ETS) System by clinicians, which also includes data on the clinical, microbiological and sociodemographic characteristics of each TB case. ETS and the national HIV and AIDS Reporting System (HARS) data were linked to determine the HIV status of cases with TB using a probabilistic matching algorithm based on patient identifiers common to both the TB and HIV datasets. This dataset included statutory notifications of cases with TB of all ages in England, Wales and Northern Ireland between 2010 and 2017.

Outcomes: Non-completion of TB treatment:

The ETS includes case reports are either entered at the clinic level or at the Health Protection Team level and includes deaths from the Office of National Statistics. Treatment non-completion was defined as cases with TB who were lost to follow-up, stopped TB treatment, still on treatment and were not evaluated (either transferred out or where the treatment outcome was unknown) by the end of the TB notification period (at 12 months for drug-susceptible TB and at 24 months for drug-resistant TB).

Table 4: Breakdown of individual treatment outcomes used to create composite outcome variable, non-completion of TB treatment

	N (%)
Overall outcome at end of notification period	
TB treatment completed	50,892 (85.4)
Died	3,172 (5.3)
Lost to follow-up	2,633 (4.4)
Still on treatment	595 (1.0)
Treatment stopped	614 (1.0)
Not evaluated	1,696 (2.9)
Total	59,602 (100)

Exposure variables:

I included sociodemographic variables (gender, age, ethnicity, place of birth, index of multiple deprivation (IMD) quintiles, the number of years since entry to the UK, history of homelessness, drug misuse, imprisonment, alcohol misuse, urban/rural classification and PHE centre). I also included clinical variables (diagnostic delay, site of TB disease, previous TB diagnosis, BCG vaccination status, HIV status, mono- and multidrug resistance (as determined by drug susceptibility testing or whole genome sequencing).

IMD quintiles represent relative levels of income, employment, health, housing and services, education, crime and living environment for small areas in England and Wales, where 1= most deprived and 5 = least deprived.

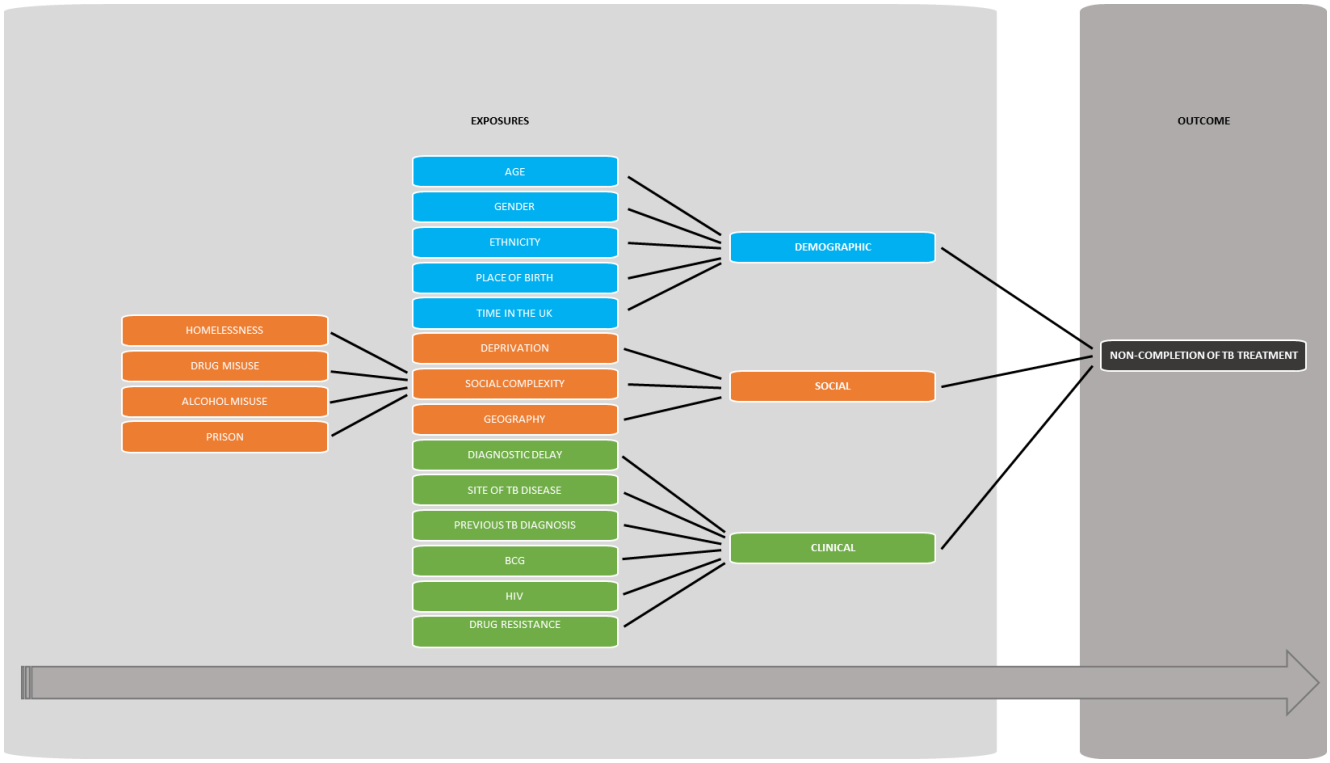


Figure 15: Schematic diagram showing demographic, social and clinical exposures variables included from the national TB surveillance dataset to assess association with non-completion of TB treatment

2.5 Statistical analysis

I analysed the data using STATA version 15.1. I completed descriptive analyses of the study population by examining the proportions of cases with TB who did not complete treatment over the study period.

I used univariable logistic regression models to assess factors that were associated with the outcome of interest, as a dichotomous outcome variable (treatment completed versus non-completion of TB treatment). For this, I calculated the proportion of TB cases stratified by each exposure variable and estimated the odds ratios (ORs).

I built a multivariable model to understand which explanatory variables predicted the outcome of interest (non-completion of TB treatment) when controlling for *a priori* confounders and any factors shown to predict the outcome of interest at the $p<0.05$ level from the univariable analyses. Owing to the large dataset, all co-variates were found to be significant at the $p\leq0.05$ level in the univariable analyses therefore decisions on which variables to retain for multivariable analysis were determined by examining the size of the effect of each co-variate, its 95% confidence intervals and statistical significance.

2.6 Results

2.6.1 Descriptive epidemiology in patients with drug-susceptible and drug-resistant TB who do not complete TB treatment between 2010 and 2017

There were 59,602 cases of TB reported to the ETS in England, Wales and Northern Ireland between 2010 and 2017. Overall, 14.6% (8,710/59,602) did not complete TB treatment and 85.4% (50,892/59,602) did complete treatment.

Table 5 shows the risk factors associated with treatment non-completion in patients with drug-susceptible and drug-resistant TB between 2010 and 2017. During this study period, non-completion of TB treatment was more prevalent amongst men (5,525/34,544, 16%) compared to women (3,175/24,990, 12.7%) and amongst cases with TB who were over 45 years (4,689/22,327, 21%).

Of 8,710 cases who did not complete TB treatment, 12.5% (1,089/8,710) had at least one social risk factor. Non completion was most frequent amongst those with greater social complexity, 27.8% (36/108 with 4 social risk factors (33%) who did not complete treatment compared to 5,336/4,5437 (11.7%) of those with no social risk factors).

Table 5: Descriptive statistics: risk factors associated with non-completion of TB treatment in patients with drug-susceptible and drug-resistant TB between 2010 and 2017

	Total	Treatment not completed n	% (95% CI)	p-value
Sex				
Female	24,990 (41.9)	3,175	12.7 (12.3 – 13.1)	<0.001
Male	34,544 (58.0)	5,525	16.0 (15.6 - 16.4)	
Not reported	68 (0.1)	10	14.7 (7.3 - 25.4)	
Age group				
0-14	2,492 (4.2)	157	6.3 (5.4 - 7.3)	<0.001
15-44	34,783 (58.4)	3,864	11.1 (10.8 – 11.4)	
≥45	22,327 (37.5)	4,689	21.0 (20.5 – 21.5)	
Ethnic group				
White	13,763 (23.1)	2,993	21.7 (21.1 - 22.4)	<0.001
Black	10,941 (18.4)	1,138	10.4 (9.8 – 11.0)	
Black Other	525 (0.9)	50	9.5 (7.2 - 12.4)	
Asian	26,311 (44.1)	3,347	12.7 (12.3 - 13.1)	
Mixed	6,861 (11.5)	785	11.4 (10.7 - 12.2)	
Not recorded	1,201 (2.1)1	397	33.1 (30.4 - 35.8)	

	Total	Treatment not completed n	% (95% CI)	p-value
UK born status				
Non-UK born	41,751 (70.1)	5,362	12.8 (12.5 – 13.2)	<0.001
UK born	16,116 (27.0)	2,693	16.7 (16.1 – 17.3)	
Not reported	1,735 (2.9)	655	37.8 (35.5 – 40.0)	
Years since entry to UK to TB notification				
0-1 years	6,950 (11.7)	1,254	18.0 (17.1 – 19.0)	<0.001
2-5 years	9,783 (16.4)	1,026	10.5 (9.9 – 11.1)	
6-10 years	7,557 (12.7)	598	7.9 (7.3 – 8.5)	
11 or more years	13,621 (22.9)	1,613	11.8 (11.3 - 12.4)	
Not reported	21,691 (36.4)	4,219	19.5 (18.9 – 20.0)	
Diagnostic delay (time from symptom onset to treatment start)				
0-2 months	17,413 (29.2)	2,575	14.8 (14.3 – 15.3)	<0.001
2-4 months	13,511 (22.7)	1,551	11.5 (10.9 – 12.0)	
≥ 4 months	15,781 (26.5)	1,625	10.3 (9.8 – 10.8)	
Not reported	12,897 (21.6)	2,959	22.9 (22.2 – 23.7)	
Site of disease				
Extra-pulmonary	27,590 (46.3)	3,108	11.3 (10.9 – 11.6)	<0.001
Pulmonary	31,666 (53.1)	5,432	17.2 (16.7 – 17.6)	
Not reported	346 (0.6)	170	49.1 (43.7 – 54.5)	

	Total	Treatment not completed n	% (95% CI)	p-value
Previous TB diagnosis				
No	52,851 (88.7)	6,798	12.9 (12.6 – 13.2)	<0.001
Yes	3,843 (6.5)	754	19.6 (18.4 – 20.9)	
Not reported	2,908 (4.9)	1,158	39.8 (38.0 – 41.6)	
BCG vaccination status				
No	12,634 (21.2)	1,908	15.1 (14.5 – 15.7)	<0.001
Yes	28,789 (48.3)	2,761	9.6 (9.3 – 9.9)	
Not reported	18,179 (30.5)	4,041	22.2 (21.6 – 22.8)	
HIV status				
Not known	57,745 (96.9)	8,388	14.5 (14.2 – 14.8)	0.001
Positive	1,857 (93.1)	322	17.3 (15.6 – 19.1)	
At least 1 social risk factor				
No	45,437 (76.2)	5,336	11.7 (11.4 – 12.0)	<0.001
Yes	5,081 (8.5)	1,089	21.4 (20.3 – 22.6)	
Not reported	9,084 (15.2)	2,285	25.2 (24.3 – 26.1)	
Number of social risk factors				
0	45,437 (76.2)	5,336	11.7 (11.4 - 12.0)	<0.001
1	3,434 (5.8)	677	19.7 (18.4 – 21.1)	
2	1,072 (1.8)	248	23.1 (20.6 – 25.8)	
3	467 (0.8)	128	27.4 (23.4 – 31.7)	
4	108 (0.2)	36	33.3 (24.6 – 43.1)	

	Total	Treatment not completed n	% (95% CI)	p-value
Not recorded	9,084 (15.2)	2,285	25.2 (24.3 – 26.1)	
History of drug misuse				
Never	51,863 (87.0)	6,515 (12.6)	12.6 (12.3 – 12.9)	<0.001
Current	400 (0.7)	81 (20.3)	20.3 (16.4 – 24.5)	
Last 5 years	400 (0.7)	56 (14.0)	14.0 (10.8 – 17.8)	
More than 5 years	144 (0.2)	17 (11.8)	11.8 (7.0 – 18.2)	
Unknown	6,795 (11.4)	2,041 (30.0)	30.0 (28.9 – 31.1)	
History of homelessness				
Never	52,056 (87.3)	6,543	12.6 (12.3 – 12.9)	<0.001
Current	621 (1.0)	160	25.8 (22.4 – 29.4)	
Last 5 years	326 (0.6)	58	17.8 (13.8 – 22.4)	
More than 5 years	130 (0.2)	16	12.3 (7.2 – 19.2)	
Unknown	6,469 (10.9)	1,933	29.9 (28.8 – 31.0)	
History of prison				
Never	50,645 (85.0)	6,201	12.2 (12.0 – 12.5)	<0.001
Current	344 (0.6)	97	28.2 (23.5 – 33.3)	
Last 5 years	511 (0.9)	96	18.8 (15.5 – 22.4)	
More than 5 years	545 (0.9)	95	17.4 (14.3 – 20.9)	
Unknown	7,557 (12.7)	2,221	29.4 (28.4 – 30.4)	
Alcohol misuse				
No	51,260 (86.0)	6,370	12.4 (12.1 – 12.7)	<0.001
Yes	2,076 (3.5)	528	25.4 (23.6 – 27.4)	

	Total	Treatment not completed n	% (95% CI)	p-value
Not recorded	6,266 (10.5)	1,812	28.9 (27.8 – 30.1)	
DST or WGS isoniazid resistance (no MDR)				
No	33,874 (56.8)	4,833	14.3 (13.9 – 14.6)	<0.001
Yes	1,954 (3.3)	384	19.7 (17.9 – 21.5)	
Not indicated	23,774 (39.9)	3,493	14.7 (14.2 – 15.1)	
DST or WGS Multidrug-resistant (to at least isoniazid and rifampicin)				
No	35,328 (59.3)	5,026	14.2 (13.9 – 14.6)	<0.001
Yes	519 (0.9)	195	27.6 (33.4 – 41.9)	
Not indicated	23,755 (39.9)	3,489	14.7 (14.2 – 15.1)	
Rural-urban classification				
Rural	53,541 (89.8)	7,188	13.4 (13.1 – 13.7)	<0.001
Urban	5,683 (9.5)	1,426	25.1 (24.0 – 26.2)	
Not recorded	378 (0.3)	96	25.4 (21.1 – 30.1)	
IMD rank by deprivation quintiles in PHE Centres				
1 (Most deprived)	18,863 (33.3)	2,400	12.7 (12.3 – 13.2)	<0.001
2	14,130 (25.0)	1,911	13.5 (13.0 – 14.1)	
3	9,160 (16.2)	1,227	13.4 (12.7 – 14.1)	
4	6,290 (11.1)	902	14.3 (13.5 – 15.2)	

	Total	Treatment not completed n	% (95% CI)	p-value
5 (Least deprived)	3,863 (6.8)	610	15.8 (14.7 – 17.0)	
Not reported	4,305 (7.6)	911	21.2 (19.9 – 22.4)	
PHE Centre				
East Midlands	3,412 (5.7)	590	17.3 (16.0 – 18.6)	<0.001
East of England	3,721 (6.2)	565	15.2 (14.0 – 16.4)	
London	22,261 (37.4)	2,526	11.4 (10.9 – 11.8)	
North East	1,120 (1.9)	201	18.0 (15.7 – 20.3)	
North West	5,508 (9.2)	822	14.9 (14.0 – 15.9)	
South East	5,387 (9.0)	756	14.0 (13.1 – 15.0)	
South West	2,291 (3.8)	474	20.7 (19.0 – 22.4)	
West Midlands	7,043 (11.8)	1,134	16.1 (15.2 – 17.0)	
Yorkshire	4,237 (7.1)	639	15.1 (14.0 – 16.2)	
Not reported	4,622 (7.8)	1,003	21.7 (20.5 – 22.9)	
Year				
2010	8,397 (14.1)	1,267	15.1 (14.3 – 15.9)	<0.001
2011	8,919 (15.0)	1,197	13.4 (12.7 – 14.1)	
2012	8,712 (14.6)	1,101	12.6 (11.9 – 13.4)	
2013	7,870 (13.2)	881	11.2 (10.5 – 11.9)	
2014	7,029 (11.8)	848	12.1 (11.3 – 12.8)	
2015	6,224 (10.4)	801	12.9 (12.0 – 13.7)	
2016	6,116 (10.3)	1,003	16.4 (15.5 – 17.4)	
2017	6,335 (10.6)	1,612	25.5 (24.4 – 26.5)	

2.6.2 Univariable analysis: factors affecting non-completion of TB treatment

The univariable model in Table 6 shows the unadjusted (crude) analysis of factors associated with the risk of non-completion of TB treatment.

Table 6: Univariable analysis: risk factors associated with non-completion of TB treatment in patients with drug-susceptible and drug-resistant TB between 2010 to 2017

	Total	**Treatment not completed n (%)**	**Unadjusted odds ratio (95% CI)**	**p-value**
Sex				
Female	24,990 (41.9)	3,175 (12.7)	1	
Male	34,544 (58.0)	5,525 (16.0)	1.31 (1.25 - 1.37)	<0.001
Not reported	68 (0.1)	10 (14.7)	1.18 (0.60 - 2.32)	0.621
Age group				
0-14	2,492 (4.2)	157 (6.3)	1	
15-44	34,783 (58.4)	3,864 (11.1)	1.86 (1.58 - 2.19)	<0.001
≥45	22,327 (37.5)	4,689 (21.0)	3.95 (3.35 - 4.66)	<0.001
Ethnic group				
White	13,763 (23.1)	2,993 (21.7)	1	
Black	10,941 (18.4)	1,138 (10.4)	0.42 (0.39 - 0.45)	<0.001
Black Other	525 (0.9)	50 (9.5)	0.38 (0.28 - 0.51)	<0.001
Asian	26,311 (44.1)	3,347 (12.7)	0.52 (0.50 - 0.55)	<0.001
Mixed	6,861 (11.5)	785 (11.4)	0.46 (0.43 - 0.51)	<0.001
Not recorded	1,201 (2.1)	397 (33.1)	1.78 (1.57 - 2.02)	<0.001
UK born status				

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value
Non-UK born	41,751 (70.1)	5,362 (12.8)	1	
UK born	16,116 (27.0)	2,693 (16.7)	1.36 (1.29 - 1.43)	<0.001
Not reported	1,735 (2.9)	655 (37.8)	4.12 (3.72 - 4.55)	<0.001
Years since entry to UK to TB notification				
11 or more years	13,621 (22.9)	1,613 (11.8)	1	
0-1 years	6,950 (11.7)	1,254 (18.0)	1.64 (1.51 - 1.78)	<0.001
2-5 years	9,783 (16.4)	1,026 (10.5)	0.87 (0.80 - 0.95)	0.001
6-10 years	7,557 (12.7)	598 (7.9)	0.64 (0.58 - 0.71)	<0.001
Not reported	21,691 (36.4)	4,219 (19.5)	1.80 (1.69 - 1.91)	<0.001
Diagnostic delay (time from symptom onset to treatment start)				
0-2 months	17,413 (29.2)	2,575 (14.8)	1	
2-4 months	13,511 (22.7)	1,551 (11.5)	0.75 (0.70 - 0.80)	<0.001
≥ 4 months	15,781 (26.5)	1,625 (10.3)	0.66 (0.62 - 0.71)	<0.001
Not reported	12,897 (21.6)	2,959 (22.9)	1.72 (1.62 - 1.82)	<0.001
Site of disease				
Extra-pulmonary	27,590 (46.3)	3,108 (11.3)	1	
Pulmonary	31,666 (53.1)	5,432 (17.2)	1.63 (1.56 - 1.71)	<0.001
Not reported	346 (0.6)	170 (49.1)	7.61 (6.14 - 9.42)	<0.001
Previous TB diagnosis				
No	52,851 (88.7)	6,798 (12.9)	1	
Yes	3,843 (6.5)	754 (19.6)	1.65 (1.52 - 1.80)	<0.001
Not reported	2,908 (4.9)	1,158 (39.8)	4.48 (4.14 - 4.85)	<0.001
BCG vaccination status				

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value
No	28,789 (48.3)	2,761 (9.6)	1	
Yes	12,634 (21.2)	1,908 (15.1)	0.60 (0.56 - 0.63)	<0.001
Not reported	18,179 (30.5)	4,041 (22.2)	1.61 (1.51 - 1.71	<0.001
HIV status				
Not known	57,745 (96.9)	8,388 (14.5)	1	
Positive	1,857 (3.1)	322 (17.3)	1.23 (1.09 - 1.39)	<0.001
At least 1 social risk factor				
No	45,437 (76.2)	5,336 (11.7)	1	
Yes	5,081 (8.5)	1,089 (21.4)	2.05 (1.91 - 2.21)	<0.001
Not reported	9,084 (15.2)	2,285 (25.2)	2.53 (2.39 - 2.67)	<0.001
Number of social risk factors				
0	45,437 (76.2)	5,336 (11.7)	1	
1	3,434 (5.8)	677 (19.7)	1.85 (1.69 - 2.02)	<0.001
2	1,072 (1.8)	248 (23.1)	2.26 (1.96 - 2.61)	<0.001
3	467 (0.8)	128 (27.4)	2.84 (2.31 - 3.48)	<0.001
4	108 (0.2)	36 (33.3)	3.76 (2.52 - 5.61)	<0.001
Not recorded	9,084 (15.2)	2,285 (25.2)	2.53 (2.39 - 2.67)	<0.001
History of drug misuse				
Never	51,863 (87.0)	6,515 (12.6)	1	
Current	400 (0.7)	81 (20.3)	1.77 (1.38 - 2.26)	<0.001
Last 5 years	400 (0.7)	56 (14.0)	1.13 (0.85 - 1.50)	0.388
More than 5 years	144 (0.2)	17 (11.8)	0.93 (0.56 - 1.55)	0.785
Unknown	6,795 (11.4)	2,041 (30.0)	2.99 (2.82 - 3.17)	<0.001

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value
History of homelessness				
Never	52,056 (87.3)	6,543 (12.6)	1	
Current	621 (1.0)	160 (25.8)	2.41 (2.01 - 2.90)	<0.001
Last 5 years	326 (0.6)	58 (17.8)	1.51 (1.13 - 2.00)	0.005
More than 5 years	130 (0.2)	16 (12.3)	0.98 (0.58 - 1.65)	0.928
Unknown	6,469 (10.9)	1,933 (29.9)	2.96 (2.79 - 3.15)	<0.001
History of prison				
Never	50,645 (85.0)	6,201 (12.2)	1	
Current	344 (0.6)	97 (28.2)	2.81 (2.22 - 3.57)	<0.001
Last 5 years	511 (0.9)	96 (18.8)	1.66 (1.33 - 2.07)	<0.001
More than 5 years	545 (0.9)	95 (17.4)	1.51 (1.21 - 1.89)	<0.001
Unknown	7,557 (12.7)	2,221 (29.4)	2.98 (2.82 - 3.16)	<0.001
Alcohol misuse				
No	51,260 (86.0)	6,370 (12.4)	1	
Yes	2,076 (3.5)	528 (25.4)	2.40 (2.17 - 2.66)	<0.001
Not recorded	6,266 (10.5)	1,812 (28.9)	2.87 (2.70 - 3.05)	<0.001
DST or WGS isoniazid resistance (no MDR)				
No	33,874 (56.8)	4,833 (14.3)	1	
Yes	1,954 (3.3)	384 (19.7)	1.47 (1.31 - 1.65)	<0.001
Not recorded	23,774 (39.9)	3,493 (14.7)	1.03 (0.99 - 1.08)	0.153
DST or WGS Multidrug-resistant (to at least isoniazid and rifampicin)				
No	35,328 (59.3)	5,026 (14.2)	1	
Yes	519 (0.9)	195 (37.6)	3.63 (3.03 - 4.34)	<0.001
Not recorded	23,755 (39.9)	3,489 (14.7)	1.04 (0.99 - 1.09)	0.118

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value
Rural-urban classification				
Rural	53,541 (89.8)	7,188 (13.4)	1	
Urban	5,683 (9.5)	1,426 (25.1)	2.16 (2.02 - 2.31)	<0.001
Not recorded	378 (0.6)	96 (25.4)	2.20 (1.74 - 2.77)	<0.001
IMD rank by deprivation quintiles in PHE Centres				
1 (Most deprived)	18,863 (33.3)	2,400 (12.7)	1	
2	14,130 (25.0)	1,911 (13.5)	1.07 (1.01 - 1.14)	0.033
3	9,160 (16.2)	1,227 (13.4)	1.06 (0.99 - 1.14)	0.116
4	6,290 (11.1)	902 (14.3)	1.15 (1.06 - 1.25)	0.001
5 (Least deprived)	3,863 (6.8)	610 (15.8)	1.29 (1.17 - 1.42)	<0.001
Not reported	4,305 (7.6)	911 (21.2)	1.84 (1.69 - 2.00)	<0.001
PHE Centre				
London	22,261 (37.4)	2,526 (11.4)	1	
East Midlands	3,412 (5.7)	590 (17.3)	1.63 (1.48 - 1.80)	<0.001
East of England	3,721 (6.2)	565 (15.2)	1.40 (1.27 - 1.54)	<0.001
North East	1,120 (1.9)	201 (18.0)	1.71 (1.46 - 2.00)	<0.001
North West	5,508 (9.2)	822 (14.9)	1.37 (1.26 - 1.49)	<0.001
South East	5,387 (9.0)	756 (14.0)	1.28 (1.17 - 1.39)	<0.001
South West	2,291 (3.8)	474 (20.7)	2.04 (1.83 - 2.27)	<0.001
West Midlands	7,043 (11.8)	1,134 (16.1)	1.50 (1.39 - 1.62)	<0.001
Yorkshire	4,237 (7.1)	639 (15.1)	1.39 (1.26 - 1.52)	<0.001
Not reported	4,622 (7.8)	1,003 (21.7)	2.17 (2.00 - 2.35)	<0.001
Year				
2010	8,397 (14.1)	1,267 (15.1)	1	

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value
2011	8,919 (15.0)	1,197 (13.4)	0.87 (0.80 - 0.95)	0.002
2012	8,712 (14.6)	1,101 (12.6)	0.81 (0.75 - 0.89)	<0.001
2013	7,870 (13.2)	881 (11.2)	0.71 (0.65 - 0.78)	<0.001
2014	7,029 (11.8)	848 (12.1)	0.77 (0.70 - 0.85)	<0.001
2015	6,224 (10.4)	801 (12.9)	0.83 (0.76 - 0.91)	<0.001
2016	6,116 (10.3)	1,003 (16.4)	1.10 (1.01 - 1.21)	<0.032
2017	6,335 (10.6)	1,612 (25.5)	1.92 (1.77 - 2.09)	<0.001

2.6.3 Multivariable analysis: factors affecting non-completion of TB treatment

The final multivariable model in Table 7 included gender, age, ethnicity, place of birth, years since entry to UK to TB notification, previous TB diagnosis, MDR-TB, number of social risk factors and TB notification year. It shows cases with TB and multidrug resistance had a four-fold increased odds of non-completion of TB treatment compared to drug-susceptible cases with TB (aOR 4.07; 95% CI: 3.36 - 4.94; p<0.001). Cases with TB with social risk factors were significantly more likely to not complete TB treatment when compared to cases with no social risk factors (p<0.001). Findings show there was an increasing trend in odds of non-completion of TB treatment and increasing social complexity: one social risk factor: aOR: 1.52; 95% CI: 1.38 - 1.67), for two social risk factors: aOR 1.72; 95% CI: 1.47 - 2.00), for three social risk factors: aOR 2.16; 95% CI: 1.73 - 2.69 and for four social risk factors: aOR 2.73; 95% CI: 1.78 - 4.18). Recent migrants who had received a TB

notification up to 5 years since arrival in the UK were significantly more likely to not complete TB treatment (p<0.001). Recent migrants who received a TB notification within 1 year of arrival in the UK (1,254/6,950, 18%) had a two-and-a-half fold increased odds of not completing TB treatment compared to those who had received a TB notification 11 years of more since arrival in the UK (aOR: 2.46; 95% CI: 2.25 - 2.69; p<0.001). Migrants who received a TB notification between two to five years of arrival in the UK (1,026 /9,783, 10.5%) had a 0.35 increased odds of not completing TB treatment (aOR:1.35; 95% CI: 1.23 - 1.48; p<0.001) and for those who arrived in the UK within 6-10 years had low risk of non-completion of TB treatment (aOR: 0.90; 95% CI: 0.81 - 1.00; p=0.045) in 8% (598/7,557) of cases compared to those who had received a TB notification 11 years of more since arrival in the UK. Cases with a previous TB diagnosis had an increased risk of TB treatment non-completion (aOR: 1.42; 95% CI: 1.30 - 1.55; p<0.001) compared to those who had not previously had TB. Cases with TB in the ≥45 year age group had over a three-and-a-half fold increased odds of not completing TB treatment (aOR: 3.55; 95% CI: 2.99 - 4.22; p<0.001) compared to the 0-14 age group. There was a modest increase in odds in the 15-44 age group (aOR: 1.70; 95% CI: 1.43 - 2.02; p<0.001). Male cases with TB had increased odds of not completing TB treatment (aOR: 1.20; 95% CI: 1.14 - 1.26; p<0.001) compared to females cases. UK born cases with TB had low risk of not completing TB treatment (aOR 0.53; 95% CI: 0.48 - 0.59; p<0.001) compared to non-UK born cases with TB.

Table 7: Multivariable analysis: risk factors associated with non-completion of TB treatment in patients with drug-susceptible and drug-resistant TB between 2010 and 2017 after adjusting for confounders

	Total	**Treatment not completed n (%)**	**Unadjusted odds ratio (95% CI)**	**p-value**	**Adjusted odds ratio (95% CI)**	**p-value**
Sex						
Female	24,990 (41.9)	3,175 (12.7)	1		1	
Male	34,544 (58.0)	5,525 (16.0)	1.31 (1.25 - 1.37)	<0.001	1.20 (1.14 - 1.26)	<0.001
Not reported	68 (0.1)	10 (14.7)	1.18 (0.60 - 2.32)	0.621	0.87 (0.43 - 1.78)	0.708
Age group						
0-14	2,492 (4.2)	157 (6.3)	1		1	
15-44	34,783 (58.4)	3,864 (11.1)	1.86 (1.58 - 2.19)	<0.001	1.70 (1.43 - 2.02)	<0.001
≥45	22,327 (37.5)	4,689 (21.0)	3.95 (3.35 - 4.66)	<0.001	3.55 (2.99 - 4.22)	<0.001

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Ethnic group						
White	13,763 (23.1)	2,993 (21.7)	1		1	
Black	10,941 (18.4)	1,138 (10.4)	0.42 (0.39 - 0.45)	<0.001	0.61 (0.56 - 0.67)	<0.001
Black Other	525 (0.9)	50 (9.5)	0.38 (0.28 - 0.51)	<0.001	0.53 (0.39 - 0.72)	<0.001
Asian	26,311 (44.1)	3,347 (12.7)	0.52 (0.50 - 0.55)	<0.001	0.74 (0.69 - 0.80)	<0.001
Mixed	6,861 (11.5)	785 (11.4)	0.46 (0.43 - 0.51)	<0.001	0.65 (0.58 - 0.72)	<0.001
Not recorded	1,201 (2.1)	397 (33.1)	1.78 (1.57 - 2.02)	<0.001	0.99 (0.85 - 1.16)	0.917
UK born status						
Non-UK born	41,751 (70.1)	5,362 (12.8)	1		1	
UK born	16,116 (27.0)	2,693 (16.7)	1.36 (1.29 - 1.43)	<0.001	0.53 (0.48 - 0.59)	<0.001
Not reported	1,735 (2.9)	655 (37.8)	4.12 (3.72 - 4.55)	<0.001	1.07 (0.93 - 1.23)	0.356

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
Years since entry to UK to TB notification						
11 or more years	13,621 (22.9)	1,613 (11.8)	1		1	
0-1 years	6,950 (11.7)	1,254 (18.0)	1.64 (1.51 - 1.78)	<0.001	2.46 (2.25 - 2.69)	<0.001
2-5 years	9,783 (16.4)	1,026 (10.5)	0.87 (0.80 - 0.95)	0.001	1.35 (1.23 - 1.48)	<0.001
6-10 years	7,557 (12.7)	598 (7.9)	0.64 (0.58 - 0.71)	<0.001	0.90 (0.81 - 1.00)	0.049
Not reported	21,691 (36.4)	4,219 (19.5)	1.80 (1.69 - 1.91)	<0.001	2.36 (2.14 - 2.60)	<0.001
Previous TB diagnosis						
No	52,851 (88.7)	6,798 (12.9)	1		1	
Yes	3,843 (6.5)	754 (19.6)	1.65 (1.52 - 1.80)	<0.001	1.42 (1.30 - 1.55)	<0.001
Not reported	2,908 (4.9)	1,158 (39.8)	4.48 (4.14 - 4.85)	<0.001	2.46 (2.24 - 2.71)	<0.001
DST or WGS Multidrug-resistant (to at least isoniazid and rifampicin)						

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
No	35,328 (59.3)	5,026 (14.2)	1		1	
Yes	519 (0.9)	195 (37.6)	3.63 (3.03 - 4.34)	<0.001	4.07 (3.36 - 4.94)	<0.001
Not recorded	23,755 (39.9)	3,489 (14.7)	1.04 (0.99 - 1.09)	0.118	1.09 (1.04 - 1.14)	0.001
Number of social risk factors						
0	45,437 (76.2)	5,336 (11.7)	1		1	
1	3,434 (5.8)	677 (19.7)	1.85 (1.69 - 2.02)	<0.001	1.52 (1.38 - 1.67)	<0.001
2	1,072 (1.8)	248 (23.1)	2.26 (1.96 - 2.61)	<0.001	1.72 (1.47 - 2.00)	<0.001
3	467 (0.8)	128 (27.4)	2.84 (2.31 - 3.48)	<0.001	2.16 (1.73 - 2.69)	<0.001
4	108 (0.2)	36 (33.3)	3.76 (2.52 - 5.61)	<0.001	2.73 (1.78 - 4.18)	<0.001
Not recorded	9,084 (15.2)	2,285 (25.2)	2.53 (2.39 - 2.67)	<0.001	1.72 (1.61 - 1.84)	<0.001
Year of TB notification						
2010	8,397 (14.1)	1,267 (15.1)	1		1	

	Total	Treatment not completed n (%)	Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
2011	8,919 (15.0)	1,197 (13.4)	0.87 (0.80 - 0.95)	0.002	0.93 (0.85 - 1.02)	0.127
2012	8,712 (14.6)	1,101 (12.6)	0.81 (0.75 - 0.89)	<0.001	0.91 (0.83 - 1.00)	0.044
2013	7,870 (13.2)	881 (11.2)	0.71 (0.65 - 0.78)	<0.001	0.82 (0.74 - 0.90)	<0.001
2014	7,029 (11.8)	848 (12.1)	0.77 (0.70 - 0.85)	<0.001	0.91 (0.83 - 1.01)	0.069
2015	6,224 (10.4)	801 (12.9)	0.83 (0.76 - 0.91)	<0.001	1.02 (0.92 - 1.12)	0.744
2016	6,116 (10.3)	1,003 (16.4)	1.10 (1.01 - 1.21)	<0.032	1.35 (1.23 - 1.49)	<0.001
2017	6,335 (10.6)	1,612 (25.5)	1.92 (1.77 - 2.09)	<0.001	2.31 (2.11 - 2.52)	<0.001

*adjusted for gender, age, ethnicity, place of birth, Years since entry to UK to TB notification, previous TB diagnosis, MDR-TB, number of social risk factors and TB notification year

2.7 Discussion

In this retrospective study, I have examined factors that affect non-completion of TB treatment in drug-susceptible and drug-resistant cases with TB from 2010 to 2017 in England, Wales and Northern Ireland. Findings show that 14.6% (8,710/59,602) did not complete TB treatment and 85.4% (50,892/59,602) did complete treatment. Non-completion of TB treatment was more prevalent among those who were over 45 years old, non-UK born White and Black African and Caribbean ethnicity and UK born Asian cases with TB. Sex, age, place of birth, a previous TB diagnosis, multidrug resistance, increasing social complexity and a TB notification within 5 years of migration to the UK were all independently associated with an increased risk of non-completion of TB treatment.

My findings show that men were more likely to not complete TB treatment, compared to women. Globally, men are reported to have higher incident TB than women, with the male to female ratio being 2:1 according to the WHO (WHO; 2019). Evidence suggests that once women are enrolled in healthcare they are more likely to adhere to treatment compared to men, leading to better treatment outcomes (van den Hof et al. 2010). However, there may be other socio-economic factors that affect sex differences in treatment completion. The hidden catastrophic costs associated with TB care, such as attending clinic appointments and transport costs may affect employment and / or lead to expenses exceeding resources, which men, as sole earners or heads of households may push them and their families into destitution. Personal agency is an important factor governing adherence behaviour. Having non-paternalistic interventions or flexible approaches to complete treatment may be more appealing to men.

I found that patients of older age more likely to not complete TB treatment. People of older age may also have preconceived beliefs of treatment, have preferences in consulting with traditional healers (Watkins, Rouse, and Plant 2004; Mata 1985) or may perceive there to be consequences of concurrent TB medication with traditional medicine. It is conceivable due to the increasing complexity of managing multiple health problems with increasing age, adhering to a lengthy TB treatment regimen may also impose difficulties for older patients with TB.

There was an increasing trend in the non-completion of TB treatment in order of increasing social complexity. This finding is consistent with other research (Craig and Zumla 2015) highlighting service and policy responses to commission integrated specialist outreach services to address and care for groups who experience multiple and overlapping clinical and social risk factors, including those who are homeless, have drug and alcohol dependence or have faced other forms of social exclusion. Other research has theorised how intentional and non-intentional TB treatment adherence may manifest amongst socially complex groups, highlighting both personal social factors, but also institutional and structural contexts and policies and the absence of sustained partnership working between hospital settings and voluntary and community sector organisations to strengthen holistic approaches to support (Craig and Zumla 2015).

I found there was a pronounced increased risk of non-completion of TB treatment amongst those who had recently migrated to the UK. Evidence suggests both legal and undocumented migrants can contribute considerably to the TB burden in European cities, with evidence suggesting that active cases largely occur during to the reactivation of latent TB infection acquired overseas rather than through recent transmission (Dahle et al. 2007). Approximately 14% of the UK population was born

overseas and predominantly most people migrate to the UK for employment and study purposes (Crawshaw and Kirkbride 2018) and may have conceivably returned to their countries of origin. It is also plausible that after arrival to the UK, social and structural barriers including legal, language and cultural issues, living conditions, barriers to mainstream services, poor knowledge of the UK healthcare system and difficulties in understanding prescribed treatment regimens, which articulate the migrant experience may contribute to poor adherence (Abarca Tomás et al. 2013; Woodward, Howard, and Wolffers 2014). As reported in The Lancet Commission on Migration and Health (Abubakar et al. 2018), which unpacks the nuanced and complex patterns that migrants may face for temporary or permanent residency and the variable effects of social, environmental and pathogenic exposures on their health and wellbeing, a myriad of positive aspirational and negative drivers influence decisions to move on. Such high mobility with poor access or entitlements to timely and high-quality care will impose a significant challenge to continuing to take treatment for TB, leading to treatment interruption and consequent onward transmission.

This retrospective study benefits from seven years of statutory TB case notifications to a widely cited national TB surveillance programme, representing comprehensive coverage of England, Wales and Northern Ireland. As a large dataset, it is possible to adjust for confounding variables and it provides lots of power to make conclusive statements about findings and the multiple number of risk factors provide various ways to assess TB treatment non-completion in patient groups.

The ETS is an operational case notification system, which is heavily reliant on the collaboration of local TB services and local Health Protection Teams. There are some limitations of its use to assess completion of TB treatment and the choice of

variables to construct a composite outcome variable. ETS contains a mix of process and outcomes measures in a way that makes the results of TB treatment outcomes difficult to interpret from a clinical perspective (i.e. those still on treatment, treatment stopped) and these may represent people who may have had their initial treatment plan modified due to adverse events or drug toxicity as opposed to not completing the TB treatment. A closer measure of non-adherence to TB treatment would have been to focus on treatment failure, however sputum smear or culture positive status at month five or later was difficult to determine due to completeness.

On the creation of the composite outcome variable, non-completion of TB treatment and the decision to include the 'not evaluated' category, the national TB surveillance team treat these as those with negative treatment outcomes. While I could have completed a sensitivity analysis, the proportion of individuals whose treatment outcomes were not evaluated, 2.9% is so small, 20% of participants accounts for all of those who did not complete their TB treatment by the end of the notification period, and so it does not seem worthwhile. For those who are still on treatment by the end of the notification period, it is reasonable to assume there may have been poor tolerance to their treatment.

In some scenarios, some associations with non-completion of TB that remained in the multivariable analysis after adjusting for confounders were driven by missing data. For 39.8% (1,158/2,908) amongst cases with TB with no record of previous TB had over a two-and-a-half fold increased odds of non-completion of TB treatment (aOR: 2.46; 95% CI: 2.24 - 2.71; $p<0.001$). This effect was more profound in 19.5% (4,219/21,691) migrants and the corresponding years since entry to the UK to TB notification (aOR: 2.36; 95% CI: 2.14 - 2.60; $p<0.001$).

Using ETS makes it difficult to be conclusive about fidelity of ingested doses in that clinicians do not have certainty that patients complete treatment and so the data may be biased on the clinicians' part in that there may be pre-conceived judgements made about socially complex groups being more like to not complete their treatment.

Approximately 15% of the missing data where a treatment outcome was not recorded was concentrated in the number of social risk factors data, which introduces bias to the findings and influencing the relationship between social risk factor variables and outcomes for non-completion of TB treatment. This highlights the challenges in understanding poor adherence risk amongst highly mobile groups with well-documented challenges with reaching and engaging with health services, namely migrants and those with social complexity.

The over-estimation of these associations with non-completion of TB treatment hampers the ability to understand the true magnitude of the impact of these factors and limits the ability to appropriately inform relevant policy-level guidance and decision-makers.

Advanced statistical methods, such as multiple imputation could have been applied to address this limitation because it allows missing data to be handled in a way that is unbiased and statistically valid. Multiple imputation has not be applied for this analysis in accordance with supervisory advice.

BCG vaccination status was included in the analysis as an explanatory variable because its routinely collected by the ETS team. BCG vaccination is given shortly after birth and while it is a measure of parents' health-seeking behaviour as opposed to an individual's and it may offer individuals a greater sense of security from TB

infection and as such it may make them less concerned about adhering to TB treatment.

The secondary analysis of ETS to examine TB treatment completions status has been a useful exercise to examine to scale of non-completion of TB treatment, however its purpose is not solely for this use and so it lacks the level of detail needed to better understand drivers of non-completion and non-adherence. Levels of engagement with treatment and care are not a static phenomenon, rather the factors that govern how patients do this with vary according to a series of intrinsic and extrinsic factors. At the time of analysis, patients' TB treatment completion status may have changed (i.e. those who were lost to follow-up may have re-engaged with their care).

At a population level there are challenges in supporting TB treatment adherence. With reference to the objectives for this study, I have been able to identify salient clinical and socio-demographic factors, which predict non-completion of TB treatment. These findings identify important groups from which to develop tailored VOT interventions for, namely some inclusion health groups and patients with multidrug-resistant TB. The recently launched Public Health England health inequalities strategy to investigate and support work in socio-economic deprivation and its links with TB may provide a framework to characterise additional social and intermediate factors, which influence TB treatment adherence, which may be included in routine surveillance reporting.

Table 8: Overall Study objectives, methodology and Chapter 2 findings

Chapter	Research question	Objective	Relevance	Methodology	Findings
2	What patient groups do not complete TB treatment	To identify factors that predict non-completion of TB treatment in a nationwide retrospective cohort of drug-susceptible and –resistant TB from 2010 to 2017	To identify patient groups who do not complete TB treatment and need additional support	A retrospective cohort analysis of cases with TB notified to the Enhanced TB Surveillance System in England, Wales and Northern Ireland between 2010 and 2017. Multivariable logistic regression models were built to identify socio-demographic and clinical factors associated with non-completion of TB treatment, loss to follow-up and mortality.	Factors affecting non-completion of TB treatment. • Being male (aOR: 1.20; 95% CI: 1.14 - 1.26) • 15-44 age group (aOR: 1.70; 95% CI: 1.43 - 2.02) ≥45 age group (aOR: 3.55; 95% CI: 2.99 - 4.22) • Recent migration to the UK (aOR: 2.46; 95% CI: 2.25 - 2.69), • Increasing social complexity (aOR: 2.73; 95% CI: 1.78 - 4.18) • multidrug resistance (aOR: 4.07; 95% CI: 3.36 - 4.94).
3	What patient groups engage with VOT	To examine the factors which affect the levels of engagement with DOT and VOT and whether this affects the level of	A quantitative assessment of the level of engagement will serve as a measure of acceptability	A secondary analysis of the UK DOT/VOT trial dataset using descriptive analysis and logistic	

Chapter	Research question	Objective	Relevance	Methodology	Findings
		observation achieved in DOT and VOT groups	and a proxy measure of accuracy in measuring true adherence in groups supported by DOT and VOT	regression to determine: a) adherence amongst patients randomised to DOT and VOT b) risk factors for the level of initial engagement in both allocated groups c) adherence amongst patients who engage with DOT and VOT	
4	How does DOT and VOT support adherence in people's lives	To describe the lived experiences and perceptions of DOT and VOT interventions in people with TB in the UK and the Republic of Moldova	A qualitative assessment of acceptability of DOT and VOT and will identify the mechanisms by which DOT and VOT work and the challenges encountered when these interventions are instigated	Semi-structured interviews with 16 UK DOT/VOT trial participants and 22 Moldovan DOT/VOT trial participants A thematic analysis was used to analyse data from emerging	

Chapter	Research question	Objective	Relevance	Methodology	Findings
				themes to understand how the different VOT approaches compared to DOT and were perceived by patients in both settings, how they fitted into patients' lives and how they may or may not have supported them in taking prescribed doses regularly.	

Chapter 3: Factors affecting the level of engagement achieved in DOT and VOT groups

3.1 Abstract

Objective: to examine the factors which affect the levels of engagement with DOT and VOT and whether they affect the level of observation achieved in DOT and VOT groups

Methods: a secondary quantitative analysis of the multi-centre randomised-controlled trial UK trial comparing asynchronous VOT to in-person DOT in supporting treatment adherence in patient with active TB in England was conducted. Initial engagement was defined as at least one week of observed doses in the allocated DOT or VOT groups. Descriptive statistics using chi-squared tests were used to compare proportions of patients who engage with DOT and VOT and achieve 80% of scheduled observations. Multivariable logistic regression was used to assess adherence amongst patients who engage with DOT and VOT.

Results: Findings show greater initial engagement with VOT (101/112, 90%) compared to DOT (56/114, 49%). Across all risk factors studied (age group, sex, migration, ethnicity, social risk factors. Patients were more likely to engage with VOT (over 70% initial engagement in all groups) than they were to engage with DOT. Among those who initially engage, those on VOT were less likely to be lost to follow-up and self-report better levels of health-related quality of life compared to DOT. High levels of initial engagement with DOT (>70%) were also seen in those aged over 55, those who had been in prison or homeless more than 5 years ago and those with current alcohol problems.

Amongst those who initially engaged with VOT 78/101, 77% had more than 80% of scheduled treatment observations completed compared to 35/56, 63% of those who engaged with DOT. Amongst those who initially engaged, after adjusting for age, sex and a history of loss to follow-up, patients assigned to VOT were two-and-a-half times more likely to maintain 80% of their scheduled treatment observations compared to those who initially engaged with DOT (aOR: 2.54; 95% CI: 1.16 - 5.58; p=0.02). Women were less likely to adhere (aOR: 0.33; 95% CI: 0.14 - 0.77; p=0.01) and those with a history of loss to follow-up were also less likely to adhere (aOR: 0.18; 95% CI: 0.07 - 0.49; p=0.001).

Discussion: The higher levels of initial engagement with VOT suggest it is a more acceptable approach to TB treatment observation compared to DOT. This may be by providing a more holistic approach to TB treatment supervision, upholding autonomy and minimising the deleterious effects of social and economic disadvantage on poor TB treatment adherence. Further qualitative work to unpack the mechanisms into how initial engagement with DOT and VOT supported regular dosing will provide important insights into the development of differentiated and tailored approaches.

3.2 Introduction

In the previous chapter, in a population-based cohort study I examined the factors that affect non-completion of TB treatment, Findings showed that at a population level, 14.6% (8,710/59,602) did not complete TB treatment and 85.4% (50,892/59,602) did complete treatment. Being male (aOR: 1.20; 95% CI: 1.14 - 1.26), in the 15-44 age group (aOR: 1.70; 95% CI: 1.43 - 2.02) ≥45 age group (aOR: 3.55; 95% CI: 2.99 - 4.22), recent migration to the UK (0 -1 years since entry to UK to TB notification: aOR: 2.46 (95% CI: 2.25 - 2.69); 2-5 years since entry to UK to TB notification: aOR: 1.35 (95% CI: 1.23 - 1.48), a previous TB diagnosis (aOR: 1.42; 95% CI: 1.30 - 1.55), increasing social complexity (for four social risk factors: aOR: 2.73; 95% CI: 1.78 - 4.18) and multidrug resistance (aOR: 4.07; 95% CI: 3.36 - 4.94) were significantly associated with non-completion of TB treatment in the multivariable model. This demonstrated that some inclusion health groups and those with multidrug-resistant disease need additional support.

In this chapter I will examine objective measures that affect the level of initial engagement with DOT and VOT and whether these affect the level of observation and optimal adherence achieved in DOT and VOT groups. The ESPACOMP taxonomy for adherence (Vrijens et al. 2012) breaks the adherence continuum down into components: initiation, implementation and discontinuation phases. Initiation occurs when a patient takes their first dose of their prescribed treatment.

Initial engagement with VOT is a prerequisite for its effectiveness in promoting TB treatment adherence. Using PAPA and the NCF as the theoretical framework, it is hypothesised that initial engagement with VOT will positively influence patients'

ability to start and adhere to their TB treatment. It is also indicative of patients' motivation to start, their perceived need for the treatment relative to their concerns of the adverse consequences of taking the treatment (as defined by the Necessity-Concerns Framework). Therefore after a patient receives their TB diagnosis and starts their treatment, and providing they have a strong perception for the necessity to take their TB treatment, have few concerns about the adverse consequences of taking the treatment and feel as though it will not impede their ability to get on with their daily life, higher levels of observation will be achieved. Patient engagement with a digital behavioural change is a dynamic process as illustrated in Figure 16.

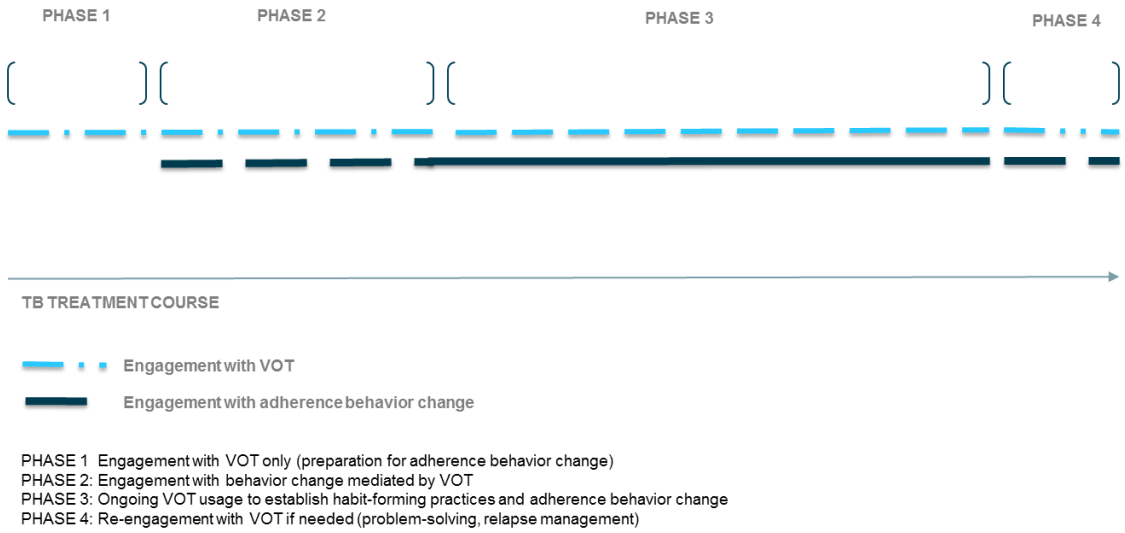


Figure 16: 'Micro' and 'macro' levels of engagement with VOT intervention

The patient's personal factors, the characteristics of VOT and the socio-cultural context will influence the level of engagement and optimal levels of adherence behaviour achieved over time. By understanding the relationship between these objective quantitative measures of engagement and whether they affect the level of observation and adherence achieved, it may be possible to determine the patient groups who benefit most from VOT.

3.3 Objective

To examine the factors which affect the levels of engagement with DOT and VOT and whether these factors also affect the level of observation achieved in DOT and VOT groups

3.4 Methods

Data on demographic, clinical, social and health-related quality of life were obtained from the UK DOT/VOT trial. The previously reported multi-centre randomised-controlled trial UK trial compared the efficacy of asynchronous VOT to in-person DOT amongst 226 patients for supporting treatment adherence in patients with active TB in England (Story et al. 2019). This is to say, this efficacy trial aimed to determine observed adherence rather than patient-important outcomes such as survival and relapse-free cure. While it is known there were increased observations achieved in the VOT intervention group, in the DOT control arm observation was less but this does not mean that treatment taken was taken to a lesser extent. In the UK finishing treatment without evidence of failure is generally considered a good enough proxy of bacteriological cure. This is because many patients will be cough-free late into treatment and therefore cannot produce a sputum sample. As such, “treatment success” (the sum of cured and treatment completed) if often used as a composite outcome. However, based on data from the London Tuberculosis Register and follow-up with clinics ascertained at the end of the trial, 83/114 (72·81%) DOT arm patients and 90/122 VOT arm patients (80·4%) showed there was no statistically significant difference in treatment completion between the DOT and VOT groups (chi-square p=0·18) as reported in the supplementary appendix of Story *et al* (Story

et al. 2019). In order to obtain cure rates, the trial would need to have been conducted in a high TB incidence setting with large enough numbers of participants to assess the effect of DOT compared to VOT on cure rates.

Patients with pulmonary or non-pulmonary TB (≥16 years) deemed eligible for DOT in England according to national clinical guidance were recruited from clinics and randomised to DOT or VOT. DOT involved in-person treatment observation three to five times per week by a healthcare or lay worker, with the remaining daily doses self-administered. In-person observation was conducted in clinic, in the community (for example at hostels or pharmacies), or in home settings. Conversely, VOT was provided by a centralised service in London. Patients were trained to record and send videos of every dose ingested seven days a week using a smartphone app developed by researchers at University of California, San Diego (Garfein, Collins, Munoz, et al. 2015). Trained VOT observers viewed these videos through a password-protected website. Patients were also encouraged to report adverse drug events on the videos. Smartphones and data plans (including UK calls and texts) were provided free of charge. DOT or VOT observation records were completed by observers until treatment or study end. The primary outcome was successful completion of 80% or more of scheduled treatment observations in the two months following enrolment.

The level of initial engagement with DOT or VOT was determined by at least one week of observation in the allocated group.

The additional objectives of the UK DOT / VOT trial included:

- To measure the impact on adherence over 6 months
- To measure impact on loss to follow up and treatment completion

- To measure effect on culture conversion and development of resistance
- To measure impact on transmission
- To measure impact on quality of life and patient satisfaction
- To assess cost effectiveness of VOT

Descriptive statistics:

To determine the factors associated with adherence in each allocated intervention group, chi-square tests stratified by DOT and VOT group were used to assess the association between risk factors and adherence, as a dichotomous outcome variable (over 80% of scheduled doses observed over TB treatment course).

This adherence is dependent both on the initial engagement with the DOT / VOT intervention and subsequent adherence to ongoing observation during the TB treatment course. I therefore conducted analyses of initial engagement and then of adherence amongst those who had initially engaged.

To compare levels of engagement achieved within each allocated intervention group, chi-square tests stratified by DOT and VOT groups were used to assess the association between risk factors and level of initial engagement with allocated DOT or VOT intervention (had at least 1 week of observation) and this was compared to those who did not initially engage with DOT or VOT (less than 1 week of observation). Figure 17 below summarises the different analytical stages:

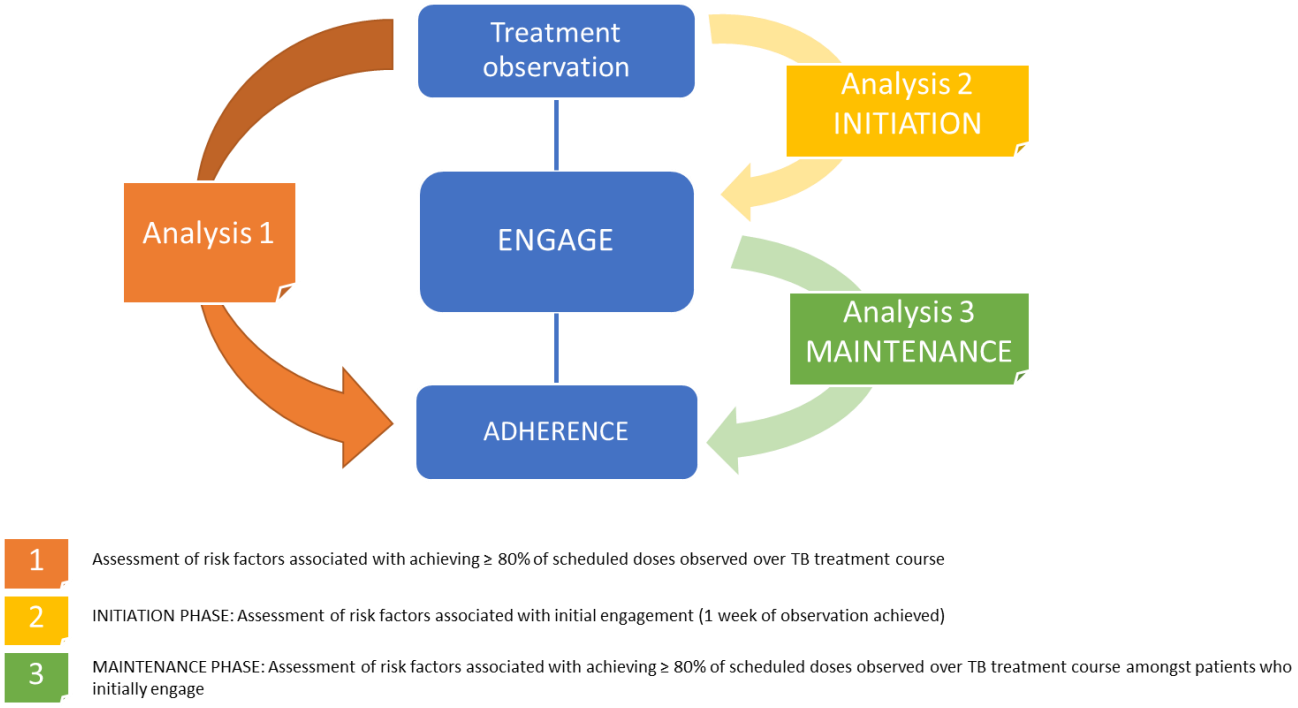


Figure 17: Schematic diagram showing different analytical stages to explore the factors that affect the levels of engagement and whether these affect the level of observation achieved in DOT and VOT groups

These analyses were then restricted to those who initially engaged with either VOT or DOT. Chi-square tests stratified by DOT and VOT were used to determine the proportions of groups by each co-variate who achieve and do not achieve adherence.

3.5 Results

3.5.1 Factors affecting treatment observation

Table 9: Assessment of risk factors associated with achieving ≥80% of scheduled doses over TB treatment course

		N (%)	80% doses not observed (%)	80% doses observed (%)	Univariate OR (95% CI)	p value
Arm	DOT VOT	114 (50.4) 112 (49.6)	79 (69.3) 34 (30.4)	35 (30.7) 78 (69.6)	1 5.18 (2.94 - 9.12)	 <0.001
Age group	16-24 25-34 35-44 45-54 55-65	41 (18.1) 84 (37.2) 50 (22.1) 30 (13.3) 21 (9.3)	20 (48.8) 45 (53.6) 27 (54.0) 12 (40.0) 9 (42.9)	21 (51.2) 39 (46.4) 23 (46.0) 18 (60.0) 12 (57.1)	1 0.83 (0.39 – 1.74) 0.81 (0.35 – 1.86) 1.43 (0.55 – 3.71) 1.27 (0.44 – 3.66)	 0.661
Sex	Male	165 (73.0)	76 (46.1)	89 (53.9)	1	
	Female	61 (27.0)	37 (60.7)	24 (39.3)	0.55 (0.30 – 1.01)	0.051
Born in UK	No	176 (77.9)	88 (50.0)	88 (50.0)	1	
	Yes	50 (22.1)	25 (50.0)	25 (50.0)	1.00 (0.53 – 1.87)	1.000
Previous TB*	No	167 (74.2)	84 (50.3)	83 (49.7)	1	
	Yes	57 (25.3)	28 (49.1)	29 (50.9)	1.05 (0.57 – 1.91)	0.878
Pulmonary disease	No	84 (37.2)	44 (52.4)	40 (47.6)	1	
	Yes	142 (62.8)	69 (48.6)	73 (51.4)	1.16 (0.68 – 2.00)	0.582
Known HIV positivity*	No	196 (89.9)	103 (52.6)	93 (47.5)	1	
	Yes	15 (6.9)	6 (40.0)	9 (60.0)	1.66 (0.57 – 4.85)	0.348
Social risk factor (any)	Never	95 (42.0)	52 (54.7)	43 (45.3)	1	
	Within 5 years	93 (41.2)	40 (40.0)	53 (57.0)	1.60 (0.90 – 2.85)	0.212

		N (%)	80% doses not observed (%)	80% doses observed (%)	Univariate OR (95% CI)	p value
	>5 years ago	38 (16.8)	21 (55.3)	17 (44.7)	0.98 (0.46 – 2.06)	
Homeless*	Never	147 (65.0)	79 (53.7)	68 (46.3)	1	
	Within 5 years	47 (20.8)	21 (44.7)	26 (55.3)	1.44 (0.74 – 2.78)	0.392
	>5 years ago	30 (13.3)	13 (43.3)	17 (56.7)	1.52 (0.69 – 3.35)	
Prison*	Never	190 (84.1)	96 (50.5)	94 (49.5)	1	
	Within 5 years	18 (8.0)	10 (55.6)	8 (44.4)	0.82 (0.31 – 2.16)	0.680
	>5 years ago	17 (7.5)	7 (41.2)	10 (58.8)	1.46 (0.53 – 3.99)	
Drug use*	Never	185 (81.9)	93 (50.3)	92 (49.7)	1	
	Within 5 years	33 (14.6)	18 (54.6)	15 (45.5)	0.84 (0.40 – 1.77)	0.203
	>5 years ago	6 (2.7)	1 (16.7)	5 (83.3)	5.05 (0.58 – 44.10)	
Alcohol*	No	183 (81.3)	95 (51.9)	88 (48.1)	1	
	Yes	38 (16.9)	13 (34.2)	25 (65.8)	2.08 (1.00 – 4.31)	0.045
Mental health problems*	No	188 (83.6)	93 (49.5)	95 (50.5)	1	
	Yes	32 (14.2)	17 (53.1)	15 (46.9)	0.86 (0.41 – 1.83)	0.702
Immigration concerns*	No	201 (89.3)	99 (49.3)	102 (50.8)	1	
	Yes	18 (8.0)	11 (61.1)	7 (38.9)	0.62 (0.23 – 1.66)	0.333

		N (%)	80% doses not observed (%)	80% doses observed (%)	Univariate OR (95% CI)	p value
Lost to follow-up (ever)	No	173 (76.9)	81 (46.8)	92 (53.2)	1	
	Yes	37 (16.4)	25 (67.6)	12 (32.4)	0.42 (0.20 – 0.89)	0.051
	Unknown	15 (6.7)	6 (40.0)	9 (60.0)	1.32 (0.45 – 3.87)	
Health-related quality of life	Above average	133 (58.9)	64 (48.1)	69 (51.9)	1	
	Below average	93 (41.2)	49 (52.7)	44 (47.3)	0.83 (0.49 – 1.42)	0.499

*if number of patients in the 'unknown' group were small these were recoded to missing to restrict p-value estimates to ensure comparisons remain between groups where there were significant numbers

Table 9 shows low levels of adherence with DOT. Overall 31% (35/114) of those assigned to DOT had more than 80% of scheduled observations completed. Amongst 70% (78/112) of those assigned to VOT were significantly more likely to have more than 80% of the scheduled doses observed (OR: 5.18; 95% CI: 2.94 - 9.12; p<0.001. Those with a history of alcohol misuse had a two-fold increased odd of having more than 80% of their scheduled doses observed (OR: 2.08; 95% CI: 1.00 – 4.31; p=0.045). Women (OR: 0.55; 95% CI: 0.30 – 1.01; p=0.051) and those with a history of being lost to follow-up (OR: 0.42; 95% CI: 0.20 – 0.89; p=0.051) were less likely to have more than 80% of the doses observed.

Table 10: Multivariable analysis using backward stepwise regression: factors affecting TB treatment observation

		Proportion who achieve 80% observed doses n/N (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)*	p value
Intervention	DOT	35/114 (30.7)	1		1	
	VOT	78/112 (69.6)	5.18 (2.94 – 9.12)	<0.001	6.63 (3.53 - 12.44)	<0.001
Gender	Male	89/165 (53.9)	1		1	
	Female	24/61 (39.3)	0.55 (0.30 – 1.01)	0.051	0.50 (0.24 - 1.02)	0.06
Age group	16-24	21/41 (51.2)	1		1	
	25-34	39/84 (46.4)	0.83 (0.39 – 1.74)	0.661	0.90 (0.37 - 2.17)	0.82
	35-44	23/50 (46.0)	0.81 (0.35 – 1.86)		0.80 (0.30 - 2.15)	0.66
	45-54	18/30 (60.0)	1.43 (0.55 – 3.71)		1.23 (0.41 - 3.71)	0.71
	55-65+	12/21 (57.1)	1.27 (0.44 – 3.66)		1.21 (0.34 - 4.37)	0.77
Alcohol	No	88/183 (48.1)	1		1	
	Yes	25/38 (65.8)	2.08 (1.00 – 4.31)	0.045	2.51 (1.06 - 5.92)	0.04

		Proportion who achieve 80% observed doses n/N (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)*	p value
Lost to follow-up	No	92/173 (53.2)	1		1	
	Yes	12/37 (32.4)	0.42 (0.20 – 0.89)	0.501	0.31 (0.13 - 0.74)	0.009
	Unknown	9/15 (60.0)	1.32 (0.45 – 3.87)		1.37 (0.38 - 4.97)	0.629

*adjusted by sex, age, alcohol and lost to follow-up

Table 10 shows after adjusting for sex, age, alcohol and loss to follow-up, those assigned to VOT had over a six and a half-fold increased odds of having more than 80% of their scheduled doses observed compared to those on DOT (aOR: 6.63; 95% CI: 3.53 - 12.44; p<0.001). A history of alcohol misuse remained a significant confounder, with 65% (25/38) having a two-and-a-half fold increased odds of having more than 80% of their scheduled doses observed (aOR: 2.51; 95% CI: 1.06 - 5.92; p=0.04). A history of loss of follow-up also confounded this association with 32% (12/37) being less likely to have 80% of the scheduled doses observed (aOR: 0.31; 95% CI: 0.13 – 0.74; p=0.009).

3.5.2 Initiation phase: Factors affecting initial engagement

Table 11: Assessment of risk factors associated with initial engagement (1 week observation achieved)

		Total N (%)	**Do not engage N (%)**	**Engage N (%)**	**Univariate OR (95% CI)**	**p-value**
Arm	DOT VOT	114 (50.4) 112 (49.6)	58 (50.9) 11 (9.8)	56 (49.1) 101 (90.2)	1 9.51 (4.62 -19.59)	<0.001
Age group	16-24 25-34 35-44 45-54 55-65	41 (18.1) 84 (37.2) 50 (22.1) 30 (13.3) 21 (9.3)	11 (29.8) 29 (34.5) 20 (40.0) 6 (20.0) 3 (14.3)	30 (73.2) 55 (65.5) 30 (60.0) 24 (80.0) 18 (85.7)	1 0.70 (0.30 – 1.59) 0.55 (0.23 – 1.34) 1.47 (0.47 – 4.54) 2.20 (0.54 – 8.96)	0.107
Sex	Male	165 (73.0)	50 (30.3)	115 (69.7)	1	
	Female	61 (27.0)	19 (31.2)	42 (68.9)	0.96 (0.51 - 1.81)	0.903
Born in UK	No	176 (77.9)	54 (30.7)	122 (69.3)	1	

		Total N (%)	Do not engage N (%)	Engage N (%)	Univariate OR (95% CI)	p-value
	Yes	50 (22.1)	15 (30.0)	35 (70.0)	1.03 (0.52 – 2.05)	0.926
Previous TB*	No	167 (74.2)	52 (31.1)	115 (68.9)	1	
	Yes	57 (25.3)	16 (28.1)	41 (71.9)	1.16 (0.60 – 2.25)	0.662
Pulmonary disease	No	84 (37.2)	26 (31.0)	58 (69.1)	1	
	Yes	142 (62.8)	43 (30.3)	99 (69.7)	1.03 (0.58 – 1.85)	0.916
Known HIV positivity*	No	196 (89.9)	64 (32.7)	132 (67.4)	1	
	Yes	15 (6.9)	3 (20.0)	12 (80.0)	1.94 (0.53 – 7.12)	0.292
Social risk factor (any)	Never	95 (42.0)	36 (37.9)	59 (62.1)	1	
	Within 5 years	93 (41.2)	21 (22.6)	72 (77.4)	2.09 (1.10 – 3.96)	0.071
	>5 years ago	38 (16.8)	12 (31.6)	26 (68.4)	1.32 (0.59 – 2.94)	
Homeless*	Never	147 (65.0)	52 35,4)	95 (64.6)	1	
	Within 5 years	47 (20.8)	12 (25.5)	35 (74.5)	1.50 (0.76 – 3.34)	0.075
	>5 years ago	30 (13.3)	5 (16.7)	25 (83.3)	2.74 (0.99 – 7.57)	
Prison*	Never	190 (84.1)	57 (30.0)	133 (70.0)	1	
	Within 5 years	18 (8.0)	8 (44.4)	10 (55.6)	0.54 (0.20 – 1.43)	0.373
	>5 years ago	17 (7.5)	4 (25.5)	13 (76.5)	1.39 (0.44 – 4.56)	
Drug use*	Never	185 (81.9)	59 (31.9)	126 (68.1)	1	

		Total N (%)	Do not engage N (%)	Engage N (%)	Univariate OR (95% CI)	p-value
	Within 5 years	33 (14.6)	8 (24.2)	25 (75.8)	1.46 (0.62 – 3.44)	0.494
	>5 years ago	6 (2.7)	1 (16.7)	5 (83.3)	2.34 (0.27 – 20.49)	
Alcohol*	No	183 (81.3)	62 (33.9)	121 (66.1)	1	
	Yes	38 (16.9)	5 (13.2)	33 (86.8)	3.38 (1.26 – 9.09)	0.007
Mental health problems*	No	188 (83.6)	57 (30.3)	131 (69.7)	1	
	Yes	32 (14.2)	10 (31.3)	22 (68.8)	0.96 (0.43 – 2.15)	0.916
Immigration concerns*	No	201 (89.3)	60 (29.9)	141 (70.2)	1	
	Yes	18 (8.0)	6 (33.3)	12 (66.7)	0.85 (0.31 – 2.37)	0.759
Lost to follow-up (ever)	No	173 (76.9)	54 (31.2)	119 (68.8)	1	
	Yes	37 (16.4)	11 (29.7)	26 (70.3)	1.07 (0.49 – 2.33)	0.641
	Unknown	15 (6.7)	3 (20.0)	12 (80.0)		
Health-related quality of life	Above average	133 (58.9)	44 (33.1)	89 (66.9)	1	
	Below average	93 (41.2)	25 (26.9)	68 (73.1)	1.22 (0.69 – 2.17)	0.491

*if number of patients in the ‘unknown’ group were small these were recoded to missing to restrict p-value estimates to ensure comparisons remain between groups where there were significant numbers

Table 11 shows that 90% (101/112) of patients assigned to VOT were significantly more likely to initially engage with VOT (OR: 9.51; 95% CI: 4.62 - 19.59; p<0.001) compared to 36% allocated to DOT. Patients with a history of alcohol misuse had a three-fold increased odds of being more likely to engage with their assigned intervention (DOT or VOT) (OR: 3.38; 95% CI: 1.26 – 9.09; p=0.007) compared to 66% (121/183) with no history of alcohol misuse.

Table 12: Multivariable analysis using backward stepwise regression: factors affecting levels of engagement

		Proportion who engage n/N (%)	**Unadjusted OR (95% CI)**	**p value**	**Adjusted OR (95% CI)***	**p value**
Intervention	DOT	56/114 (49.1)	1		1	
	VOT	101/112 (90.2)	9.51 (4.62 - 19.59)	<0.001	9.81 (4.63 - 20.77)	<0.001
Gender	Male	115/165 (69.7)	1		1	
	Female	42/61 (68.9)	0.96 (0.51 - 1.81)	0.903	1.14 (0.54 - 2.45)	0.728
Age group	16-24	30/41 (73.2)	1	0.107	1	
	25-34	55/84 (65.5)	0.70 (0.30 – 1.59)		0.66 (0.25 - 1.69)	0.38
	35-44	30/50 (60.0)	0.55 (0.23 – 1.34)		0.52 (0.18 - 1.48)	0.22
	45-54	24/30 (80.0)	1.47 (0.47 – 4.54)		1.23 (0.34 - 4.39)	0.75
	55-65+	18/21 (85.7)	2.20 (0.54 – 8.96)		1.41 (0.29 - 6.85)	0.67
Alcohol	No	121/183 (66.1)	1		1	
	Yes	33/38 (86.8)	3.38 (1.26 – 9.09)	0.007	5.15 (1.69 - 15.68)	0.004

*adjusted by sex, age, alcohol

Table 12 shows after adjusting for sex, age and a history of alcohol misuse, those assigned to VOT had almost a ten-fold increased odds of engaging with VOT (aOR: 9.81; 95% CI: 4.63 - 20.77; p<0.001) compared to those on DOT. Those with a history of alcohol misuse had a five-fold increased odds of engaging with either DOT or VOT (aOR: 5.15; 95% CI: 1.69 - 15.68; p=0.004) compared to those who had no history of alcohol misuse.

3.5.3 Maintenance phase: Factors affecting adherence amongst those who initially engage

Table 13: Assessment of risk factors associated with achieving ≥80% of scheduled treatment doses during TB treatment course amongst those who initially engage

		Total N (%)	**80% doses not observed amongst those who engage N (%)**	**80% doses observed amongst those who engage N (%)**	**Univariate OR (95% CI)**	**p value**
Arm	DOT	56 (35.7)	21 (37.5)	35 (62.5)	1	
	VOT	101 (64.3)	23 (22.8)	78 (77.2)	2.03 (1.00 - 4.15)	0.051
Age group	16-24	30 (19.1)	9 (30.0)	21 (70.0)	1	
	25-34	55 (35.0)	16 (29.1)	39 (70.9)	1.04 (0.39 - 2.77)	0.941
	35-44	30 (19.1)	7 (23.3)	23 (76.7)	1.41 (0.45 - 4.45)	
	45-54	24 (15.3)	6 (25.0)	18 (75.0)	1.29 (0.38 - 4.31)	
	55-65	18 (11.5)	6 (33.3)	12 (66.7)	0.86 (0.24 - 3.00)	
Sex	Male	115 (73.3)	26 (22.6)	89 (77.4)	1	
	Female	42 (26.8)	18 (42.9)	24 (57.1)	0.39 (0.18 - 0.83)	0.015

		Total N (%)	80% doses not observed amongst those who engage N (%)	80% doses observed amongst those who engage N (%)	Univariate OR (95% CI)	p value
Born in UK	No	122 (77.2)	34 (27.9)	88 (72.1)	1	
	Yes	35 (22.3)	10 (28.6)	25 (71.4)	0.97 (0.42 - 2.22)	0.935
Previous TB*	No	115 (73.3)	32 (27.8)	83 (72.2)	1	
	Yes	41 (26.1)	12 (29.3)	29 (70.7)	0.93 (0.42 - 2.05)	0.861
Pulmonary disease	No	58 (36.9)	18 (31.0)	40 (69.0)	1	
	Yes	99 (63.1)	26 (26.3)	73 (73.7)	1.26 (0.62 - 2.58)	0.522
Known HIV positivity*	No	132 (88.6)	39 (29.6)	93 (70.5)	1	
	Yes	12 (8.1)	3 (25.0)	9 (75.0)	1.26 (0.32 - 4.90)	0.741
Social risk factor (any)	Never	59 (37.6)	16 (27.1)	43 (72.9)	1	
	Within 5 years	72 (45.9)	19 (26.4)	53 (73.6)	1.04 (0.48 - 2.26)	0.720
	>5 years ago	26 (16.6)	9 (34.6)	17 (65.4)	0.70 (0.48 - 2.26)	
Homeless*	Never	95 (60.5)	27 (28.4)	68 (71.6)	1	
	Within 5 years	35 (22.3)	9 (25.7)	26 (74.3)	1.15 (0.48 - 2.76)	0.868
	>5 years ago	25 (15.9)	8 (32.0)	17 (68.0)	0.84 (0.33 - 2.18)	0.726
Prison*	Never	133 (84.7)	39 (29.3)	94 (70.9)	1	

		Total N (%)	80% doses not observed amongst those who engage N (%)	80% doses observed amongst those who engage N (%)	Univariate OR (95% CI)	p value
	Within 5 years	10 (6.4)	2 (20.0)	8 (80.0)	1.66 (0.34 - 8.17)	0.736
	>5 years ago	13 (8.3)	3 (23.1)	10 (76.9)	1.38 (0.36 - 5.30)	
Drug use*	Never	126 (80.3)	34 (27.0)	92 (73.0)	1	
	Within 5 years	25 (15.9)	10 (40.0)	15 (60.0)	0.55 (0.23 - 1.35)	0.201
	>5 years ago	5 (3.2)	0 (0.0)	5 (100.0)	--	--
Alcohol*	No	121 (77.1)	33 (27.3)	88 (72.7)	1	
	Yes	33 (21.0)	8 (24.2)	25 (75.8)	1.17 (0.48 - 2.86)	0.725
Mental health problems*	No	131 (83.4)	36 (27.5)	95 (72.5)	1	
	Yes	22 (14.0)	7 (31.8)	15 (68.2)	0.81 (0.31 - 2.15)	0.679
Immigration concerns*	No	141 (89.8)	39 (27.7)	102 (72.3)	1	
	Yes	12 (7.6)	5 (41.7)	7 (58.3)	0.54 (0.16 - 1.79	0.310
Lost to follow-up (ever)	No	119 (75.8)	27 (22.7)	92 (77.3)	1	
	Yes	26 (16.6)	14 (55.9)	12 (46.2)	0.25 (0.10 - 0.61)	0.009
	Unknown	12 (7.6)	3 (25.0)	9 (75.0)	0.88 (0.22 - 3.48)	
Health-related	Above average	89 (56.7)	20 (22.5)	69 (77.5)	1	

		Total N (%)	80% doses not observed amongst those who engage N (%)	80% doses observed amongst those who engage N (%)	Univariate OR (95% CI)	p value
quality of life						
	Below average	68 (43.3)	24 (35.3)	44 (64.7)	0.53 (0.26 - 1.07)	0.077

*****if number of patients in the 'unknown' group were small these were recoded to missing to restrict p-value estimates to ensure comparisons remain between groups where there were significant numbers

Table 13 shows amongst those initially engaged with the DOT or VOT intervention they were assigned to, 38% of patients were more likely to not achieve over 80% of their scheduled doses observed if they were assigned to DOT compared to 23% of those on VOT. However, adherence was more frequent amongst those on VOT (77%) compared to DOT (63%) (p=0.049). Amongst those who initially engaged, adherence less frequent amongst women (57%) compared to men (77%) and those with a history of loss to follow-up also were more likely to not adhere to treatment (46%) compared to those with no history of loss to follow-up (77%).

The univariable analysis shows patients assigned to VOT and initially engaged with it were twice as likely to have more than 80% of their scheduled doses observed compared to DOT (OR: 2.03 95% CI: 1.00 - 4.15; p=0.051). Women were less likely to adhere (OR: 0.39 95% CI: 0.18 – 0.83; p=0.015). Those with a history of loss to follow up were also less likely to maintain 80% observation of their scheduled doses (OR: 0.25 95% CI: 0.10 - 0.61; p=0.009).

Table 14: Multivariable analysis using backward stepwise regression: factors affecting levels of engagement

		Proportion who achieve 80% doses achieved amongst those who engage n/N (%)	**Unadjusted OR (95% CI)**	**p value**	**Adjusted OR (95% CI)***	**p value**
Arm	DOT	35/56 (62.5)	1		1	
	VOT	78/101 (77.2)	2.03 (1.00 - 4.15)	0.051	2.54 (1.16 - 5.58)	0.02
Age group	16-24	21/30 (70.0)	1		1	
	25-34	39/55 (70.9)	1.04 (0.39 - 2.77)	0.941	1.88 (0.63 - 5.60)	0.26
	35-44	23/30 (76.7)	1.41 (0.45 - 4.45)		1.89 (0.53 - 6.68)	0.32
	45-54	18/24 (175.0)	1.29 (0.38 - 4.31)		1.88 (0.51 - 6.87)	0.34
	55-65	12/18 (66.7)	0.86 (0.24 - 3.00)		1.39 (0.35 - 5.46)	0.64
Sex	Male	89/115 (77.4)	1		1	
	Female	24/42 (57.1)	0.39 (0.18 - 0.83)	0.015	0.33 (0.14 - 0.77)	0.01
Lost to follow-up (ever)	No	92/119 (77.3)	1		1	
	Yes	12/26 (46.2)	0.25 (0.10 - 0.61)	0.009	0.18 (0.07 - 0.49)	0.001

		Proportion who achieve 80% doses achieved amongst those who engage n/N (%)	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)*	p value
	Unknown	9/12 (75.0)	0.88 (0.22 - 3.48)		0.74 (0.17 - 3.15)	

*adjusted by sex, age, history of being lost to follow-up

Table 14 shows after adjusting for age, sex and a history of loss to follow-up, patients assigned to VOT and who initially engaged with it were two-and-a-half times more likely to maintain 80% of their scheduled treatment observation compared to those who initially engaged with DOT (aOR: 2.54; 95% CI: 1.16 - 5.58; p=0.02). Women were less likely to adhere (aOR: 0.33; 95% CI: 0.14 - 0.77; p=0.01) and those with a history of loss to follow-up were also less likely to adhere (aOR: 0.18; 95% CI: 0.07 - 0.49; p=0.001).

Risk factor and univariable analysis have also been stratified by DOT and VOT, showing that patients on DOT were not able to achieve high levels of adherence compared to VOT. Full results for these are in the Supplementary tables in Appendix Section 6.2.

3.6 Discussion

In this secondary analysis of the UK DOT/VOT trial, I've examined factors that affect TB treatment adherence in patients allocated to DOT and VOT groups, the factors that affect the level of engagement with DOT and VOT interventions and assessed factors that affect adherence amongst those who initially engage with DOT and VOT interventions. Findings show participants who initially engaged with VOT had a 2.54 increased odds of improved TB treatment adherence compared to those who initially engaged with DOT (aOR: 2.54; 95% CI: 1.16 - 5.58; p=0.02). This finding was confounded by an association with sex (women - aOR: 0.33; 95% CI: 0.14 - 0.77) and by a history of loss to follow-up (aOR: 0.19; 95% CI: 0.07 - 0.52; p=0.001).

The higher levels of initial engagement with VOT across all patient groups demonstrate it is a more acceptable approach to TB treatment observation

compared to DOT and shows that VOT may be a more flexible intervention to overcome personal, health service-related and structural factors, which may impede people from completing their treatment course. Research has shown that missed doses early in treatment are predictive of later treatment discontinuation, arguing for the importance of early intervention (Stagg et al. 2020). This is consistent with my results and underscores the importance of improved adherence amongst those who initially engaged with VOT.

My findings also showed that over 70% of participants who were aged over 55, had a prison history, a history of homelessness (more than 5 years ago) and those with current alcohol problems initially engaged with DOT. Despite the evidence showing that TB treatment outcomes for those supported by DOT were no better than self-administered treatment (Karumbi and Garner 2015) and previously reported issues with DOT, these patient groups represent those who may have multiple and complex needs, which require more intensive support systems and staffing oversight. This provides some indication of groups DOT and staffing support may be triaged to for purposes.

I found all age groups were more likely to engage with VOT, showing that generational factors had no bearing on acceptability as VOT as an intervention. Some evidence shows that older populations may face challenges adapting to new technological tools to support adherence (Westerman and Davies 2000). However, evidence from a VOT trial in Vietnam showed that following initial training participants of older age were able to learn how to use VOT technology (Nguyen et al. 2017).

The findings show there are gender inequalities in that women were less likely to achieve treatment adherence with DOT or VOT compared to men. Despite initially

engaging with DOT or VOT this indicates there may be personal, health system-related or structural factors that impeded women from maintaining high levels of observation and accessing the benefits of either of these interventions throughout the course of their treatment. In a quasi-experimental study, which included formative research, in-depth qualitative interviews and an assessment of VDOT among women in Ghana, only a third (32%) were willing to submit videos of themselves for monitoring by their nurses, with some citing mistrust for using internet as reasons for not transferring such information (Badzi 2020). Lack of agency, power dynamics in household structures, caring responsibilities may affect the amount of time they can maintain high observation levels in these initiatives. Despite all this, all groups do better on VOT so it may be helping to overcome these barriers. There is a paucity of evidence that show there are gender-specific differences in treatment adherence outcomes and so further work is required to explore this.

The finding that those with a history of being lost to follow-up were less likely to achieve treatment adherence is unsurprising given that they are overlapping outcomes associated with a series of demographic and socioeconomic factors or exposures including homelessness, food insecurity, poverty, low education attainment, gender, poor health care worker-patient communication, unemployment, lack of social supports (Tola et al. 2015). These multiple and overlapping risk factors typically characterise the extremes of social exclusion and the lack of engagement with services can represent deeply entrenched and a longstanding mistrust of services and authorities due to repeated experiences of feeling let down.

This secondary analysis of an RCT dataset benefits from a large sample size of 226 participants in that it provides lots of power to make conclusive statements about the results and the multiple number of risk factors provide various ways to assess levels

of initially engagement and levels of observation and adherence in patient groups. It is also able to make more conclusive statements about the fidelity of treatment adherence outcomes for those allocated to the VOT intervention due to the high levels of true observation of scheduled doses.

A key statistical limitation to this analysis relates to the multiple significance testing of the dataset, which may have affected the robustness of the effect estimates in the multivariable analysis.

A more granular understanding of patient perspectives and experiences of DOT and VOT in different cultural settings will unpack the mechanisms into how engagement with DOT and VOT supported regular dosing and will provide important insights into how to develop differentiated and tailored clinical strategies.

Table 15: Overall study objectives, methodology, Chapter 2 and 3 findings

Chapter	Research question	Objective	Relevance	Methodology	Findings
2	Which patient groups do not complete TB treatment	To identify factors that predict non-completion of TB treatment in a nationwide retrospective cohort of drug-susceptible and –resistant TB from 2010 to 2017	To identify patient groups who do not complete TB treatment and need additional support	A retrospective cohort analysis of cases with TB notified to the Enhanced TB Surveillance System in England, Wales and Northern Ireland between 2010 and 2017. Multivariable logistic regression models were	Factors affecting non-completion of TB treatment. • Being male (aOR: 1.20; 95% CI: 1.14 - 1.26) • 15-44 age group (aOR: 1.70; 95% CI: 1.43 - 2.02) ≥45 age group (aOR: 3.55; 95% CI: 2.99 - 4.22) • Recent migration to the UK (aOR: 2.46; 95% CI: 2.25 - 2.69),

Chapter	Research question	Objective	Relevance	Methodology	Findings
				built to identify socio-demographic and clinical factors associated with non-completion of TB treatment.	• Increasing social complexity (aOR: 2.73; 95% CI: 1.78 - 4.18) • Multidrug resistance (aOR: 4.07; 95% CI: 3.36 - 4.94).
3	What patient groups engage with VOT	To examine the factors which affect the levels of engagement with DOT and VOT and whether affects the level of observation achieved in DOT and VOT groups	A quantitative assessment of the level of engagement will serve as a measure of acceptability and a proxy measure of accuracy in measuring true adherence in groups supported by DOT and VOT	A secondary analysis of the UK DOT/VOT trial dataset using descriptive analysis and logistic regression to determine: a) adherence amongst patients randomised to DOT and VOT b) risk factors for the level of initial engagement in both allocated groups c) adherence amongst patients who engage with DOT and VOT	• 90% initially engaged with VOT compared to 49% initially engaged with DOT • VOT over 70% initial engagement in all groups: - age group - sex - migration - ethnicity - social risk factors - loss to follow-up - health-related quality of life • DOT over 70% initial engagement - aged over 55, - prison history - history of homelessness

Chapter	Research question	Objective	Relevance	Methodology	Findings
					(more than 5 years ago) - current alcohol problems • Amongst those who engaged with VOT, (78/101, 77% had more than 80% of scheduled treatment observations completed compared to (35/56, 63% of those who engaged with DOT. • Patients with TB who initially engaged with VOT had a 2.54 increased odds of improved TB treatment adherence compared to those who initially engaged with DOT (aOR: 2.54; 95% CI: 1.16 - 5.58; p=0.02). • Women were less likely to adhere (aOR: 0.33; 95% CI: 0.14 - 0.77; p=0.01)

Chapter	Research question	Objective	Relevance	Methodology	Findings
					• Those with a history of loss to follow-up were also less likely to adhere (aOR: 0.18; 95% CI: 0.07 - 0.49; p=0.001).
4	How does DOT and VOT support adherence in people's lives	To describe the lived experiences and perceptions of DOT and VOT interventions in people with TB in the UK and the Republic of Moldova	A qualitative assessment of acceptability of DOT and VOT and will identify the mechanisms by which DOT and VOT work and the challenges encountered when these interventions are instigated	Semi-structured interviews with 16 UK DOT/VOT trial participants and 22 Moldovan DOT/VOT trial participants. A thematic analysis was used to analyse data from emerging themes to understand how the different VOT approaches compared to DOT and were perceived by patients in both settings, how they fitted into patients' lives and how they may or may not have supported them in taking prescribed doses regularly.	

Chapter 4: Lived experiences and perceptions of DOT and VOT interventions in patients with TB supported in the UK and the Republic of Moldova: a qualitative study

4.1 Abstract

Objective: To describe the lived experiences and perceptions of DOT and VOT interventions in patients with TB and explain how their characteristics and functions facilitated or impeded treatment observation in the UK and the Republic of Moldova.

Methods: A qualitative research study was embedded into UK and Moldova trials comparing the efficacy of asynchronous VOT to DOT for supporting adherence to understand the acceptability of both interventions and to capture the personal and socio-ecological dimensions that influence TB treatment adherence. Semi-structured interviews were conducted with 16 participants in the UK trial: ten TB patients (three MDR-TB) received VOT and six received DOT. In the Moldovan trial, semi-structured interviews were conducted with a convenience sample of 22 participants: 13 patients received VOT and 9 received DOT. Transcripts were translated and coded, and Data were analysed using thematic analysis. Themes were mapped onto the Capability-Opportunity-Motivation-Behaviour (COM-B) model, Theoretical Domains Framework (TDF) and Behaviour Change Wheel (BCW) to identify how the VOT and DOT functions, strategies and its policy categories elicit treatment adherence outcomes. Findings will be used to support public health leaders and commissioners with decision-making on the roll-out and practical application of VOT in different contexts.

Results: From the UK, five participants were female and 11 were male. The age of participants ranged from 20-68 and majority 12/16 were non-UK born. From Moldova, twelve participants were female and ten were male. The age range was 20-65 and all participants were based in Chișinău.

The COM-B model and TDF provided explanatory frameworks highlighting how VOT acted on key behaviour change domains and utilised key strategies to facilitate adherence behaviour change. VOT facilitated patient-provider interactions served as a prompt/reminder to address forgetfulness through regular personalised messages from VOT observers, building rapport and habit-forming practices. VOT was a flexible, time- and cost-saving alternative to DOT and supported patients with split dosing or negotiated timing of dosing to manage side effects and pill burden. VOT also served as an incentive through provision of a smartphone and data plan, free domestic calls, text messages and internet access linking patients to providers, banking and social support services. In turn these ‘capability and ‘opportunity’ components of the model enhanced ‘motivation’ by supporting patients to re-gain autonomy, self-responsibility and establish regular dosing. There were mixed views on privacy with concerns on how video clips would be used, shared and may compromise confidentiality and increase stigma.

The Behaviour Change Wheel identified seven key functions (‘active ingredients’) of VOT: Enablement (increasing means/reducing barriers to increase capability), Education (increasing knowledge or understanding), Persuasion (using communication to induce positive or negative feelings or stimulate action), Training (imparting skills), Incentivisation (creating expectation of reward), Restriction (using

rules to reduce opportunity to engage in target behaviour) and Environmental restructuring (changing the physical or social context).

Conclusions: The COM-B model, TDF and BCW have enabled a systematic and comprehensive understanding of how VOT targets key determinants of treatment adherence behaviour and how it performed as a flexible and personalised case management tool supporting care. Findings present insights into how VOT bridged the 'digital divide' amongst socially complex groups who require additional support and motivation to adhere to TB treatment. Overall findings contextualise favourable trial findings demonstrating how VOT promoted adherence in both a low- and middle TB incidence settings.

4.2 Introduction

In the previous chapter, I found there were greater levels of initial engagement with VOT compared to DOT. Across all risk factors studied (age group, sex, migration, ethnicity and social risk factors) patients were more likely to engage with VOT (over 70% initial engagement in all groups) than they were to engage with DOT. Among those who initially engage, those on VOT were less likely to be lost to follow-up and self-report better levels of health-related quality of life compared to DOT. High levels of initial engagement with DOT (>70%) were also seen in those aged over 55, those who had been in prison or homeless more than 5 years ago and those with current alcohol problems. I also found at amongst those who initially engaged VOT were more likely to adhere to their TB treatment compared to those who initially engaged with DOT. This suggest VOT is a more acceptable approach to patients deemed eligible for DOT who are receiving TB treatment.

Our UK team was the first team to evaluate VOT through an RCT and because of this we were advising a number of international teams. One example was the UK government's Cabinet Office's Behavioural Insights Team (BIT), who had partnered with an NGO in Moldova and had secured funding with UNDP and the Global Fund

to evaluate VOT in Moldova. I was keen to embed qualitative aspects into both the UK and Moldova trial to examine how VOT fitted unto people's lives. By securing a small grant from the Royal Society of Tropical Medicine and Hygiene made it possible to do this.

In this chapter I will provide a qualitative assessment of the acceptability of VOT and DOT. Here I will aim to describe the lived experiences and perceptions of DOT and VOT interventions in patients with TB and explain how their characteristics and functions facilitated or impeded treatment observation in the UK and the Republic of Moldova.

Addressing TB diagnosis and treatment adherence have been prioritised as part of the TB elimination agenda in low-incidence countries, particularly in groups where evidence shows barriers to adherence include pill burden, side effect management, denial of TB diagnosis, depression/fatalism, fear, stigmatisation and unintentional non-adherence (forgetting and/or difficulties in understanding dosing in combination and frequency) and early improvement of symptoms. The long duration, complexity of TB treatment regimens and socio-economic difficulties can make it difficult for patients to complete treatment as prescribed (Kaona et al. 2004; Horsburgh, Barry, and Lange 2015; Munro, Lewin, Smith, et al. 2007; D'Ambrosio et al. 2014; Kik et al. 2009; Story et al. 2007; Dara et al. 2012; Falzon et al. 2016). The relative nature of these factors and how they intersect can vary between patients and within the same individual over time. As such, this may impose challenges on a patient's quality of life and treatment adherence behaviour.

Whilst patient support interventions have been systematically reviewed and evaluated (van Hoorn et al. 2016; Karumbi and Garner 2015; Liu et al. 2015; Suwankeeree and Picheansathian 2014; Heuvelings et al. 2017; de Vries et al.

2017), few randomised-controlled trials of such interventions have embedded qualitative approaches to unpack the patients lived experiences of interventions. As part of both the UK- and Republic of Moldova-based randomised-controlled trials comparing the efficacy of DOT to VOT approaches, concurrent qualitative studies have been applied to elicit context-specific experiences of DOT and VOT in supporting treatment adherence. In the interests of TB control, identifying mechanisms underpinning drivers of and barriers to adherence from perspectives of TB patients may provide insight into how acceptable DOT and VOT approaches are, how they fit into patients' lives to achieve treatment success and elicit favourable health outcomes.

4.3 Aim and objectives

The aim of this qualitative research study is to describe the lived experiences and perceptions of DOT and VOT interventions in patients with TB in the UK and the Republic of Moldova.

The objectives are to:

a) Use the COM-B model to explain how DOT and VOT interventions target the individual level determinants of adherence behaviour (capability, opportunity, motivation) that influence TB treatment observation.
b) Use the Theoretical Domains Framework (TDF) to identify the policy strategies necessary to change mechanisms of TB treatment adherence behaviour.

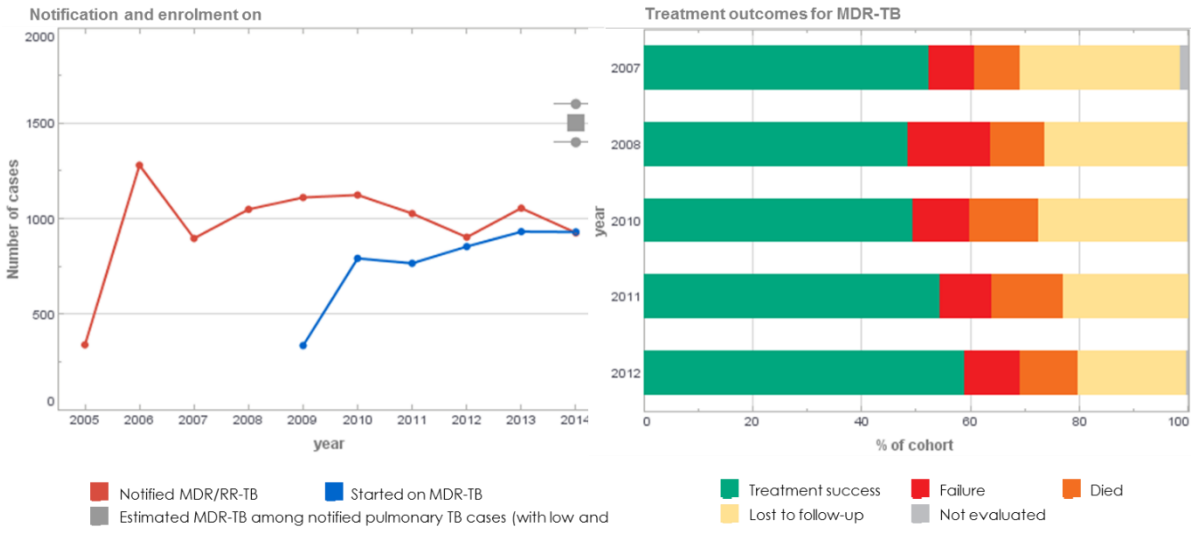
c) Use the Behaviour Change Wheel to explain how VOT functions ('active ingredients') target the linked policy categories to elicit improved observation to support decision-making on commissioning of DOT and VOT interventions.

Findings will be used to produce a unifying model that explains adherence behaviour to support public health leaders and commissioners with decision-making on the roll-out and practical application of VOT in different contexts.

4.4 TB epidemiology and TB treatment challenges in the Republic of Moldova

At the start of my collaboration with the UK government's Cabinet Office's BIT and Act for Involvement (AFI), who were leading on DOT/VOT trial implementation in Moldova, the MDR-TB rates were amongst the highest in the world. Amongst new TB cases in 2016, an estimated 28% developed MDR-TB. TB and MDR-TB notification rates had not decreased significantly since 2012 ("WHO Regional Office for Europe. Review of the National Tuberculosis Programme in the Republic of Moldova, 4–15 February 2013") (Figure 18). As such, TB control and prevention was

a key priority for the country and for the WHO Regional Office for Europe.



Source: WHO Regional Office for Europe

Figure 18: TB epidemiology in the Republic of Moldova

It has been reported that there was significant onward transmission of TB and MDR-TB in the country occurring among hospital patients and workers, attributed to the large number of TB cases unnecessarily hospitalized for a prolonged durations and to poor adoption of airborne infection control measures (Droznin, Johnson, and Johnson 2017). External to hospital settings, delayed diagnosis of infectious cases was thought to be an important contributor to transmission. Poor socio-economic factors were also reported to lead to reactivation of TB infection and impeded timely diagnosis and TB treatment completion. From a historical standpoint, geo-political factors arising from the collapse of the Soviet Union led to socio-economic hardship and disruption of the healthcare system, drug shortages and poorer quality of available medicines (Raviglione et al. 1994). The lack of sustainable incentive mechanisms in place for physicians and patients have contributed to poor treatment

adherence and high default rates, strongly influenced by migration ("WHO Regional Office for Europe. Review of the National Tuberculosis Programme in the Republic of Moldova, 4–15 February 2013").

The Ministry of Health has followed the WHO-recommended DOT during 2000-2004 and has used the Stop TB Strategy which includes DOT since 2006 ("WHO Regional Office for Europe. Review of the National Tuberculosis Programme in the Republic of Moldova, 4–15 February 2013"). Typically in Moldova, the TB patient pathway consisted of two phases: The first is the intensive phase where almost all patients are institutionalised in one of eight specialised TB hospitals. The duration of the inpatient treatment depends directly on sputum culture conversion from positive to negative, which lasts on average between 2-6 months. The second is the continuation phase during which patients continue their treatment under the supervision of the family doctor until treatment completion. In towns and district centres the continuation phase is carried out by the regional phtiziopneumology service. The continuation phase lasts until the completion of the tuberculosis treatment and usually lasts between 4 months for fully susceptible tuberculosis and 24 months for multidrug resistant disease.

Based on a small sample of patient interviews conducted by The Behavioural Insights Team it was reported that for some patients DOT served as a barrier to treatment adherence. DOT implementation in Moldova involved in-person treatment observation by a doctor or nurse every day in clinic. This is reported to be time consuming and imposed material costs for the patient. The alternative, for DOT to be administered at home by roving personnel, was resource-intensive and was only available to a small number of patients in Moldova.

In addition to this, for some patients side effects following dosing meant that DOT was poorly implemented in practice. Anecdotal reports indicated that patients with side effects had to travel every day to pick up their medication but then to avoid needing to travel when feeling unwell after dosing would take it home rather than have their treatment observed by a health worker.

4.5 Methods

An overview of the qualitative methodological steps followed is provided in Figure 19

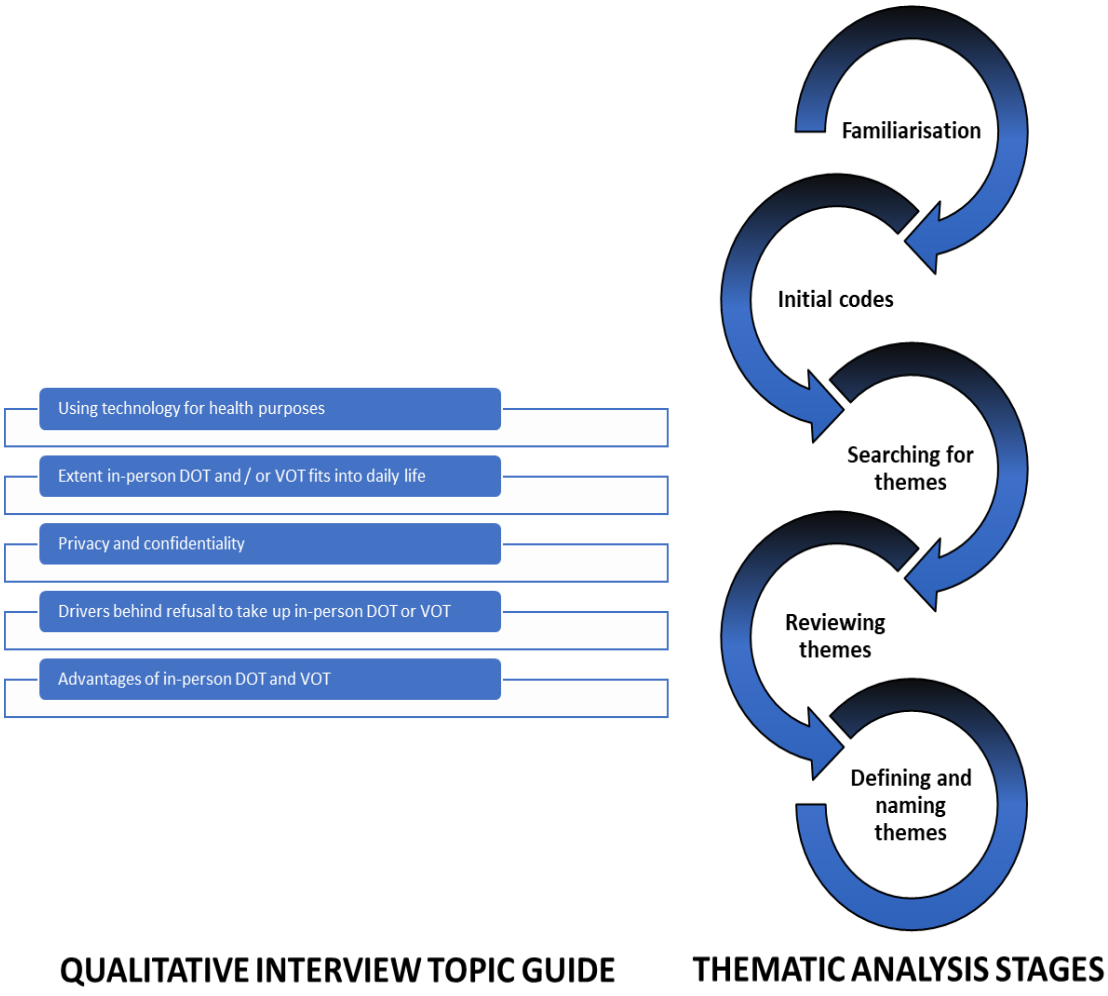


Figure 19: Schematic diagram showing the qualitative methodology applied to understand lived experiences of DOT and VOT trial participants in UK and Moldova

4.5.1 Theoretical frameworks

This qualitative study draws upon the multidimensional determinants of adherence to TB treatment and to long-term medication, which have been elaborated by researchers to explain individual-level (Horne 2001; Horne et al. 2013; Horne et al. 2019; Horne et al. 2009; Horne et al. 2005; Jones et al. 2021; Leventhal, Leventhal, and Contrada 1998), socio-behavioural and ecological frameworks (Munro, Lewin, Swart, et al. 2007; Munro, Lewin, Smith, et al. 2007; Arakelyan et al. 2021; Kielmann et al. 2018; Kielmann K 2019). Drawing on these theories, I have mapped the lived experiences and perspectives of patients supported by DOT and VOT interventions in both the UK and Moldova trials on to the COM-B model categories (behavioural targets – capability, opportunity and motivation), the 'hub' of the BCW (Michie, van Stralen, and West 2011) and the Theoretical Domains Framework (TDF) (Michie et al. 2005) to identify the strategies necessary to change mechanisms of TB treatment adherence behaviour.

The Behaviour Change Wheel (BCW) will be used to characterise VOT and DOT by their 'functions' and these will be linked back to COM-B behavioural targets. This will provide a richer understanding on how the 'active ingredients' of VOT and DOT facilitated or impeded treatment observation in the UK and the Republic of Moldova, which in turn will support decision-making on the roll-out and application of VOT.

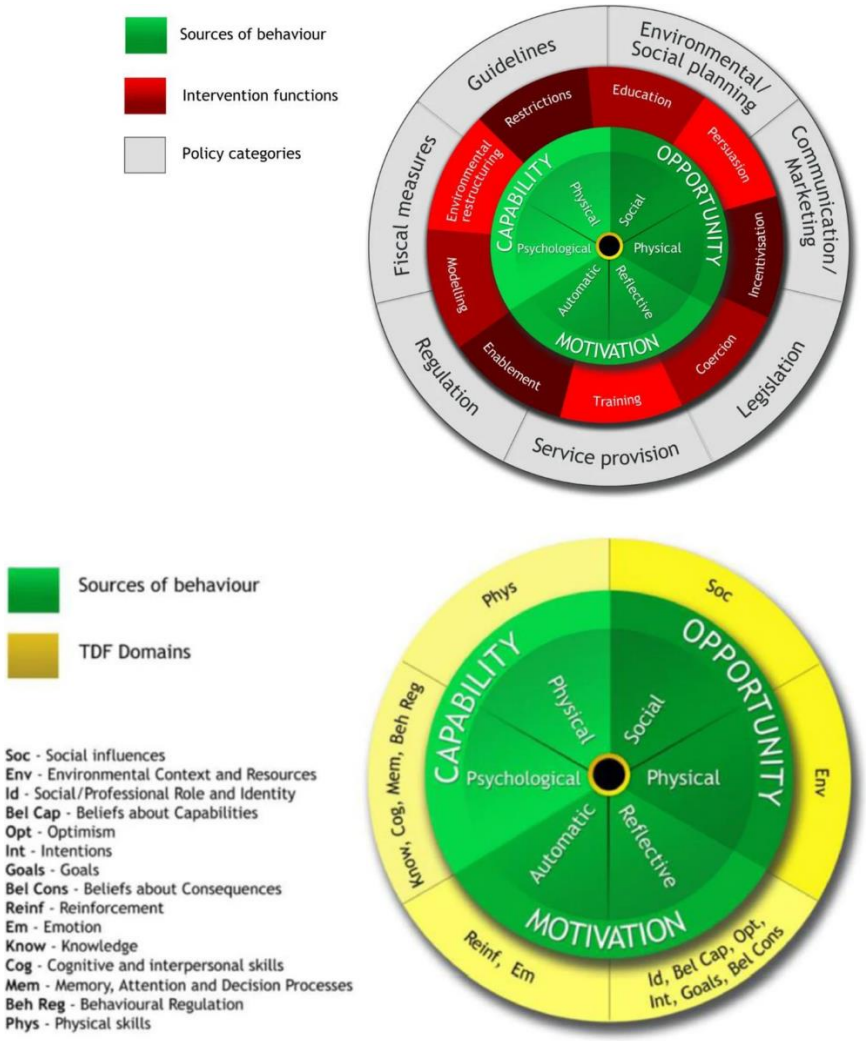


Figure 20: The Behaviour Change Wheel (BCW) (above) and the relationship with the Theoretical Domains Framework (TDF)

4.5.2 Sampling and recruitment from UK DOT/VOT randomised controlled trial

interviews were conducted at the UCL Farr Institute in London, during my tenure as a public health researcher supporting the NIHR-funded TB Reach programme team, supported by the team members, which hosted the programme. I conducted the majority of the interviews and in the UK and I provided training to the teams in the UK and Moldova on the principles of qualitative research, its rationale as a research method and interview methods to enrich quantitative data yielded by the trials.

I used heterogeneous sampling, a purposive sampling technique used to capture a wide range of diverse perspectives relating to the thing that you are interested in studying. In this instance I aimed to recruit patients with an array of treatment experiences based on the intervention they were randomised to as described below.

Working with the TB Reach programme manager, I identified groups of VOT trial participants at least 16 years old, who were receiving or had completed TB treatment and had capacity to provide consent. There were no exclusions by language. Two participants indicated their first spoken language was not English (Tigrinya and Romanian) were included. Of the 30 VOT trial participants identified, 17 accepted an invitation to participate in an interview. Of the remaining 13 who did not participate, one declined due to a family bereavement, calls could not be connected to five potential participants' phones and seven did not answer to their phones despite frequent calls. All participants provided informed consent prior to the start of the interview. Data for 17 semi-structured interviews was collected between November 2016 and April 2017.

The groups of interest and the numbers recruited in each group are as follows:

a) Participants randomised to VOT and continued until treatment completion (6 participants)
b) Participants with MDR-TB who received VOT until treatment completion (3 participants)
c) Participants randomised to VOT but switched to DOT (1 participant)
d) Participants randomised to VOT who never started VOT (1 participant)
e) Participants randomised to DOT and continued until treatment completion (5 participants)
f) Participants randomised to DOT but switched to VOT (1 participant)

g) Participants randomised to DOT who never started DOT (none recruited)

Participants were incentivised for their time through £30 supermarket gift cards.

4.5.3 Sampling and recruitment from Moldovan DOT/VOT randomised controlled trial

Through funding support from my RSTMH small grant, awarded in April 2016 (reference number GR000594) I completed a 1-week field trip to Chișinău, the capital city of Moldova in December 2016. The purpose of this trip was to provide qualitative interview training to the AFI trial staff to obtain patient views on being observed taking treatment for the management of tuberculosis, observe patient recruitment and VOT trial procedures.

The AFI trial staff conducted semi-structured interviews between January and May 2017 with a convenience sample of 22 participants with drug-susceptible TB embedded in a Moldovan trial (Ravenscroft et al. 2020) comparing the efficacy of asynchronous VOT to clinic-based DOT for supporting adherence: 13 patients received VOT and 9 received DOT. Informed consent was provided before the start of each interview. Similarly to the UK trial cohort, my sampling frame was determined by the interventions they were allocated to:

a) Randomised to DOT and continued until treatment completion (9 participants)
b) Randomised to VOT continued until treatment completion (13 participants)
c) Randomised to DOT and switched to VOT (none recruited)
d) Randomised to VOT and switched to DOT (none recruited)

4.5.4 Interview topic guides

The interview topic guides were co-produced with my primary supervisor with input from VOT trial coinvestigators and case managers from the UCLH Find & Treat Service and accounted for literature on theories of adherence behaviour in relation to TB treatment (Munro, Lewin, Swart, et al. 2007). The guides were designed to capture patients' views of the practicalities of treatment observation through either in-person DOT or VOT interventions for socially complex patients with TB. In consultation with AFI trial staff the interview questions were adapted for Moldova trial participants and to support translation from the Romanian-Moldovan dialect into English. Prompts were used where necessary to encourage participants to elaborate on information they provided and encouraged participants to address the question being asked. The duration of the interviews was expected to last up to 25 minutes, after accounting for time to express any other views of their experiences taking treatment for TB not addressed in the answers previously given.

4.5.5 Research ethics

Ethical approval for the UK VOT trial was received on 20th March 2014 from the NRES Committee East of England - Essex, Research Ethics Committee. Project Reference number: 10/H0302/51. An amendment to the ethics application for the Moldova VOT trial was granted by the UCL Research Ethics Committee on 5th October 2016.

4.5.6 Data management and analysis

Interviews were conducted using a Sony Digital Dictation Machine (ICD-PX240) and I uploaded them to a UCL laptop where they were transcribed with Microsoft Word.

With respect to the interview data collected from the UK I transcribed the majority of the transcripts (15/17) and the remaining two (2/17) were transcribed by a member of the TB Reach programme team.

I transcribed the interviews verbatim maintaining the local vernacular, to maintain closeness to the nature of the data and all interviews were double-checked against voice files for accuracy and completeness. Interview data collected in Moldova was transcribed into the local Romanian-Moldovan language by the AFI staff using the audio files and a local translation services contracted by UNDP was sourced to complete English translation for all 22 interview transcripts.

Interview data from both the UK and Moldova participants were imported to NVIVO version 11.4.1 (QSR International) for qualitative data organisation and coding.

I have used thematic analysis (Braun and Clarke 2006) for managing and analysing qualitative data. The five steps of thematic analysis are as follows:

1. Familiarisation – developing an in-depth knowledge of the data through repeated listening to the audio files, reading and re-reading the transcripts and associated notes.

2. Generating initial codes – coding interesting features of the data in a systematic fashion across the entire dataset, collating data relevant to each code

3. Searching for themes – collating codes into potential themes, gathering all data relevant to each potential theme.

4. Reviewing themes – checking the themes work in relation to coded extracts (level 1) and entire dataset (level 2), generating a thematic ‘map’ of the analysis.

5. Defining and naming themes – ongoing analysis to refine the specifics of each theme and the overall story the analysis tells; generating clear definitions and names for each theme.

After all the interviews had been transcribed, the first step of the analytical process involved multiple readings of the transcripts. I used NVIVO for data management and to assign initial codes that were developed from themes by the research questions and the interview topic guides. I used the first five transcripts from the UK cohort to develop a draft coding frame. This was also developed from reflexive discussions with VOT trial team members, UCLH Find & Treat case managers and an MSc Global Health student as a way to increase coding rigour. I developed new codes to fit around new sections of transcript data that did not fit into pre-existing codes. Both pre-existing and newly-defined codes were then applied to the remaining transcripts. In an iterative manner, I developed a coding tree with 'parent-child' nodes using the generated themes from the coded transcripts. The coding tree (Appendix 6.3) was later reduced by merging and re-organising themes. The coding tree contained the dominant themes and sub-themes and included brief sections of quotes. Subsequently the themes were reduced and refined into a manageable hierarchy of themes for discussion as part of a 'data clinic' with my supervisory team, VOT trial investigators and members of the Find & Treat team to maintain objectivity and strengthen rigour. The UCLH Find & Treat team is a specialist outreach service that tackles TB among homeless people, drug/alcohol users, vulnerable migrants and people who have been in prison. Discussions from the 'data clinic', which extended into 'UK-Moldova VOT trial knowledge exchange' meetings with VOT trial investigators from the Moldova team and WHO Digital Health Task Force enabled mapping and interpretation (Appendix 6.4), which sought to identify and articulate

descriptive and analytical themes, enabling me to build theory or understand how the study population experience a particular phenomenon and how these answer research questions.

4.5.7 Reflexivity

Being reflexive serves to critically acknowledge and examine who I am as a researcher, the role I had in the collecting and analysing of the data and the impact this will have had on the participants as part of the overall research process (Green & Thorogood; 2010). I practised reflexivity by considering how a range of my personal characteristics, such as my age, gender, social position may have influenced the dialogue and discussion during the participants' interviews and the authenticity of their personal accounts they shared with me. I was mindful that the interview sessions for all of the UK participants I interviewed would have been the first time that they will have met me and much of their trust will have already have been built with their assigned VOT observers, who conducted a few interviews. With respect to the VOT Moldova trial participants, all interviews were conducted in their native dialect in my absence and so trust in this cultural context may have had a bearing on the implementation. My previous experience as a study coordinator in other observational studies exploring risk factors that influence TB transmission whilst based at a TB outpatient clinic for over four years provided invaluable experience in understanding the personal and social circumstances faced by patients with TB. This experience was gained through attending weekly multidisciplinary meetings, shadowing TB specialist nurses during risk assessment

patient sessions and through determining eligibility for recruitment for my research study. This provided an appreciation of the complexity of adhering to TB regimens.

4.6 Results

4.6.1 Characteristics of interview participants by DOT and VOT observation group

DOT/VOT trial participants were deemed eligible for DOT, which meant they had a history of social complexity, had MDR-TB, HIV, had previously had TB and/or had mental health problems. Some of these characteristics were shown to be important determinants of non-completion of TB treatment and interview participants with some of these characteristics were also shown to initially engage and adhere to their TB treatment.

UK participants

Sixteen participants completed interviews, of which five were randomised to in-person DOT, six TB patients in addition to three who were MDR-TB patients were randomised to VOT, one TB patient randomised to DOT switched to VOT and one TB patient randomised to VOT switched to DOT and three. Of the study population, five were female and 11 were male. The mean age was 37 years old (range 20-68). Twelve participants were non-UK born, the countries of which included Eritrea, India, Indonesia, Morocco, Pakistan, Romania, Rwanda, Sri Lanka, Turkey and Zimbabwe. Four participants were UK-born. Thirteen participants were receiving the standard ‘short-course’ 6-month TB treatment regimen and three participants were receiving MDR-TB treatment regimen.

Moldova participants

Twenty-two participants completed interviews, of which nine were randomised to in-person DOT and 13 randomised to VOT. Participants' ages ranged from 20 to 65 years old. Of those allocated to DOT, three were male and six were females. With respect to participants supported by VOT, seven were male and six were female. All participants were from Chișinău. All participants were receiving the standard 'short-course' 6-month TB treatment regimen.

4.6.2 Mapping lived experiences and perceptions of TB treatment observation and DOT and VOT interventions onto the COM-B model and TDF

Table 16: Mapping lived experiences and perceptions of TB treatment observation and DOT and VOT interventions onto the COM-B model and TDF

COM-B		TDF strategy required to promote TB adherence behaviour change	Definition	TDF Strategy present in VOT and/or DOT	
				VOT	DOT
Capability	Psychological	Knowledge	An awareness of the existence of something.	✓	✓
		Skills: cognitive and interpersonal	An ability or proficiency acquired through practice.	✓	
		Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives.	✓	✓
		Behavioural regulation	Anything aimed at managing or changing objectively	✓	

COM-B		TDF strategy required to promote TB adherence behaviour change	Definition	TDF Strategy present in VOT and/or DOT	
				VOT	DOT
			observed or measured actions.		
	Physical	Skills: physical	An ability or proficiency acquired through practice.		
Opportunity	Social	Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings or behaviours.		
	Physical	Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behaviour.		
Motivation	Reflexive	Social/professional role and identity	A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting.		
		Beliefs about capabilities	Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put		

COM-B		TDF strategy required to promote TB adherence behaviour change	Definition	TDF Strategy present in VOT and/or DOT	
				VOT	DOT
			to constructive use.		
		Optimism	The confidence that things will happen for the best or that desired goals will be attained.		
		Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way.		
		Goals	Mental representations of outcomes or end states that an individual wants to achieve.		
		Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behaviour in a given situation.		
	Automatic	Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus.		
		Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the		

COM-B		TDF strategy required to promote TB adherence behaviour change	Definition	TDF Strategy present in VOT and/or DOT	
				VOT	DOT
			individual attempts to deal with a personally significant matter or event.		

4.6.2.1 **Capability – psychological**

Knowledge

For both VOT and DOT participants there was a clear awareness of the existence of an illness that needed management:

“I was a bit uncomfortable with it cos I thought I would probably have to go and visit a few more different institutions..hear my illness with a few more different people..at first.”

(randomised to VOT)

“plus I knew I’d got the illness..it just plays around in your mind”

“the pharmacy for me was about 15 to 20 minutes walk especially with the illness and the symptoms it was quite difficult."

(randomised to DOT)

Skills: cognitive and interpersonal

There were clear examples for VOT participants who had acquired a level or proficiency in following the VOT process to demonstrate they had ingested their doses:

“so the process was very quick all I had to do was erm wake up in the morning…give them my patient number and record the patient video and send it..that’s all."

(randomised to DOT and switched to VOT)

Memory, attention and decision processes

Amongst participants in the UK randomised to VOT or switched to VOT, unanimously believed that being observed taking treatment for TB was a necessity and recognised its importance as a means of support in adhering to medication. Participants reported that clear explanations of the rationale for VOT and it processes using a video app to record themselves taking their medications and assurances of extra support in the form of patient-provider interactions:

"when the whole thing was explained to me..that I thought about how it's gonna help me..in person..then I thought you know what..it's actually a really good programme" (randomised to VOT)

"Being observed, yeah it's a good thing like to be honest instead of going like to the hospital every single day it's better it's like their monitoring me every single day they're monitoring how I'm taking me medication because no one like to take their medicine so it's like you're under the impression that you have to take the medicine because if you don't take it the next day they let me know why it's important for me to take the medicine…it's good to be observed and I'm really happy they did it like..carefully and they were keen to make me feel better about this and I'm happy to be part of this.." (randomised to VOT)

Another participant echoes this faith in the doctor's recommendation for extra support in the form of observed treatment:

"The doctor said you need to take it..I accept what the doctor say..I'm here taking it" (randomised to VOT)

Perspectives on the necessity to be observed taking treatment for TB were more varied amongst participants in Moldova, indicating that policies should be reflective of the different ways in which health may be valued in different groups and treatment observation intervention should be recommended for those with a history of non-adherence:

"The individual who wants to get treated should receive treatment even without a tablet. I would have followed the treatment even without a tablet, it's for myself, it's my health" (randomised VOT)

"I think this is necessary only for those who don't follow the treatment, for them to be under special control, those who do not want to be treated" (randomised VOT)

"I think it's not necessary. Of course, you cannot trust everyone, there are different people" (randomised VOT)

Behavioural regulation

VOT served as a prompt or reminder to address unintentional non-adherence, such as forgetfulness or poor recall through regular personalised messages from VOT observers, building rapport and habit-forming practices:

"Each time I look at the phone I just have to remember to take my medicines" (randomised to VOT)

"When I first take medication and then I fall asleep and then I remember..and I say "Oh medication!" and then I say "not yet" I say "ok" and I have to wake up take medication and then do video sometimes before..but now everytime I did take medication now that's it..it's very easy..but ..it's easy to take medication" (randomised to VOT)

VOT participants were able to demonstrate how they regulated their adherence behaviour and how they established routines:

"with me it's straightforward I swallow my medication at once..I don't just take one tablet..I take all of it at once..it's straightforward I just put on the phone press record..get ready my medication..swallow and that's it"

(randomised to VOT)

4.6.2.2 Capability – physical

Skills: physical

In the UK there were clear instances of how VOT was reported to have promoted systemised or ritualised medication practices:

"I fixed my times..cos erm I think that it was easier for me to do that first thing in the morning and then just get it out of the way..rather than..cos the the thing is they expected me to take the medication on an empty stomach so that would have been the best thing for me to wake up and take the medication and lie down for 30 minutes..40 minutes until the medication has been absorbed..then I can go and have my breakfast.. (randomised to VOT)

"Well I'm used to it…the preparation is only like 5 minutes I have to like take banana...I have to take water..I have to prepare the video [speaking rhythmically] I have to make sure the video is on correct..make sure everything is see..5 minutes.." (randomised to VOT)

"..my doctor..nurses they satisfy so when you taking the video taking the medicine..regularly..[that's why they are with you]" (randomised to VOT)

"It's like you have to continue with the medicine because if you miss one day you have to start from the beginning..that's what they advised me..because of these things I had to take it I'm being monitored…that was in my head..yes I have to send the videos and there is no way you can..the important thing of this app is you can't change data and you can't even watch it ..you have to take it..it's a good thing." (RDVOT-078)

"Yes..they want it..like you know..they want..they want to make sure I'm taking the medication..and what for this one to give this to me if not take the video.." (randomised to VOT)

Amongst participants in Moldova, positive perspectives also highlighted clear instances demonstrating how VOT encouraged regular dosing and habit formation:

"Yes, because I know I have to take them […] I have to record myself. I think this thing motivated me" "this motivated me because I was monitored every day" (randomised VOT)

"VOT is much better, I woke up in the morning and the first thing I would do was to use the tablet and take the pills" "you wake up in the morning, like in the army, you know you should take the pills and you're free until tomorrow morning" (randomised VOT)

"However, it is good not to miss the moment, it became a reflex" (randomised VOT)

Similarly to other participants, in the UK it is articulated how a lack of motivation could manifest itself as non-adherence in the absence of observation:

"and I'm not gonna lie.. there were times..I just didn't..I just didn't wanna take them..the nurses coming and being there..supervising me taking them..was brilliant..it did help.." (randomised to DOT)

4.6.2.3 **Opportunity - social**

Social influences

The development of rapport with VOT observers allowing patients to feel cared for and provided a sense of security and comfort:

"If you have a chance and you can afford to give phone it will help patient to feel important…that's what I felt…I don't have anything…they're giving me phone…they're really caring about my situation and everything…so yeah…that's what I felt" (randomised to VOT)

"it was very helpful honestly..it builds you confidence and you feel loved as well when you meet people.." (randomised to VOT)

There was also an instance where VOT was being used to prove legitimacy and to maintain trust with the VOT observer:

she wasn't going to believe me…she said "no you have to show me" I guess…I know… she was doing her job so I was like ….no I took it so one day I just put it…there was like a box and I couldn't find it…and what I wanted to do…I used to take medicine before I go to sleep so it wouldn't affect me that much I would just go to sleep for long so I just took it in my hand I just had it ...she said "no don't do this" I said "why, don't you trust me"… she said " no I do but we need to see what kind of medicine you are taking" so this is something…it's annoying but it's helpful [laughs quietly] (randomised to VOT).

There were also instances where DOT provided clear opportunities to benefit from additional physical support for complex social circumstances. For a participant randomised to DOT, he was able to accommodate several nurses who visited his home from 8am to observe his treatment five-times weekly:

"It's fine. I knew I'd be awake for that time…just after eight o'clock ..I'd be awake by then…and once then watch me take my medication and they asked me if I wanted anymore..anymore help..there wasn't just one who helped me..three of them actually..not all at the same time obviously..one day it would be someone else..then Thursday it would be someone else..one would observe me take my medication and the other one would ask me if I wanted anything else..and that was it..so I was fine with that." (randomised to DOT)

Conversely, home-based and pharmacy DOT were reported by some to be invasive, inconvenient, stigmatising and costly in both the UK and Moldova:

"yeah..doctor said it's up to you..its' ok with me…cos I do find it hard to travel about..cos I've got to take a train and then another train..and then I've got to get a lift from my landlord..(randomised to DOT)

"Face-to-face observation was working it was just..I didn't want to go in there everyday..and plus there were people around and it was supervised as well..I had to take it in front of them when there were people around…there was a lot of medication..so it was uncomfortable..cos I had to take about eight..nine tablets which is about four different antibiotics and I did find it quite uncomfortable especially waiting…sometimes they will be serving someone else and I will be waiting around..and plus I knew I'd got the illness..it just plays around in your mind…" (randomised to DOT)

"I would have felt uncomfortable if they learned that, not even in our home everyone knows […] I am ashamed" #VB0801 (randomised VOT, later passed to DOT)

4.6.2.4 **Opportunity – physical**

Environmental context and resources

Pill burden and the onset of side effects are important medication-related factors that can, in combination with other factors contribute to non-adherence. In the UK there were clear examples of how VOT supported split dosing or negotiating timing of dosing to manage side effects and pill burden:

"I mean.. because you're taking medications everyday…it's a lot of medication plus…it gives you… side effects…you don't feel..alright….I still get burns in my chest….like….because it's heavy…so sometimes you do get fed up you don't wanna take it….you're taking that many tablets…if affects your body from inside…like…because all the tablets…are like hot…and powerful…so sometimes you don't get like…like if the phone wasn't there….so maybe I would've missed few days…I'm not gonna lie….if the nurse wasn't there…and the phone wasn't watching me…I would've missed a few days…yeah I don't feel like taking tablets today…it does help you that way" (randomised to VOT)

"..sometime I have to go with my Mum sometime out so I'll take sometime medicine early..like 10..11 o'clock in the morning..and sometime I have to go to the

hospital..like today I go to appointment 12 o'clock so I just came half-past one I just take the medicine" (MDR-TB patient on VOT)

This male also expressed a lack of autonomy, helplessness and concern about his side effects and their impact on his quality of life:

"I still don't know what's happening with my life because there are some side effects I'm having which is really hard for me to handle…I don't work because of that I feel so weak..it's been nearly a year..I don't do anything." (RDVOT-078)

This pronounced emotional representation of the disruptive impact of side effects on his usual activities over the course of one year in this statement appears to indicate an internal struggle yet this does not seem to translate to a low necessity belief, rather he appears to be resigned to halting his way-of-life at the expense of continuing with his TB treatment regimen.

He goes on to describe how sleep would serve as a means of escapism from the effect of the side effects:

"I used to take medication before I go to sleep so it wouldn't affect me that much I would just go to sleep for long.." (RDVOT-078)

These summative representations of threat that an empirical TB regimen poses on this male's life demonstrate how uncertainty of the overall health outcome, from the patient's perspective may have culminated in a depressive state.

Broadly UK participants did not express VOT violated their privacy as they knew a VOT observer would be viewing their clips and that these clips were encrypted

No I'm not worried about..(randomised to VOT)

I'm sick so what's wrong with me take my medication…no…I mean I didn't find nothing wrong with it….I mean how could you find [anything] wrong with it….maybe people feel….I didn't feel nothing wrong with it (randomised to VOT switched to DOT)

I was a bit worried when I was actualy taking the footage and submitting I knew who I was sending it to but I was a bit uncomfortable (randomised to VOT)

I didn't want it to be be public and the fact that they told me it would only go to that person and that it would be deleted eventually I was ok with that (randomised to VOT)

Erm..no because I was told it was for a study..so I assume whoever's doing the study could watch them..erm I don't have a problem..I'm comfortable..I agreed to do the study..as long as whoever it watching them is going to help someone then I'm fine with it (randomised to VOT)

To be honest there is nothing…what ever you people are doing is to help us…so I…why it wasn't anything private…I was taking medicine..and …if you are showing

that video to someone it's for a good cause…that's what I believe (randomised to VOT)

No..because I was told…it was encrypted as well…all the videos that are sent was encrypted.. (randomised to VOT)

There we some examples where participants had not revealed their diagnosis to their family members or friends and had some concerns that the discovery of video clips or being seen recording clips may breach privacy:

I didn't tell them that I got TB and whatever…I just say.."doctor want me to take medication with the camera"..that's it! (randomised to VOT)

it would have made a difference because this is my personal phone..that I go with everywhere..my friends..so sometimes you can have friends who are nosey.. (randomised to VOT)

In contrast, participants in Moldova were more circumspect on how data collected through video clips would be used and stored. There were also concerns amongst participants on being publicly identified either through the collection of personal identifiers or through national media through TB awareness campaigns:

"You know. Every normal person has an instinct of self-preservation and I was concerned" "After all, I want no one to see" (randomised VOT)

"Life is long and I don't trust the databases, even if these stay sealed, I don't believe it, sometime they might go public" "The internet is big, technologies are thinly developed and rather than information I don't need surfacing after a while, it is better I am left only with the doctor and the nurse, so that other people don't know who I am" (randomised VOT and switched to DOT)

"On TV they often show information on tuberculosis and I was afraid that they might show me as an example"

Emergent themes indicated VOT was a flexible, time- and cost-saving alternative to DOT. Findings indicated that participants were able to personalise VOT allowing it to suit their needs, providing privacy and support them in re-gaining autonomy:

"Five minutes.yeah..perfect..and you just get one with your day.." (randomised to VOT)

“it saves you money…time…otherwise what they wanted to do..the nurse wanted to come everyday visit to make sure you were taking your medication so that way the nurse can do something about it so just do a visit at home...the phone thing is better…just record it and send it to them. It saves the money and time for both the people.” randomised to VOT

“Like you don’t have to call your doctors all the time I can send a text to them and let them know my situation” randomised to VOT

The convenience that VOT provided were also expressed amongst participants in

Moldova who reflected on experiences of DOT as part of their previous TB

diagnoses:

“I was coming to the polyclinic every day to administrate the pills and this used to be much more difficult […] Instead of spending time and coming to the polyclinic every day, I could do something else” “I save a lot of time, I don’t have to come here (in the polyclinic) (randomised VOT)

“Coming in every day is very difficult” (randomised VOT)

“Going to the polyclinic every day is inconvenient, it distracts me from house affairs…with VOT I would have more free time and do other things” (randomised VOT)

The most frequently reported characteristic of DOT in both the UK and Moldova was

its tendency to impede the opportunity to undertake normal daily activities:

“..it was really hard for me going..to the pharmacy every morning.. the thing is I’ll have to wake up..then I’ll have to go to the pharmacy without having any breakfast because I had to take the medication empty stomach..so I’ll come back from the pharmacy I’ll have to wait another…30 to 45 minutes till I can have something to eat..then I can go about my day..” (randomised to DOT switched to VOT)

“yeah..doctor said it’s up to you..its’ ok with me…cos I do find it hard to travel about..cos I’ve got to take a train and then another train..and then I’ve got to get a lift from my landlord..” (randomised to DOT)

“to the clinic I have to go everyday far away..so to me it’s better to be the phone” (randomised to DOT)

“I prefer sending videos because as I told you..you know I couldn’t go everyday in the hospital.” (randomised to VOT)

For a participant randomised to DOT was exasperated in explaining how daily visits to the outpatient TB clinic for in-person DOT were inconvenient, challenged his ability to adhere to his regime and imposed challenges on his livelihood. He describes how he discussed this with his case manager and reports that self-administration has led to better outcomes as he nears treatment completion, despite missed appointments:

"yeah I've been doing that since I come out of hospital..I haven't really seen a nurse..I mean..I can't..I understand the medical point of view but at the same time..I'm a working guy you know..I've got..a little business where..I can't afford to..come to the hospital everytime..I had to make that clear to Thomas..just to like..I just CAN'T keep coming to the hospital every week just to pick up tablets..you know..we tried to make arrangements whether I come back on a week basis or a couple of week basis ..you know..I just can't keep coming to the hospital just to pick up tablets you know..just a whole day wasted for me..so as far as that's concerned I haven't really seen anyone on a day-to-day basis..I've just been going through this treatment..taking my treatment..erm feeling a HELL of a lot better since ..I must admit..without a doubt..erm and I was supposed to go and see the doctor yesterday which Thomas was telling me would've kind of given me the all clear.."

(randomised to DOT)

In Moldova, attending daily in-person DOT sessions at polyclinics was hampered by poor weather conditions and limited transport options, an explicit instance of a missed dose and a batch collection of tablets for unobserved treatment:

"On the day when there was a lot of snow, as there was neither transport means […] then I didn't drink the pills" randomised DOT)

"One time when I went to the village and took pills for the next four days"

(randomised DOT)

"One day […] it was icy outside and I was feeling bad, feeling afraid to get on the road […] I was concerned about breaking a hand or a leg" (randomised DOT)

A patient supported by DOT in the UK, who struggled with her pill burden describes daily visits three-times weekly by a case manager in addition to phone calls twice

weekly from the clinical team supported her pain management during treatment and coping during mental health crises:

"It started three days a week and THEN..because of how..she went back and told them that the pain that I was going through…also my mental health..like I said it was ALL too much for me so what they kept on doing was sending Rachel three times a week and the called me twice a week so they were covering up the full five days a week..so yeah..which I found helpful as well..so I wasn't alone." (randomised to DOT)

Qualitative interviews were also able to qualify missed DOT observations and doses in Moldova whereby participants sought requests from polyclinic case managers for batch collections of tablets for holidays, weekends or for longer periods of times:

"I wrote a request and they were issued to me" (randomised to DOT)

"Yes. It happened once. I had to leave for a week. Everyone has a situation. Because you follow the treatment for a fairly long period. I had such case once. But I often have to go to relatives abroad, besides I have diabetes. But the polyclinic doesn't give pill. I had to beg filled with tears. It's right there are different cases. Once evey six months or a year and its hard to solve this problem. (randomised to DOT)

"Only on a Friday, I was taking medicine for the weekend" (randomised to DOT)

"They give them on hands if days off or holidays coincide." (randomised to DOT)

"On the day when there was a lot of snow, as there was neither transport means, nor the wife was at work, then I didn't drink the pills (randomised to DOT)

"Yes…5 [days] at most." (randomised to DOT)

4.6.2.5 **Motivation - reflective**

Beliefs about capabilities

Patients' beliefs, otherwise known as necessity-concerns about TB treatment and about TB itself may be salient to achieve adherence. The Neccesity Concerns

Framework, a theoretical model for medication beliefs and the importance of illness representations, as described in Levanthal's Common-Sense Model may influence evaluations of treatment necessity and concerns.

Participants were explicit in describing fear of the potential impact that TB would have and was presently having on their lives. In the extract below this perception of TB, characterised by its explicit relationship with impending death, this female from Indonesia expresses the necessity for treatment support:

"Because I'm scared..it's gonna die or something..because that is dangerous you know..it's TB..it's dangerous so I need someone to support with that..with the TB medication and stuff like that" ((randomised to VOT))

There also appears to be an indication of resilience when faced with the likelihood of taking treatment. This statement also highlights an example of how a participant uses a necessity belief to arrive at a common-sense evaluation about taking treatment for TB that are consistent with 'positive pharmaceutical schema'; that is to say that given her beliefs of TB and its consequences, treatment for it was important to achieve a positive outcome.

"It's not a thing it's necessary..it's absolutely..I expected it..this is what I need to do…" (randomised to VOT)

Intentions

There were conscious decisions to maintain treatment observation through VOT in order to re-gain health and wellbeing:

"I wanna get better..that's it..there's no point you like sending video and then if you not happy..you have to get better and have to be happy as well to take medication..that is the thing"

(randomised to VOT)

"I've been down with some of my medication..stopping my medication for no reason..so this opportunity..this gave me an opportunity to take my medication whenever I had to take it..I felt good."

(randomised to VOT)

Goals

There were also clear examples of links between positive necessity beliefs and goal-oriented outcomes, such as to re-gain one's health and to return to work:

"No..it's good..cos you know I used to it..I wanna get better..that's it...you have to get better and have to be happy as well to take medication..that is the thing" (randomised to VOT)

"Yes..of course this is treatment for my HEALTH" (randomised to VOT)

"So I have to finish my treatment and I want to go back to work..I look forward to work" (randomised to VOT)

Beliefs about consequences

An MDR-TB participant echoes the fear of death at the hands of a challenging lengthy regimen:

"[3-4 second pause] [long intake of breath] it wasn't easy..the fact that you are taking these drugs plus it was like two years..and I'm thinking like "Oh my God!" [LAUGHTER] for two years?...Am I going to survive?" (randomised to VOT)

It's not clear whether this statement is consistent with a negative pharmaceutical schema, that is to say that she is suspicious of pharmaceuticals, perceiving them to be fundamentally harmful and attributable to the additive nature of MDR-TB regimens taken for longer periods of time in comparison to regimens for susceptible TB strains. Yet this cognitive and emotional representation of treatment threat appears to call into question her ability to overcome TB as a threat to her life and its likely consequences and perhaps the potential for control and cure.

Other participants describe feelings of entrapment imposed by the regimen:
"It's like prison inside.." (randomised to VOT)

A female in her late 40s from Zimbabwe with MDR-TB stated:
"I just didn't think it was going to end" (randomised to VOT)

One male participant uses the concept of boredom to describe a lack of autonomy when faced with the prospect of adhering to a regimen yet recognising it as the solution to the alleviation of any symptoms and the desire to be cured:

"I know it's boring..boring..when someone is sick you don't have choice..you have to take it..you know..you have to stuck on it because no one need to suffer..you know..I don't want to suffer you know..I want to recover as soon as possible.." (randomised to VOT).

This statement of concern begins as a less emotive representation of TB and treatment yet may also represent his 'hardiness' and decision for adhering to his regimen after reconciling his necessity beliefs with that of his concerns as a means to recover from TB.

Concerns in this male are manifested through his explicit fear of the prospect of commencing empirical treatment for TB:

"I was scared…I was really scared because when I started taking it I wasn't sure..even doctor wasn't sure that I have TB..and somehow I believe..still I believed it was..it was..shot in the dark.. (randomised to VOT)

In the following extract a participant draws attention to what she perceives to be a negative consequence of the TB medication (red urine), yet through dialogue with her clinician she is able to reassure her that her TB treatment is taking effect.

She states: *"…when I take medication when I do pee-pee it's red I was so scared..screaming so I ask doctor..the doctor said it's beautiful so the medication is working" (randomised to VOT)*

It also highlights she appears to be still willing to bypass her concern after receiving a 'pharmacokinetic-type' health message for the sake of continued treatment and ultimately control and cure.

4.6.2.6 **Motivation - automatic**

Reinforcement

Established ritualised medication-taking behaviour using a smartphone via the VOT process increased the probability of increased observations response by arranging a dependent relationship with the phone as the incentive:

"the pharmacy for me was about 15 to 20 minutes walk especially with the illness and the symptoms it was quite difficult so once they actually gave me the phone I got used to the whole thing..recording…"

(randomised to DOT and switched to VOT)

"what I did I put the phone here …I put the glass of water…I put my tablets here…took my tablets…I put the phone here…it would've taken me the same time even without the phone…the phone is just like a recording then isn't it…its' just there right isn't it…all I…I just hold it in my hand because I just..I just put it in the thingy then I just take the tablets…and then that's it…and then I just send it"

"like if the phone wasn't there….so maybe I would've missed few days…I'm not gonna lie….if the nurse wasn't there…and the phone wasn't watching me…I would've say a few days…yeah I don't feel like taking tablets today…it does help you that way"

(randomised to VOT)

Emotion

In the following extract emotional and cognitive representations of TB treatment are observed being processed in parallel with his necessity beliefs for treatment and adherence to VOT. This participants appears to overcomes their necessity concerns,

perceived difficulty to adhere and disorientating side effects and makes a common-sense evaluation to remain supported through VOT:

"..no one wants to take medicine but if I didn't have to take some videos I would've missed some days…like I was in Manchester but I didn't want to make excuse but I really didn't like it because it's too hard when you take the medicine because you feel really dizzy.."

This the extent of alternative health threats, including a possible cancer diagnosis the participant was contending with are expressed:

"..and when I was asking the doctor and the hospital..they said we can't give you exact assurance that it's TB..can be TB..or it can be something else..even I wasn't sure..in cancer department for two weeks..first it came with brain tumour the cancer then they said..like it's a shadow.. and so many thing was going on and I'm just…I'm not even old enough to handle these things so I was really disconnected with the level. And I was like what's happening with me?" (randomised to VOT)

He continues: *"..and then doctor help me a lot they used to come every single day for routine check-up and even they used to come and talk…cos I was…I was…and I was in the room for all the long….they used to tell me go to the TB rooms…there it's not going to affect anyone cos…we don't have that thing cos it's in the head…if it's in the chest…then it goes… the virus goes to other people but it has nothing to do with your treatment you one is perfect so you can go…and I thought why it's happening with me…why it's me….they supported me a lot…and….it did work…(randomised to VOT)*

In this extract the delivery of a health message on how TB is transmitted based on pathophysiology helps this participant understand his TB illness better leads to him de-isolating himself and that his perceived side effects were not connected to his TB treatment. He was reassured by the ongoing support he received from his clinician.

These examples provide some insight into how health messages using a common-sense rationale for continued use of TB treatment may support patients allay or bypass necessity-concerns.

4.6.3 Links between COM-B targets, VOT functions and policy categories

Findings show VOT targeted 7 key COM-B model intervention functions to elicit improved observation

VOT functions	COM-B model components					
	C - Ph	C - Ps	M - Re	M - Au	O – Ph	O - So
Education						
Persuasion						
Incentivisation						
Coercion						
Training						
Restriction						
Environmental restructuring						
Modelling						
Enablement						

Key: C-Ph = Capability-physical; C-Ps = Capability-psychological; M-Re = Motivation -reflexive; M-Au = Motivation-automatic; O-Ph = Opportunity-physical; O-So = Opportunity-social

Table 17: Links between components of COM-B model and VOT intervention functions

The policy categories and behaviour change techniques amongst trial participants that have been identified, as described by the Behaviour Change Wheel include: Enablement (increasing means/reducing barriers to increase capability), Education (increasing knowledge or understanding), Persuasion (using communication to induce positive or negative feelings or stimulate action), Training (imparting skills), Incentivisation (creating expectation of reward), Restriction (using rules to reduce opportunity to engage in target behaviour) and Environmental restructuring (changing the physical or social context). Modelling (providing an example for people

to aspire to) and Coercion (creating expectation of cost) were excluded as it was not relevant in in this study.

Behaviour source targeted in VOT intervention	**VOT intervention functions**	**Policy category**	**VOT characteristics / mode of delivery**
Capability – physical **Skills: physical -** promoted systemised or ritualised medication practices	Training: instructions on how to lay out each drug on a labelled laminated medication sheet with a space for each drug and take each drug individually whilst recording the VOT clip on the smartphone.	Communication Guidelines Regulation Service provision	Video-observed treatment was provided by a centralised service in London. VOT clips read by a research study nurse/VOT observer daily during weekdays with weekend clips read on Mondays and communicate with / provide feedback to patient
Capability – psychological **Knowledge -** clear awareness of the existence of an illness that needed management **Skills: cognitive and interpersonal -** acquired a level or proficiency in following the VOT process to demonstrate they had ingested their doses **Memory, attention and decision processes -** clear explanations of the rationale for VOT and it processes using a video app to record themselves taking their medications and assurances of extra support in the form of patient-	Credible / trusted sources of guidance and information Training: self and VOT observer monitoring of adherence behaviour Education: prompts / cue, feedback on adherence behaviour, self and VOT observer monitoring of adherence behaviour Enablement: enhancing motivation and self-responsibility and re-gaining a sense of autonomy	Communication Guidelines Regulation Service provision	Video-observed treatment was provided by a centralised service in London. VOT clips read by a research study nurse/VOT observer daily during weekdays with weekend clips read on Mondays and communicate with / provide feedback to patient

Behaviour source targeted in VOT intervention	VOT intervention functions	Policy category	VOT characteristics / mode of delivery
provider interactions promoted a necessity for treatment observation **Behavioural regulation -** prompt or reminder to address forgetfulness or poor recall through regular personalised messages from VOT observers, building rapport and habit-forming practices			
Motivation – reflexive **Beliefs about capabilities -** resilience and expressions of necessity beliefs to arrive at a common-sense evaluations about taking TB treatment **Intentions -** conscious decisions to maintain treatment observation through VOT in order to re-gain health and wellbeing **Goals -** links between positive necessity beliefs and goal-oriented outcomes, such as to re-gain one's	Training: self and VOT observer monitoring of adherence behaviour Education: prompts / cue, feedback on adherence behaviour, self and VOT observer monitoring of adherence behaviour Credible / trusted sources of guidance and information Incentivisation: provision of a smartphone and data plan, free domestic calls, text messages and internet access linking patients to healthcare providers, banking and social support services.	Communication Guidelines Regulation Service provision	Video-observed treatment was provided by a centralised service in London. VOT clips read by a research study nurse/VOT observer daily during weekdays with weekend clips read on Mondays and communicate with / provide feedback to patient

Behaviour source targeted in VOT intervention	VOT intervention functions	Policy category	VOT characteristics / mode of delivery
health and to return to work **Beliefs about consequences -** TB as a threat to life and its likely consequences; treatment as the source to alleviate symptoms, for control and cure			
Motivation - automatic **Reinforcement –** increased and ritualised medication-taking behaviour using a smartphone as incentive **Emotion -** emotional and cognitive representations of TB treatment are processed in parallel with necessity beliefs for treatment adherence using VOT.	Credible / trusted sources of guidance and information Enablement: enhancing motivation and self-responsibility and re-gaining a sense of autonomy Prompts / cues / reminders Incentivisation: provision of a smartphone and data plan, free domestic calls, text messages and internet access linking patients to healthcare providers, banking and social support services.	Communication Guidelines Regulation Service provision	Video-observed treatment was provided by a centralised service in London. VOT clips read by a research study nurse/VOT observer daily during weekdays with weekend clips read on Mondays and communicate with / provide feedback to patient
Opportunity – social **Social influences -** development of rapport with VOT observers allowing patients to feel cared for and provided a sense of security and comfort	Credible / trusted sources of guidance and information Prompts / cues / reminders Incentivisation: provision of a smartphone and data plan, free domestic calls, text messages	Communication Guidelines Regulation Service provision	Video-observed treatment was provided by a centralised service in London. VOT clips read by a research study nurse/VOT observer daily during weekdays with weekend clips read on Mondays and

Behaviour source targeted in VOT intervention	VOT intervention functions	Policy category	VOT characteristics / mode of delivery
	and internet access linking patients to healthcare providers, banking and social support services.		communicate with / provide feedback to patient
Opportunity – physical **Environmental context and resources -** VOT supported split dosing or negotiating timing of dosing to manage side effects and pill burden	Enablement: enhancing motivation and self-responsibility and re-gaining a sense of autonomy Environmental restructuring Incentivisation: provision of a smartphone and data plan, free domestic calls, text messages and internet access linking patients to healthcare providers, banking and social support services.	Communication Guidelines Regulation Service provision	Video-observed treatment was provided by a centralised service in London. VOT clips read by a research study nurse/VOT observer daily during weekdays with weekend clips read on Mondays and communicate with / provide feedback to patient

Table 18: Links between components of COM-B model and VOT intervention functions and policy categories

4.6.4 Factors affecting engagement with VOT under trial conditions

Using the **D**igital Health **E**n**G**agement **MO**del (DIEGO) themes (O'Connor et al. 2016) it is possible to theorise why engagement with VOT under trial conditions supported TB treatment adherence in inclusion health groups for whom there is evidence of problems engaging with their care and services.

Personal agency and motivation

People with immigration concerns will experience psychosocial stresses due to issues on legal status and being 'ordinarily resident', an important determinant of entitlement to healthcare access in a host country. This removes a great deal of personal control and freedoms from a migrant and their right to unfettered equitable access to healthcare. The importance of rapport between the patient and the VOT observer emerged as an important characteristic of the VOT service provided, regular personalised messages, which served as reminders. Other triggers which served to motivate participants included confirmation of receipt of video clips, or follow-up messages or calls when clips were not received. These characteristics reinstated personal agency and self-worth:

"It was very helpful honestly..it builds you confidence and you feel loved as well when you meet people.." (randomised to VOT)

"Actually we had a connection when she showed me whatever was going on..so it was good..it was good that I met her and that she would be part of some of the people who was going to be watching the videos..so yeah" (randomised to VOT)

I felt like…is she actually doing it or is it the computer? That's human nature. Cos when I was texting her the replay was like "thank you for your message" every time and then I realised it's not an automatic message…message comes every time you send a text and later she replied "ok I will discuss with the doctors and I'll let you know" so I spoke to her on the phone…so it wasn't the robot" (randomised to VOT)

Because whenever I meet them they ask me they're always sending me the..whenever I record the clips..they always text back..so whenever I do the mistake they will explain me why did you take..this is the medicine..you mistake this and that..this can of messages they give to me and I was accept and I was answer back (randomised to VOT)

Personal life and values

Participants valued the flexibility and convenience that VOT provided by enabling participants to split their doses during the day enabling them to maintain an active

personal life, employment nurture social and familial connections and to manage the side effects of the treatment:

"It saves a lot of time..a lot of effort..erm I think in a way it's..more efficient…cos the thing is I'll get to wake up in the morning and take the medication first thing in the morning..rather than worry about anything else..and going to the pharmacy and getting ready..it's like..that way it's more efficient…erm..plus you get more..reminders if you forget..so all in all I think it was good for me (randomised to VOT)

"You know sometime I have to go with my Mum sometime out so I'll take sometime medicine early..like 10..11 o'clock in the morning..and sometime I have to go to the hospital..like today I go to appointment 12 o'clock so I just came half-past one I just take the medicine (randomised to VOT)

"Sometime I take my medication…late…but then they got the time nine to five…whatever…but it you do it like you stuck to the time… it's twelve o'clock you have to go take your medication….sometime you want to take it late…because of the side effects…them fings.. I need more freedom so I can take it before twelve o'clock in the night (randomised to VOT)

Engagement and recruitment approach

In order to reach a population with social complexity and inherent problems in adhering to TB treatment, recruitment was targeted at participants who would be eligible to DOT. The 50:50 random allocation approach was used fairly assign participants to the DOT/VOT trial to minimise the effect of bias from known and unknown confounders. Participants seemed indifferent to the recruitment strategy used but it was clear being randomised to VOT supported flexibility and some participants also believed there was a civic duty to further health innovation:

"The random..programme..if they select you..you get..you get selected..so I was like out my name down I'll fill out the form..I'll give you the consent..and actually when I thought..the whole thing went through and they came back to me and you've been selected..and they'lll give you a phone..and I thought about it..and I thought [PACE QUICKENS, SMILES] ..ok I think this will be a very brilliant thing for me because doing it from home rather than..cos it was really hard for me going to..going to the pharmacy every morning..and breakfast (randomised to VOT)

"When they explained at the beginning…like it was helping other people…like..it was more a study fing to see how it works for other people…I didn't mind…because if it helps…because that's how you learn…anyway…innit…we learn things from the past and then we learn things to go in the future..innit..I mean if they didn't design it how

would the next people know…so in a way I didn't mind…I mean..I never mind doing study fings…if it helps someone in the future…(randomised to VOT)

Whilst VOT participants had previously expressed that VOT provided security and confidentiality, a sense of reassurance, it also provided a level of detachment from stigmatisation imposed by the paternalistic aspects of DOT, which infantilises participants:

"first I thought it was childish…because I mean….like….I'm an old person….I'm…sick (randomised to DOT switched to VOT)

..I didn't want to go in there everyday..and plus there were people around and it was supervised as well..I had to take it in front of them when there were people around…there was a lot of medication..so it was uncomfortable..cos I had to take about eight..nine tablets which is about four different antibiotics and I did find it quite uncomfortable especially waiting…sometimes they will be serving someone else and I will be waiting around..and plus I knew I'd got the illness..it just plays around in your mind…here I think it's more private..and I do it in my own personal time..and I can keep everyday the same time..dosage..everything I can do that without no issue..so yeah it was very helpful..for me..coming on a personal level. (randomised to DOT)

Quality of VOT

The quality of the interaction between patients and VOT observers was enhanced by the provision of a free smartphone with a data plan, free domestic calls and text messages, which facilitated easy communication between patients and care providers, well as connectivity to other external services to gain social and economic support such as through primary care practitioners and banking services. The UK DOT/VOT trial reported that VOT participants were also more likely to report side effects than those on VOT, which is also an important determinant of quality of interaction with VOT:

"Just to communicate on how we are feeling ..because at times I really felt rough..with the treatment you know when I was getting the injections..and whatever..oh it was horrible..yeah..the side effects" (randomised to VOT)

"Sometime side effects…you don't feel..alright….I still get burns in my chest….like….because it's heavy…so sometimes you do get fed up you don't wanna take it….you're taking that many tablets…if affects your body from inside…like…because all the tablets…are like hot…and powerful…so sometimes you don't get like…like if the phone wasn't there….so maybe I would've missed few days" (randomised to VOT).

Findings suggest the high level of resource-intensity attached to implement of DOT in practice as a means to engage socially complex groups with services. This is supported by quantitative findings which showed that initial engagement with DOT was over 70% amongst those who were aged over 55, had a prison history, a history of homelessness (more than 5 years ago) and had current alcohol problems. The high degree of resource-intensity to bridge the gap between care-giver (TB clinical nurse specialists, outreach or DOT workers) and socially complex patients is supported by confirming evidence in the qualitative findings, three- to five-times weekly:

"I knew I'd be awake for that time…just after eight o'clock ..I'd be awake by then…and once then watch me take my medication and they asked me if I wanted anymore..anymore help..there wasn't just one who helped me..three of them actually..not all at the same time obviously..one day it would be someone else..then Thursday it would be someone else..one would observe me take my medication and the other one would ask me if I wanted anything else..and that was it..so I was fine with that." (randomised to DOT)

"It started three days a week and THEN..because of how..she went back and told them that the pain that I was going through…also my mental health..like I said it was ALL too much for me so what they kept on doing was sending Rachel three times a week and the called me twice a week so they were covering up the full five days a week..so yeah..which I found helpful as well..so I wasn't alone." (randomised to DOT)

4.7 Discussion

For this qualitative research study, I aimed to describe the lived experiences and perceptions of DOT and VOT interventions in patients with TB in the UK and the

Republic of Moldova. The COM-B model was used to explain the lived experiences, perceptual and practical factors that influence TB treatment observation with respect to DOT and VOT interventions. The TDF was used to identify the policy strategies necessary to change mechanisms of TB treatment adherence behaviour. The Behaviour Change Wheel was used to explain how VOT functions ('active ingredients') target the linked policy categories to elicit improved observation to support decision-making on commissioning of DOT and VOT interventions. At an individual-level, findings showed VOT acted on 'capability' element of the COM-B model by facilitating interaction, regular personalised reminders and personal support through the VOT observer, which strengthened the necessity to take TB treatment. VOT also acted on the physical and social opportunity to take treatment through the provision of a smartphone with a data plans, free domestic calls and text messages. Patients supported by VOT also had flexibility and the physical opportunity to split their dosing over the course of the day either for side effect management or to enable them to continue their usual daily activities. Both the capability and opportunity components of the COM-B model enhanced the motivation in patients, enabling them to establish ritualised and systemised practices for daily dosing and minimise forgetfulness and poor recall. Other triggers which served to motivate participants included confirmation of receipt of video clips, or follow-up messages or calls when clips were not received.

For some socially complex patients with mental health problems who struggled with pill burden, DOT was also found to enhance motivation and provided the social opportunity for patients to draw psycho-social support from in-person face-to-face visits to their homes and establish habit-forming practices triggered by expectant nurse home visits. There were many instances in which patients supported through

DOT felt cared for as part of their in-person sessions. Conversely, there were also other instances where pharmacy- and home-based DOT stigmatised and disempowered patients and travel for clinic-based DOT was inconvenient, invasive and stigmatising. DOT was also shown to impede upon patients' ability to maintain their livelihoods due to the expectation to travel to and from clinic for in person visits. A combination of any one of these factors may have influenced patients in questioning the necessity to adhere to treatment, thus negatively influencing their motivation.

Based on the Behaviour Change Wheel, VOT consists of seven key functions ('active ingredients'). Enablement (increasing means/reducing barriers to increase capability), Education (increasing knowledge or understanding), Persuasion (using communication to induce positive or negative feelings or stimulate action), Training (imparting skills), Incentivisation (creating expectation of reward), Restriction (using rules to reduce opportunity to engage in target behaviour) and Environmental restructuring (changing the physical or social context and expectation of treatment observation).

Across its seven functions, VOT acted on four of the Behavioural Change Wheel policy categories. Thorough communication, VOT observers were seen as trusted and credible sources of information who communicated the rationale of VOT and importance of TB treatment adherence and provided training on how to follow the VOT method. Through communication, patients received reminders and feedback on their adherence behaviour. VOT was a flexible means through which to support VOT observers and healthcare professionals to follow clinical guidance and regulations for patients who would otherwise have been eligible for DOT. VOT provided a centralised service provision model supporting daily observation during weekdays

with weekend clips read on Mondays, providing a flexible and personalised case management tool to support care for socially complex groups who ordinarily face barriers in accessing services and professionals and require additional support and motivation to adhere to TB treatment.

Comparison to previous literature

My findings are partly consistent with systematic review evidence by van den Berg *et al* (van de Berg et al. 2018) qualitative outcomes of and experiences of VOT interventions in low incidence settings, which reported that VOT was an acceptable patient support intervention due to its convenience, privacy, flexibility (Wade et al. 2012; Chuck et al. 2016) and ability to reduce travel time (Garfein, Collins, Munoz, et al. 2015). My findings showed there were mixed views on privacy and confidentiality in the UK and Moldova, and so whilst my work is broadly transferrable or generalisable to other settings, these are two issues for which may affect VOT's acceptability and require further engagement with service users and professionals to provide assurance and actions to limit risks of data breaches.

Strengths and limitations

Both concurrent qualitative studies embedded in randomised controlled DOT/VOT trial designs in the UK and Moldova have provided an in-depth and nuanced understanding of the lived experiences and perspectives of patients with TB supported by DOT and VOT. The integration of quantitative with qualitative findings have provided different perspectives of DOT and VOT, which has made it possible to enhance the interpretation of the results and provide insights into how VOT can

provide individualised adherence support for specific inclusion health groups who need additional support.

There was divergence in perspectives on the extent to which VOT provided privacy, in that UK participants were assured that their confidentiality was upheld, whereas Moldovan participants lacked trust in data systems with a belief that their video clips would be exposed publicly and they would be identified through TB awareness campaigns. The interpretation of these qualitative studies also benefit from drawing up multiple insights through discussions as part of a 'data clinic' with my supervisory team, VOT trial investigators from both the UK and Moldova study groups. Members of the UCLH Find & Treat team were also involved to maintain objectivity and strengthen rigour and validity of results, particularly to provide a providers' perspective from mainstream services, which was lacking from the empirical data. These discussions from the 'data clinic' informed high-level discussions with the membership of the WHO Digital Health Task Force, as part of 'UK-Moldova VOT trial knowledge exchange' meetings as another approach to strengthen rigour and plausibility. The reliability of the interview data was ensured through recoded qualitative interviews and transcripts written in verbatim, which were readily available for importation into NVivo for ongoing analysis.

In terms of how transferable or generalisable the sample was to the population they were drawn from, interview participants represent a small convenience sample, in that only participants who could be reached through phone or as part of clinic follow-ups were approached for recruitment. This high level of diversity contributed particular experiences, which may not necessarily represent the experiences of all who are supported through TB treatment on DOT or VOT. A key challenge in conducting research with socially complex groups is the inherent difficulty for

mainstream services to find, reach and engage them in their care and the provision of a £30 supermarket voucher in addition to the reimbursement of travel expenses were used to incentivise UK participants. It is likely people who were recruited were more motivated to join the trial therefore this heterogenous sample may have selected those who were more likely to have achieved optimal results through treatment.

There are some limitations to the approach used for this qualitative study. From a methodological standpoint, the interview topic guide was not framed around the BCW and other theoretical frameworks. Instead, the topic guide pragmatically sought to elicit broad experiences of the practicalities of treatment observation with DOT and VOT under trial conditions (i.e. semantic themes). It included prompts and focused on particular practical issues, as opposed to motivations and concerns. This limits the ability to understand how the role of patients' attitudes and decisions about their treatment influence their perception for the necessity for treatment and concerns about adverse consequences. The interview topic guide did not include questions on patients' initial engagement with their allocated group and at the time, Due to the different times that both the secondary analysis and the qualitative study were completed, I underestimated the initiation phase of treatment as an important line of qualitative enquiry or part of the continuum of patient adherence to completion. This would have made it possible to better interrogate patient groups with a history of being lost to follow-up and women and their observed adherence relationship.

Conversely, owing to developing a proof-of-concept trial in Moldova (Ravenscroft et al. 2020) meant that socially complex patients and patients with multidrug-resistant

TB were excluded from the trial and so findings in the sample from Moldova will more accurately relate to the acceptability of VOT in patients with drug-susceptible TB. With respect to working with the interview data from the Moldova DOT/VOT trial, developing initial and analytic codes from transcripts translated from Moldovan-Romanian to English may have reduced some of the nuanced perspectives of patients' lived experiences of each intervention. To add to this, whilst some interviews were observed by me to ensure its conduct was in alignment with the interview topic guide and in keeping with agreed methods and, strategies to prompt additional information from participants when brief answers to questions were given were not always forthcoming. This was mainly due to the short 1-week duration of my field trip to Moldova. As such, the inability to listen and re-listen to audio files and corroborate these with the written interview transcripts to develop codes, subsequent theories and find disconfirming evidence was limited. By being able to prompt additional responses into why some VOT participants felt as though their privacy could be breached and reinforced stigma may have provided important insights into the use of technology for health purposes in settings where innovative solutions to tackling TB in high multidrug-resistant TB-prevalent settings. With respect to recall bias, all participants were approached at the end of their treatment or had recently completed their treatment and it is expected that the perspectives provided as part of this study are reliable. Individual-level effects of DOT and VOT on adherence originate from those who were randomly allocated to DOT or VOT on a 50:50 basis, with options to switch arms (based on pre-defined criteria), using indirect questioning asked sought to establish individual preferences, beliefs and evaluations of DOT and VOT so minimised social desirability bias.

Secondary analysis of the DOT/VOT trial dataset started in Spring 2018 whereas the qualitative data collection data collection and analysis started much earlier Autumn / Winter 2016, The compilation of this thesis has enabled me to reflect on the how the key principles for qualitative design could have been better applied, which would have started by using COM-B and BCW as the theoretical framework as the scaffolding from which to hang findings from the quantitative studies in Chapter 2 and Chapter 3. This would have informed my qualitative research questions and interview topic guides, the sampling frame and recruitment methods I would have wanted to employ in both settings. The timescales for recruiting participants for the qualitative aspects were determined by two main factors a) the trial implementation timescales in UK and Moldova and b) maximising opportunities to obtain a convenience sample from a socially complex population with difficulties service engagement. The absence of a robust qualitative workstream built into the overarching RCT study design at the outset introduced some of the limitations of the qualitative methods.

Conclusions

The application of the COM-B model and BCW have enabled a systematic and comprehensive understanding of the experiences of patients supported by VOT and DOT, which have added depth to the quantitative findings reported in the UK trial (Story et al. 2019) and Moldova trial (Ravenscroft et al. 2020). This has unpacked the complexity underpinning how VOT performs in trial conditions and has provided an identification of factors that improve adherence and has provided granularity into how VOT fares as an intervention to promote adherence. VOT was designed to be an alternative and flexible approach to DOT, which sought to alleviate the practical

and material barriers costs imposed on socially complex patients, yet provided remote access and support to a trained VOT observer.

The WHO recommends VOT as a “suitable alternative” to DOT (WHO; 2017). The Perceptions and Practicalities Approach has provided a simple behavioural framework to understand how VOT acts on perceptual and practical barriers of adherence in relation to TB. This is underpinned by intrinsic factors, motivation and ability and moderated by extrinsic factors, opportunity and triggers to establish habit-forming ritualised practices coupled by the development of a rapport through regular text reminders and remote support at times of psycho-social crises.

Table 19: Overall study objectives, methodology, Chapter 2, 3 and 4 findings

Chapter	Research question	Objective	Relevance	Methodology	Findings
2	What patient groups do not complete TB treatment	To identify factors that predict non-completion of TB treatment in a nationwide retrospective cohort of drug-susceptible and –resistant TB from 2010 to 2017	To identify patient groups who do not complete TB treatment and need additional support	A retrospective cohort analysis of cases with TB notified to the Enhanced TB Surveillance System in England, Wales and Northern Ireland between 2010 and 2017. Multivariable logistic regression models were built to	Factors affecting non-completion of TB treatment. • Being male (aOR: 1.20; 95% CI: 1.14 - 1.26) • 15-44 age group (aOR: 1.70; 95% CI: 1.43 - 2.02) ≥45 age group (aOR: 3.55; 95% CI: 2.99 - 4.22) • Recent migration to the UK (aOR: 2.46; 95% CI: 2.25 - 2.69)

Chapter	Research question	Objective	Relevance	Methodology	Findings
				identify socio-demographic and clinical factors associated with non-completion of TB treatment.	• Increasing social complexity (aOR: 2.73; 95% CI: 1.78 - 4.18) • Multidrug resistance (aOR: 4.07; 95% CI: 3.36 - 4.94).
3	What patient groups engage with VOT	To examine the factors which affect the levels of engagement with DOT and VOT and whether affects the level of observation achieved in DOT and VOT groups	A quantitative assessment of the level of engagement will serve as a measure of acceptability and a proxy measure of accuracy in measuring true adherence in groups supported by DOT and VOT	A secondary analysis of the UK DOT/VOT trial dataset using descriptive analysis and logistic regression to determine: a) adherence amongst patients randomised to DOT and VOT b) risk factors for the level of initial engagement in both allocated groups c) adherence amongst patients who engage with DOT and VOT	• 90% initially engaged with VOT compared to 49% initially engaged with DOT • Amongst those who engaged with VOT, (77/101, 77% had more than 80% of scheduled treatment observations completed compared to (35/56, 63% of those who engaged with DOT. • VOT over 70% initial engagement in all groups: • age group • gender • migration • ethnicity

Chapter	Research question	Objective	Relevance	Methodology	Findings
					• social risk factors • loss to follow-up • health-related quality of life • DOT over 70% initial engagement • aged over 55, • prison history • history of homelessness (more than 5 years ago) • current alcohol problems • Patients with TB who initially engaged with VOT had a 2.54 increased odds of improved TB treatment adherence compared to those who initially engaged with DOT (aOR: 2.54; 95% CI: 1.16 - 5.58; p=0.02). • Women were less likely to adhere (aOR: 0.33; 95% CI: 0.14 - 0.77; p=0.01) • Those with a history of loss to

Chapter	Research question	Objective	Relevance	Methodology	Findings
					follow-up were also less likely to adhere (aOR: 0.18; 95% CI: 0.07 - 0.49; p=0.001).
4	How does DOT and VOT support adherence in people's lives	To describe the lived experiences and perceptions of DOT and VOT interventions in people with TB in the UK and the Republic of Moldova	A qualitative assessment of acceptability of DOT and VOT and will identify the mechanisms by which DOT and VOT work and the challenges encountered when these interventions are instigated	Semi-structured interviews with 16 UK DOT/VOT trial participants and 22 Moldovan DOT/VOT trial participants. A thematic analysis was used to analyse data from emerging themes to understand how the different VOT approaches compared to DOT and were perceived by patients in both settings, how they fitted into patients' lives and how they may or may not have supported them in taking prescribed	**COM-B Behaviour source targeted in VOT intervention** **Capability – physical** **Skills: physical -** promoted systemised or ritualised medication practices **Capability – psychological** **Knowledge** - clear awareness of the existence of an illness that needed management **Skills: cognitive and interpersonal -** acquired a level or proficiency in following the VOT process to demonstrate they had ingested their doses **Memory, attention and decision processes -** clear explanations of the rationale for VOT and it processes using a video app to record themselves taking their medications and assurances of extra support in the form of patient-provider interactions promoted a necessity for treatment observation

Chapter	Research question	Objective	Relevance	Methodology	Findings
				doses regularly.	**Behavioural regulation -** prompt or reminder to address forgetfulness or poor recall through regular personalised messages from VOT observers, building rapport and habit-forming practices **Motivation – reflexive** **Beliefs about capabilities -** resilience and expressions of necessity beliefs to arrive at a common-sense evaluations about taking TB treatment **Intentions -** conscious decisions to maintain treatment observation through VOT in order to re-gain health and wellbeing **Goals -** links between positive necessity beliefs and goal-oriented outcomes, such as to re-gain one's health and to return to work **Beliefs about consequences -** TB as a threat to life and its likely consequences; treatment as the source to alleviate symptoms, for control and cure **Motivation - automatic**

Chapter	Research question	Objective	Relevance	Methodology	Findings
					Reinforcement – increased and ritualised medication-taking behaviour using a smartphone as incentive **Emotion -** emotional and cognitive representations of TB treatment are processed in parallel with necessity beliefs for treatment adherence using VOT. **Opportunity – social** **Social influences -** development of rapport with VOT observers allowing patients to feel cared for and provided a sense of security and comfort **Opportunity – physical** **Environmental context and resources -** VOT supported split dosing or negotiating timing of dosing to manage side effects and pill burden The Behavioural Change Wheel policy categories VOT exhibits include: Enablement (increasing means/reducing barriers to increase capability), Education (increasing knowledge

Chapter	Research question	Objective	Relevance	Methodology	Findings
					or understanding), Persuasion (using communication to induce positive or negative feelings or stimulate action), Training (imparting skills), Incentivisation (creating expectation of reward), Restriction (using rules to reduce opportunity to engage in target behaviour) and Environmental restructuring (changing the physical or social context).

Chapter 5: Discussion

This final chapter considers the practical and policy recommendations informed by consolidated findings from the retrospective population-based cohort analysis of factors affecting non-completion of treatment, quantitative analysis of level of engagement with DOT and VOT and qualitative study of lived experiences and perspectives of DOT and VOT, including the contribution of knowledge of groups who need adherence support. I explored different methods of integrating findings from different study designs, for example by applying a triangulation protocol and convergence coding matrix (O'Cathain, Murphy, and Nicholl 2010; Farmer et al. 2006). However, it has been more useful to apply a pragmatic approach to report the disparate findings from my doctoral research, each with different methods and strengths and weaknesses. In combination, these inform recommendations on triaging patients based on groups who engage with DOT and VOT and achieve optimal adherence levels to facilitate individualised or differentiated care to DOT or VOT and implications for the practical nationwide roll-out of VOT and its policy directions.

5.1 Integration of findings

A key strength of this doctoral thesis is that it provides a comprehensive understanding of why patients interacted with VOT in the ways in which they did and offers explanations of the contexts which influenced effect estimates for the different levels of effective initial engagement. All studies (Chapter 2, Chapter 3 and Chapter 4) examine the scale of the problem of non-completion of TB treatment among risk groups, user acceptability of VOT and DOT using quantitative and qualitative lines of

inquiry, respectively to support integration of findings to inform individualised or differentiated clinical care strategies.

These findings support UK guidance to develop and implement integrated and patient-centred services, which link to outreach, pharmacy and mental health services as well as apply enhanced case management from diagnosis to treatment to address the ongoing health and social care needs of inclusion health groups. It is plausible that VOT enabled improved TB treatment adherence by minimising the deleterious effect social risk factors have on poor treatment adherence by removing the practical and material barriers to access care by facilitating remote access to trained and dedicated VOT observers, to support treatment supervision and provide pastoral and psycho-emotional support thereby making it more convenient and negating the necessity to travel into clinic from three to five times per week to attend DOT sessions. Approximately 60% of the UK DOT/VOT trial participants had at least one social risk factor, including mental health problems.

I found that cases with drug-resistant TB had a four-fold increased risk of non-completion of treatment, which may conceivably relate to the lengthy regimen, which may last up to 24 months. Treatment for MDR-TB requires at least five active drugs dependent on the resistance profile as well as second-line injectable drugs which can induce toxicity, side effects and impose pill burden on patients with TB. As such, treatment adherence can be much lower compared to that of drug-susceptible TB, as reported by WHO to be 55% globally

DOT is a core element of TB service provision in the UK and internationally and is generally delivered as part of enhanced case management for socially complex TB cases and it is intended to reduce the risk of these patients disengaging with services prior to TB treatment completion. As such, existing NICE guidance (NICE;

2016) recommends that patients with complex social factors and those with a history of non-adherence who received a TB notification are supervised through in-person DOT through their treatment because they are deemed to impede TB treatment adherence. These findings provide some evidence that whilst these standards and guidelines on the use of DOT are being implemented in practice as a means to engage inclusion health groups with services, it is a resource-intensive option and the economic costs to services, whereby it costs £5,700 ($7,340) for five-times per week DOT or £3,420 ($4,403) for three-times per week DOT (Story et al. 2019). Given the level of resource for DOT provision the lack of engagement in stark contrast to those on VOT and the widespread negative views of those supported provides an important addition to shape practice and policy directions on VOT provision as a flexible, effective and acceptable alternative.

Inclusion health groups are characterised by the synergistic interaction of multiple intersecting risk factors and poor social conditions (Story et al. 2007; van Hest et al. 2014; Anderson et al. 2016) that give rise to bio-psychological consequences, including disparity and discrimination leading to exceptionally poor health outcomes, as described by Singer and Clair (Singer and Clair 2003). Syndemic theory (Singer and Clair 2003) can be used to explain how at a population-level the increasing rates of two or more specific health conditions or consequences of the diseases and their interaction can cluster in a population or location. With respect to the focus for this thesis, TB is an important example of how social deprivation, disadvantage and poor access to mainstream services in urban centres in Western Europe intersect and increases the likelihood of exposure to TB due to living in poorly ventilated and overcrowded and/or inadequate living conditions or through other social factors (Story et al. 2007; van Hest et al. 2014; Anderson et al. 2016). The synergistic

interaction with extreme social conditions, such as undocumented or insecure migrant status exemplifies the extreme afflictions in individual patients from inclusion health populations (Abubakar et al. 2018; van Hest et al. 2014). People who are socially deprived may turn to addiction as a means of coping with their precarious social circumstances. Drug misuse can also lead to social disadvantage and socioeconomic disadvantage may, in turn lead to drug misuse and dependency. A history of drug misuse underscores the strong and reciprocal relationship that exists between social factors and drug misuse, all of which negatively impact on health status (Weiss et al. 2004; Story et al. 2007; Bradbury and Lewer 2021). Although some migrants move from their home countries due to 'push' and 'pull' factors, which may include structural and economic changes to meet labour market shortages, such as in healthcare along documented and legal pathways (Abubakar et al. 2018). There are also scenarios where undocumented migrants may be trafficked or through forced migration are escaping conflict and seeking asylum (Abubakar et al. 2018). The effect of socio-economic conditions and ambiguity on legal status and perceived fears of prejudice and discrimination may influence health-seeking behaviour and lead to poor health outcomes (Abubakar et al. 2018). Due to the multiple and complex determinants that can manifest themselves at various stages of their migration trajectory from pre-migration, transit, arrival in host country (Abubakar et al. 2018) and in return syndemic theory can also be used to explained how amongst those with immigration concerns in the host country can determine their health outcomes.

Whilst VOT was not originally designed to cover the PAPA, NCF or COM-B constructs, the integration of findings from Chapter 3 and 4 provides evidence for how VOT components target the perceptual and practical dimensions that govern

adherence behaviour, motivation and ability. As such, VOT can be added to the series of adherence support options for TB. The conceptual framework in Figure 21 provide pathways for how the VOT components promote adherence with respect to TB amongst inclusion health groups through the PAPA lens.

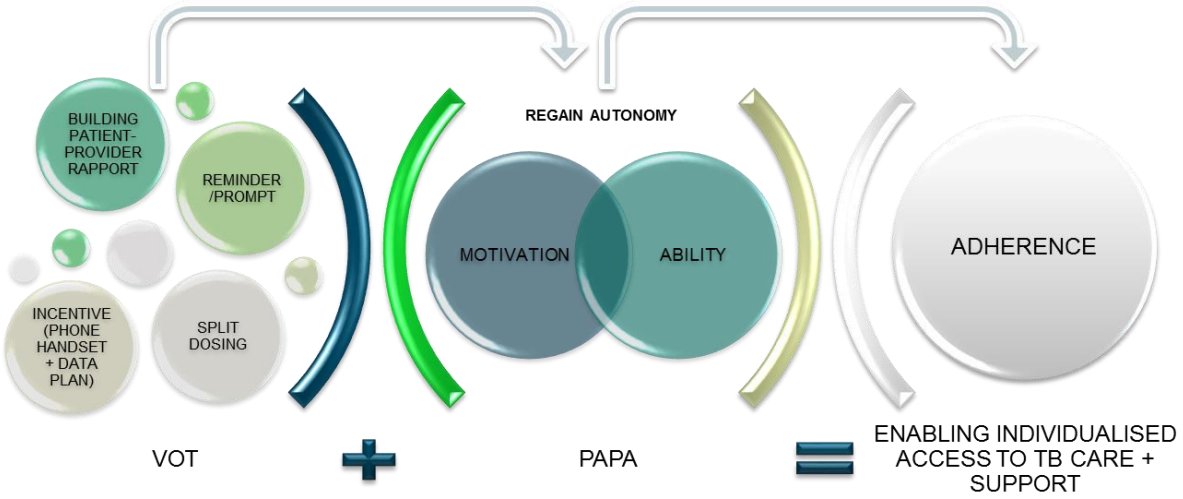


Figure 21: Conceptual framework of how VOT promotes adherence to TB treatment using the PAPA framework

There are a number of key strengths of this PhD thesis. It has been possible to provide important quantitative and qualitative insights into how VOT performs as a case management tool. It has been possible to show how VOT acts at an individual patient level in promoting adherence and how it acts on the perceptual and practical barriers of adherence. It has been possible to show that there are high levels of engagement and positive experiences of VOT, which suggest it is a more acceptable approach compared to DOT. This PhD thesis benefits from seven years of TB case notification data with a large national coverage across the UK, which has provided the statistical power to make strong and conclusive statements about the strength of associations between exposures and non-completion of TB treatment. Through a

large DOT/VOT trial sample size (Story et al. 2019; Story et al. 2020) it has been possible to assess levels of observation amongst those who engage with DOT and VOT to make conclusive statements about TB treatment adherence outcomes amongst at risk patient groups. It has also been possible to provide in depth and nuanced perspectives and lived experiences of people on DOT and VOT, which has benefited from a data clinic and knowledge exchange meetings to strengthen rigour and plausibility.

There are a number of limitations with this PhD thesis. Crucially, owing to the different time frames the individual studies were carried out limited the ability to coherently explore the quantitative study results with qualitative studies. In particular it was not possible to draw sample of participants with different levels of engagement and adherence in both DOT and VOT groups and examine their perspectives and lived experiences of treatment and support through DOT and VOT because the qualitative work started in 2016 to 2017, secondary analysis of the DOT/VOT trial dataset started in 2018 and I was able to get permissions and start analysis of the ETS from early in 2019.

While my employment on an NIHR-funded behavioural intervention development study between 2016 and 2017 exposed me to a series of adherence behaviour theories, there was no senior co-investigator with a qualitative background involved in the DOT/VOT trial and so a decision was made by the investigators to focus the qualitative component of the trial on the practical ways in which DOT and VOT fitted into patient lives as opposed to experiences of TB disease and its treatment. As such, the interview topic guides were not framed around the PAPA and NCF theoretical frameworks from study inception. This has limited the ability to ground my findings in theory and understand the role patients' attitudes and decisions they

make about their treatment and its influence on perception and concerns of adverse consequences of their treatment for those supported by DOT and VOT. In addition, due to the different study timescales, the interview topic guides did not include questions on patients' initial engagement with their allocated DOT and VOT group, because at the time I under-estimated that this would be an important line of inquiry and its role as part of the treatment adherence continuum. If this had been done this would have made it possible to better interrogate the patient groups with a history of loss to follow-up and women about their observed treatment and relationship with DOT and VOT, and views on the use of technology for treatment observation purposes.

While the ETS has provided a very useful understanding of the scale of patient needs and groups who needed additional support with their treatment, the degree of missingness of data on treatment completion mainly among those who were socially complex, highlights the biases amongst clinicians, which may reflect the judgements and groupthink amongst clinicians and this missingness may over-estimate the relationship between these variables and treatment non-completion.

The qualitative study relied on a convenience sample of participants who could only be reached by phone and these may represent those who engaged with their treatment and may have been more motivated to join the trial and had only positive experiences to share and so this introduces selection bias and these views may not be generalisable and may not represent the diversity of views of those on DOT and VOT.

The Moldova trial team ran a proof-of-concept VOT trial, which excluded MDR-TB and socially complex patients and so the qualitative findings represent those who with drug-susceptible TB and patients without social challenges. Working with

translated interview data may have reduced the level of nuanced perspectives from patients' lived experience of DOT and VOT interventions.

5.2 Recommendations to policy and practice

Findings from the retrospective cohort analysis of factors affecting non-completion of TB treatment show that at a population-level in the UK patients with TB are unable to complete TB treatment within their TB notification period and require longer periods of follow-up. Coping with the inherent complexity of TB regimens, duration of TB treatment and overcome the personal, socio-cultural and health system-related factors that can impede adherence warrants a timely, effective, cost-effective individualised, patient-centred and supportive approach offered by VOT.

Drawing upon the evidence I've collected in this thesis and to support the development of recommendations for the commissioning and roll-out of VOT to individually target at risk groups, I have used the e-Health Implementation Toolkit (e-HIT), underpinned by Normalisation Process Theory (Murray, May, and Mair 2010; Murray et al. 2010) to assess a range of factors (intervention, workforce, context) to support decision-making on the successful implementation of VOT into routine practice. Below is an extract from the e-HIT results.

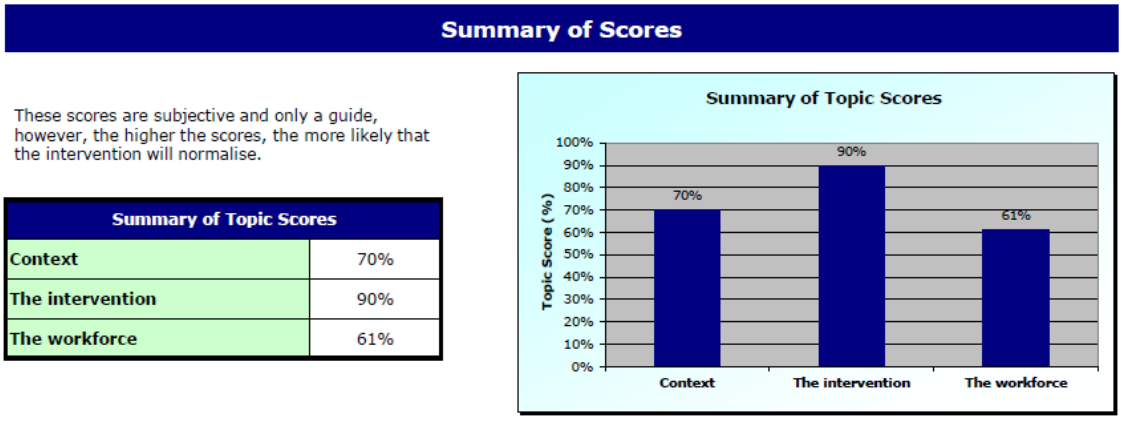


Figure 22: e-HIT tool summary of scores to guide decision-making on implementation of VOT into routine practice

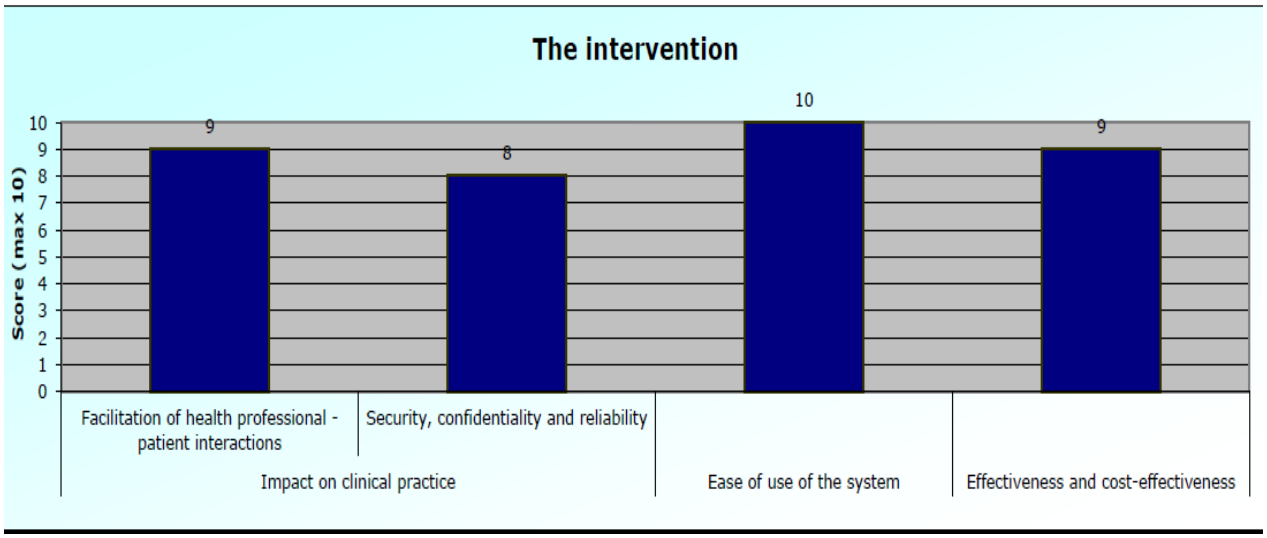


Figure 23: e-HIT tool score on intervention component: to guide decision-making on implementation of VOT into routine practice

While the DIEGO model (O'Connor et al. 2016) has provided a useful framework to theorise how inclusion health groups engaged with VOT under trial conditions, e-HIT underpinned by NPT (Murray, May, and Mair 2010; Murray et al. 2010) is a theory which offers trialists a consistent framework that can be used to describe, assess and enhance implementation potential. Based on the intervention in the trial context, my findings show VOT facilitated patient-provider health care interactions, enabling faster and more accurate assessment of true adherence, it was easy to use and fit

for purpose and has been well-evaluated under RCT condition to assess efficacy and cost-effectiveness. My findings also show that while the VOT intervention was credible in terms of security, confidentiality and reliability, patients had concerns about their privacy.

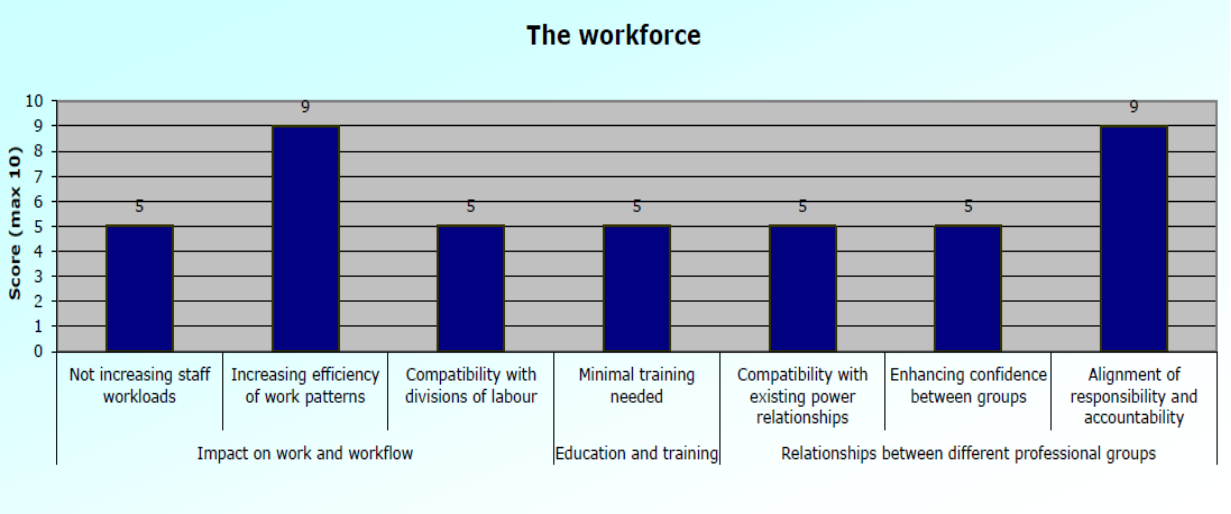


Figure 24: e-HIT tool score on workforce component: to guide decision-making on implementation of VOT into routine practice

VOT processes will promote the systemisation of collecting and evaluating population level adherence data, which is likely to improve the efficiency and the working patterns of the healthcare workforce, enabling them to focus resource intensity on patients who need adherence support. Focusing responsibility and accountability on a centralised VOT service of the delivery of care and treatment adherence outcomes will enhance the success of the intervention. However, due to a lack of resource it has not been possible to evaluate this or other domains for impact of work and workflow, education and training and relationships between different professional groups.

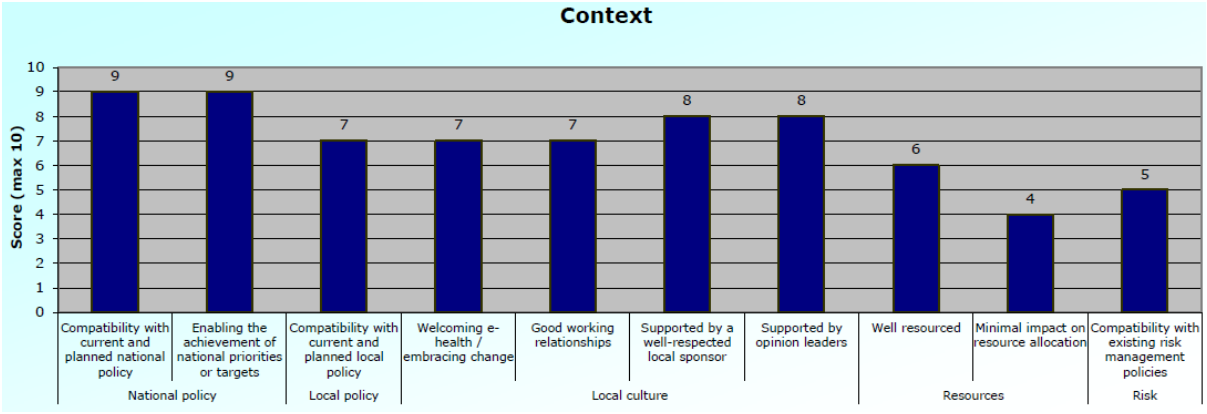


Figure 25: e-HIT tool score on context component: to guide decision-making on implementation of VOT into routine practice

It can be deduced that securing NIHR programme grant funding to assess the efficacy of VOT compared to DOT under trial conditions suggests it was compatible with and enabled achievement of current and planned national priorities and had the support of key opinion leaders to ensure its success. However a lack of resource has limited my ability through this doctoral research study to assess factors influencing the role of national and local policy, culture, resources and risk on the implementation and roll-out of VOT into routine practice.

In a systematic review by Ngwatu and colleagues (Ngwatu et al. 2018) who examined the impact of digital health technologies on TB treatment, compared with direct in-person treatment observation , VOT may improve efficiency, save money, reduce burden on provide convenience for patients and healthcare staff, and facilitates patient-provider interactions (Story et al. 2019). In studies, which compared VOT in USA, Mexico and Belarus to high-functioning DOT programmes suggest that there was no difference in adherence, which suggest that high adherence can be achieved at much lower health system costs (Garfein, Collins, Muñoz, et al. 2015; Sinkou et al. 2017). As such, in low-income settings where digital

interventions are cheaper and/or are easier to implement, VOT may serve as a viable, beneficial and flexible alternative to DOT (ASCENT). The qualitative findings in my thesis show there are mixed views of VOT's acceptability in different settings, which suggest a "one size fits all" approach may not apply.

Based on the scores from e-HIT to determine whether VOT should be rolled-out on a national basis and universally applied to all group at risk of poor TB treatment adherence, my view is roll-out can commence but in parallel, its implementation should be monitored. This should include further work to examine the wider context and perspectives of the TB workforce for their buy-in to ensure they understand the change and embrace VOT's potential and benefits to patients' outcomes and health system cost-effectiveness. Monitoring the roll-out of VOT should involve engagement with the TB workforce to examine staff attitudes to support learning on what adaptations could be made to VOT to inform how it fits service delivery needs and to minimise "technology fatigue". Such work would need to include perceptions of digital system functions and its potential impact on a reduction staff headcounts, which may affect staff morale, changes in workflow and hierarchy if a centralised VOT service is implemented, training new staff and shifts in workplace culture and due to new ways of working.

The growing evidence base shows that VOT sits within a widening landscape of DATs, which capitalise on the growing prevalence of inexpensive, mobile and communications technologies to promote self-reported dose ingestion and adherence monitoring, whilst also empowering people to take their treatment independently while maintaining communication and building rapport with healthcare professionals. Integrated care models for case management can combine leading DATs together such as VOT, 99DOTS and evriMED/MERM devices, along with

provider reported adherence (Patricia Moscibrodzki; Steven Parkinson; Raphael Ferry; Nnamdi Nwaneri; and William Thies 2021; WHO 2018; Subbaraman et al. 2018). 99DOTS is a low-cost solution that uses inexpensive packaging (envelopes or stickers) so that when someone dispenses a dose, the packaging reveals a hidden toll-free number that can be called to register daily adherence. EvriMED/MERM (Medication Event Reminder Monitor) is a digital pillbox that provides daily visual and audible reminders for both daily dosing and refills (Patricia Moscibrodzki; Steven Parkinson; Raphael Ferry; Nnamdi Nwaneri; and William Thies 2021; WHO 2018; Subbaraman et al. 2018; Liu et al. 2023). All approaches transmit data to a server that a healthcare professional can remotely view and use to enable enhanced adherence support. The system also allows switching between technologies based on patient/ provider preference in a seamless manner (Patricia Moscibrodzki; Steven Parkinson; Raphael Ferry; Nnamdi Nwaneri; and William Thies 2021; WHO 2018; Subbaraman et al. 2018), which may enable DATs to be used according to patient need and/or due to changes in patient's social circumstances and adherence behaviour depending on the levels of support needed.

As the evidence and country-level experience has emerged, WHO and the European Respiratory Society and other leading technical and funding partners have developed outlines for target product profiles for DATs to help guide and facilitate implementation into service delivery models since 2015 (Falzon et al. 2016). In 2020 WHO proposed VOT as one of the options to support adherence in its target product profiles for TB preventative treatment (WHO 2020).

Implications for patients

The major contribution that this thesis' findings make to the literature is that it crucially demonstrates the individual effects of VOT in promoting adherence TB treatment in all groups at risk of non-adherence to TB treatment. The higher levels of initial engagement and experiences of VOT suggest it is a more acceptable approach to TB treatment observation compared to DOT by providing a more holistic approach to TB treatment supervision, upholding autonomy and minimising the deleterious effects of social and economic disadvantage on poor TB treatment adherence. The integrated findings presented in this thesis also suggest DOT may support groups with more multiple and complex needs and these groups will require more intensive measures to support their adherence through specialist integrated care services.

Concerns of privacy, confidentiality and data sharing were evident from the qualitative research findings, which underscores the importance of engaging with socially complex populations, who frequently experience digital exclusion. Low levels of education, a lack of digital skills, confidence and motivation can all contribute towards digital exclusion and may deepen feelings of mistrust and fear of the rapid expansion of digital innovations. An identification of digital literacy needs amongst patients and an exploration of the potential for VOT to include patient-friendly digital literacy training modules, signposting to appropriate support and services may improve understanding and trust.

Medications for shorter regimens are all oral and this will be more amenable to VOT throughout care, and by virtue will be better tolerated.

Implications for service providers

The successful integration of VOT into clinical strategies is predicated on the acceptance that necessity-concerns (i.e. patients' treatment beliefs) are important for adherence to treatment. Supporting an evaluation of treatment necessity and concerns can be achieved through the application of the 3-step PAPA framework (1. Necessity beliefs; 2. Concerns; 3. Practicalities), to complement an informed choice of whether a VOT or DOT intervention could be more beneficial and preferrable to patients. This supports a no-blame approach to facilitate an honest and open discussion where the patient feels able to report poor adherence and express doubts and concerns about the treatment that many patients are reluctant to report, according to Nunes et al in (NICE; 2009) Such an approach goes beyond defaulting to DOT as the standard to putting all patients for whom there may be a risk of poor adherence (as defined in the NICE TB guidance). Instead given the evidence of VOT effectiveness, this would extend the informed adherence concept, where informed choices are made based on patients' necessity beliefs, the practical factors that affect their ability to adhere, which in turn could inform the levels of service provision support that could be provided through either DOT or VOT.

A personalised clinical decision support tool that assesses risk of poor adherence based on risk groups (Chapter 2), which integrates this thesis' quantitative and qualitative evidence on engagement and acceptability of VOT (Chapter 3 and 4) could serve as a useful clinical aid to inform clinicians' decisions on offering VOT to patients at the start of their treatment or during sustained periods of poor adherence or personal crises.

There is variation in the structure of how TB services are organised in England, from the provision of TB specialist services, TB clinical nurse specialists, outreach/link

workers and DOT workers with acute and community provision. This highlights the need for a centralised VOT model as an enhanced case management tool with the potential to extend technology infrastructure, share learning and best practice with local hubs that could provide VOT adherence support to integrated care models and to dedicated health and advocacy services for asylum seekers, refugees and undocumented migrants, who reside in temporary accommodation and receive wrap-around support.

Implications for policy

DOT has long served as a central strategy for monitoring and supporting TB treatment adherence internationally and to achieve a step change to reimagine how VOT can be integrated as a flexible alternative requires further work is required to engage service providers in assessing health system readiness for VOT, its role in addressing delivery of care and building the health system infrastructure to ensure that it fits the local context outside of trial conditions.

Since WHO has recommended that VOT may serve as a flexible alternative to DOT depending on the availability of video communication technology and can be appropriately organised and delivered by healthcare staff and patients (conditional recommendation, very low certainty in the evidence).

The NHS is based on founding principles that it should be freely accessible to all (Delamothe 2008). DATs like VOT risk failure to fulfil their potential in bridging the digital divide without an in-depth understanding of the nature of the multiple barriers that lead to poor access to health services and continuity of care experienced by inclusion health groups. The poor experiences of being repeatedly turned away from

services or being badly treated, language and literacy barriers and a lack of awareness of entitlements to NHS services and fear of punitive action after accessing services limit inclusion health groups' ability to access services on an equal footing to the rest of the population can exacerbate inequalities in health outcomes in inclusion health groups compared to the general population. The ability to leverage the adherence data generated from VOT will be hampered if these system level challenges are not addressed concurrently.

The COVID-19 pandemic has accelerated the expansion of VOT approaches internationally due to the emphasis on prevention of transmission and need to focus on essential services has resulted in the reduction of outpatient appointments. This has led to a dramatic reduction in new cases presenting to TB services globally (WHO 2021), yet at the same time an increase in reporting of adverse events has been published, which further underscores the important benefits of VOT as part of service delivery (Borisov et al. 2019; Visca et al. 2020).

The latest WHO TB treatment guidelines update published in 2017 (WHO; 2017) highlight the potential contributions of VOT alongside other technologies like SMS and medication monitors in supporting adherence and treatment delivery for patients and programmes.

My doctoral research findings provide important insights into how VOT performs as a patient-centred enhanced case management tool and can be tailored to the needs of inclusion health groups, which extends the evidence base underpinning guidance issued by the WHO Digital Health Taskforce. Further work is required to better understand how VOT may be tailored to patient groups who may have low perceived

necessity and high levels of concerns about their treatment outside of trial conditions. Additional research that considers service providers' perspectives to inform health system readiness would be beneficial to ensure its acceptance and advance our understanding of VOT for health protection and global health security.

Appendix

6.1 UK VOT trial results

Trial Population

Recruitment began on September 1, 2014 and continued until October 1, 2016 when the study's independent trial steering committee advised stopping recruitment based on interim analysis results. Follow-up continued until December 31st 2016. Flow through the study is summarized in Figure 1.

ITT analyses included 114 patients randomized to DOT and 112 randomized to VOT. Baseline characteristics of patients are shown in Table 1. Patients were mainly young adults born outside the UK. A high proportion (58%) had a history of homelessness, imprisonment, drug use, alcohol problems, or mental health problems. The baseline characteristics were similar in the two arms.

Patients were substantially more likely to engage initially with VOT (101/ 112, 90%) than DOT (56/ 114, 49%). Levels of initial engagement with VOT exceeded 70% in all sub-groups, but with DOT were particularly low (<50%) in younger adults, foreign-born patients and those without social risk factors or mental health problems (Table 1). Amongst the 56 patients who initially engaged with DOT, 27 had home-based DOT, 20 clinic-based, and nine community-based (e.g. local pharmacy). DOT was scheduled thrice-weekly for 14 patients, and five times per week for the remainder.

Treatment Observation

The level of observation achieved in each study arm is shown in Figure 2. In the ITT analysis, 78/ 122 (70%) of VOT patients successfully achieved the primary outcome (≥ 80% scheduled observations successfully completed during the first two months), compared to 35/ 114 (31%) of DOT patients: adjusted odds ratio (aOR), 5.48; 95%

confidence interval (CI), 3.10 to 9.68; P<0.001 (Table 1). The sensitivity analysis excluding corrupted videos showed similar effects (Table 1). In the restricted analysis, the proportions with the primary outcome were 78/ 101 (77%) for VOT and 35/ 56 (63%) for DOT: aOR 2.52; 95% CI, 1.17 to 5.47; P=0.019.

For the secondary outcome (proportion of scheduled observations successfully completed over the first two months), in the ITT analysis, 5,091/ 6,474 (79%) scheduled observations were successfully completed on VOT, compared to 1,774/ 3,922 (45%) on DOT. The mean proportions of doses observed per patient were 36% for DOT and 78% for VOT (P<0.001). In the restricted analysis, the overall proportions were 5,091/ 5,893 (86%) for VOT and 1,774/ 2,418 (73%) for DOT. Full results for the secondary outcome are shown in Supplementary Appendix Table S5.

High observation rates were maintained in the VOT arm, but they rapidly declined in the DOT arm (Figure 3). Over the full follow-up period (up to six months) 12,422/ 16,230 (77%) of scheduled observations were completed in the VOT arm compared to 3,884/ 9,882 (39%) of scheduled observations in the DOT arm. In the restricted analysis over the full follow up period 12,422/ 14,907 (83%) of scheduled observations were completed in the VOT arm compared to 3,882/ 6,351 (61%) in the DOT arm.

Observation completion rates were higher for VOT than DOT in all sub-groups (Supplementary Appendix Table S2).

Other Outcomes

There were no significant differences in positive sputum cultures at two months following treatment onset, treatment completion, loss to follow-up or numbers of hospital admissions (Supplementary Appendix). Side effect reporting rates were higher (total 368 for VOT and 184 for DOT), and numbers of unscheduled outpatient

appointments lower (169 for VOT and 233 for DOT), in patients on VOT compared to DOT.

Average staff time per dose observed was 65 minutes (53 minutes travel and 12 minutes observation) for home-based DOT, 10 minutes for community-based and 14 minutes for clinic-based. Staff reported that they could perform approximately 10 VOT observations per hour.

Costs of providing DOT over six months were estimated at £5,700 ($7,339) per patient for five-times per week, and at £3,420 ($4,403) for three-times per week treatment. For daily VOT, costs were estimated at £1,645 ($2,118) per patient (in a service managing 100 patients, see Supplementary Appendix).

In semi-structured qualitative patient interviews conducted at the end of treatment (seven apiece for VOT and DOT), patients valued the flexibility and convenience of VOT. Patients also reported that VOT allowed them to maintain privacy as they did not have to explain why they were regularly visiting clinic or being visited by a healthcare worker.

For quality assurance, 315 VOT videos were randomly selected for review by a second observer. The observers agreed on whether or not all pills were taken in 305 (97%) videos.

Table 1: Characteristics of the patients at baseline by allocated intervention and initial engagement.*

	DOT				VOT			
	Allocated		Restricted†		Allocated		Restricted	
	N	%	N	%	N	%	N	%
TOTAL	114		56		112		101	
Age group (years)								
16-34	61	53.5	27	48.2	64	57.1	58	57.4
35-54	45	39.5	22	39.3	35	31.3	32	31.7
55+	8	7.0	7	12.5	13	11.6	11	10.9
Sex								
Male	83	72.8	42	75.0	82	73.2	73	72.3
Female	31	27.2	14	25.0	30	26.8	28	27.7
Born in UK								
No	83	72.8	37	66.1	93	83.0	85	84.2
Yes	31	27.2	19	33.9	19	17.0	16	15.8
Previous tuberculosis								

No	82	71.9	40	71.4	85	75.9	75	74.3
Yes	30	26.3	15	26.8	27	24.1	26	25.7
Pulmonary								
Yes	73	64.0	37	66.1	69	61.6	62	61.4
No	41	36.0	19	33.9	43	38.4	39	38.6
Social risk factor‡								
Never	48	42.1	15	26.8	47	42.0	44	43.6
>5 years ago	19	16.7	10	17.9	19	17.0	16	15.8
Within 5 years	47	41.2	31	55.4	46	41.1	41	40.6
Homeless								
Never	77	67.5	31	55.4	70	62.5	64	63.4
>5 years ago	14	12.3	10	17.9	16	14.3	15	14.9
Within 5 years	23	20.2	15	26.8	24	21.4	20	19.8
Prison								
Never	93	81.6	44	78.6	97	86.6	89	88.1
>5 years ago	9	7.9	7	12.5	8	7.1	6	5.9
Within 5 years	11	9.6	4	7.1	7	6.3	6	5.9

Drug use								
Never	96	84.2	44	78.6	89	79.5	82	81.2
>5 years ago	2	1.8	2	3.6	4	3.6	3	3.0
Within 5 years	15	13.2	10	17.9	18	16.1	15	14.9
Alcohol problems								
No	91	79.8	38	67.9	92	82.1	83	82.2
Yes	21	18.4	18	32.1	17	15.2	15	14.9
Mental health problems								
No	94	82.5	44	78.6	94	83.9	87	86.1
Yes	18	15.8	12	21.4	14	12.5	10	9.9

* There were no significant differences in the baseline characteristics between allocated groups.

† Restricted analysis: initial engagement with intervention (at least one week of observation in allocated arm).

‡ History of homelessness, imprisonment, drug use or alcohol problems, mental health problems.

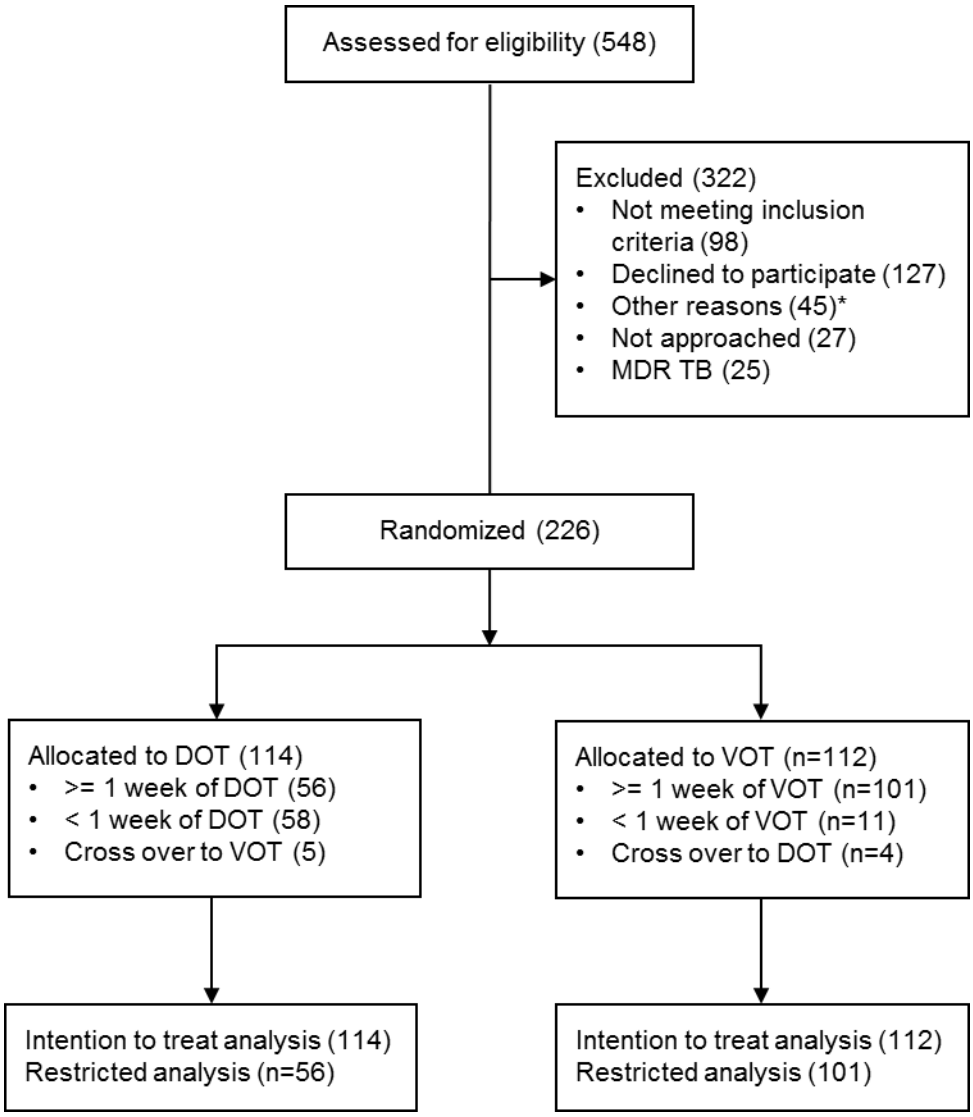
Table 2: Observation at two months

	DOT		VOT			
	N *	**%**	**N**	**%**	**aOR** † **(95% CI)**	**P Value**
Intention-to-treat						
Total	114		112			
Main	35	30.7	78	69.6	5.48 (3.10-9.68)	<0.001
Sensitivity	35	30.7	68	60.7	3.60 (1.91-6.79)	<0.001
Restricted						
Total	56		101			
Main	35	62.5	78	77.2	2.52 (1.17-5.47)	0.019
Sensitivity	35	62.5	68	67.3	1.44 (0.75-2.75)	0.27

* Number of patients who had ≥ 80% observations successfully completed in the first two months following randomization (the primary outcome).

† aOR, adjusted odds ratio. ITT analysis adjusted for time since start of treatment, age, sex; Restricted analysis additionally adjusted for current social risk factor (homelessness, imprisonment, drug use, alcohol problems, immigration concern), ever lost to follow up, no recourse to public funds, mental health problems

FIGURE 1: Enrollment and randomization



* The most common “other reason” for failing to enrol patients (32/ 45) was the clinic staff considering that the patient needed intensive face-to-face support due to emotional, medical or physical reasons or because of imminent risk of loss to follow up.

† Since loss to follow up was integral to the primary outcome, this measure is not listed separately in the CONSORT.

FIGURE 2: Level of observation

Each row represents one patient. Each dot represents one scheduled treatment observation day. Observed (black) and unobserved (gray) scheduled doses are shown for each patient in the study through the course of follow-up. Patients are ordered according to their length of treatment time remaining after randomization.

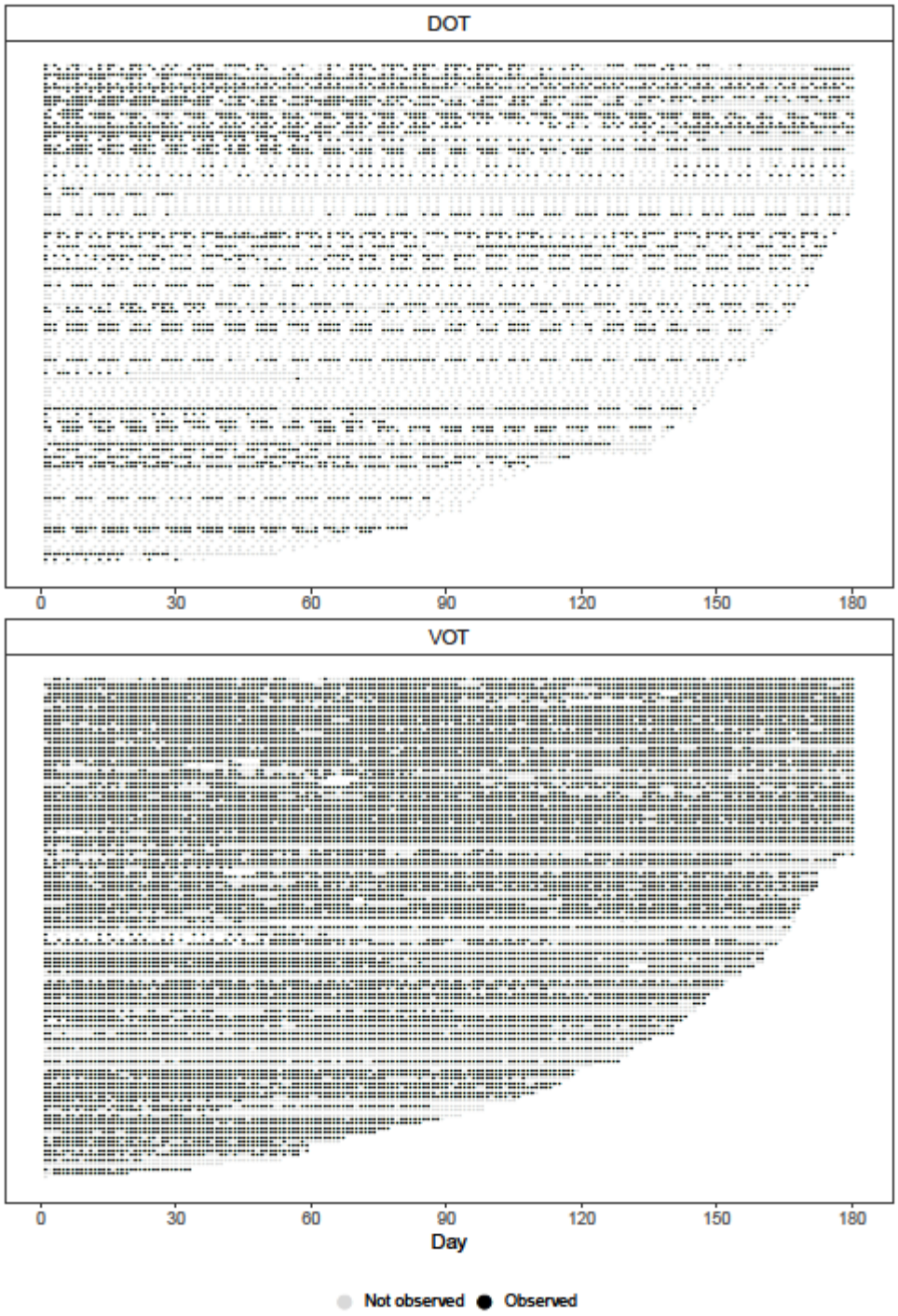


FIGURE 3: Proportion of participants with 80% or more of scheduled doses observed through treatment

Above bars are numbers of patients who had scheduled treatment observations in each month following randomization and numbers who completed 80% or more scheduled observations. Error bars are 95% confidence intervals.

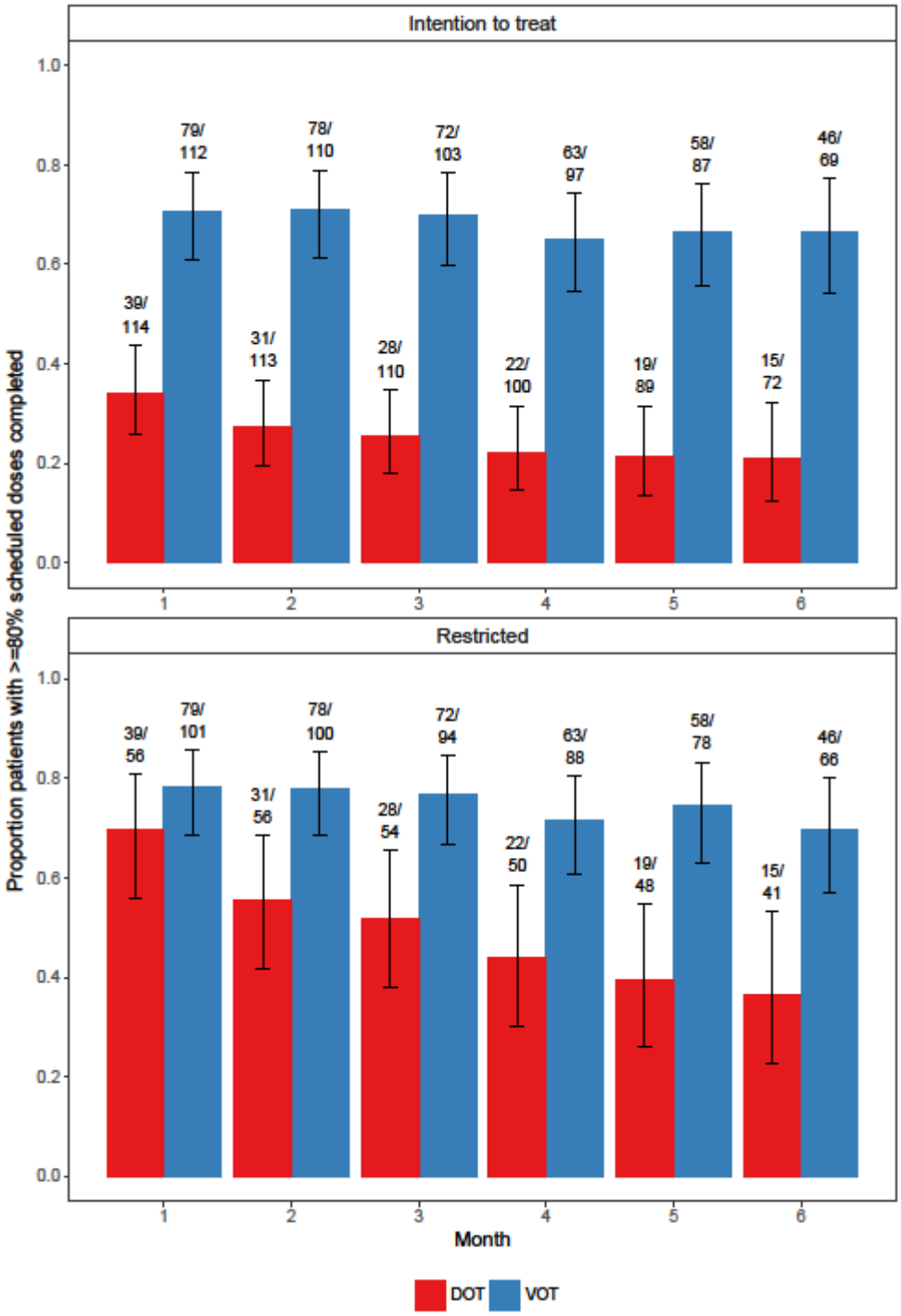


TABLE S1: Analyses conducted.

Study outcomes	Primary outcome (binary) ≥80% scheduled observations successfully	Main secondary outcome (continuous)

	completed in the two months following enrollment		Proportion of scheduled treatment observations successfully completed in the two months following enrollment and through treatment
Analysis strategy	Intention-to-treat Patients classified according to arm to which they were originally allocated		Restricted Excluding patients with less than one week of observation in allocated arm.
Successful observations	Main DOT: All medicines observed VOT: All medicines observed; received but corrupted video clips	Sensitivity A DOT: All medicines observed VOT: All medicines observed	Sensitivity B DOT: Some or all medicines observed; reported self-administered therapy VOT: Some or all medicines observed; received but corrupted video clips; other technical issues with clips

TABLE S2: Numbers and proportion of patients with over 80% of scheduled doses observed over the first two months by trial arm and baseline characteristics.

		DOT		VOT	
		N	**≥80% observed (%)**	**N**	**≥80% observed (%)**
Total		114	35 (31.0)	112	78 (69.0)
Age group	16-34	61	15 (24.6)	62	45 (72.6)
	35-54	45	16 (35.6)	35	25 (71.4)
	55+	8	4 (50.0)	13	8 (61.5)
Sex	Male	83	29 (34.9)	82	60 (73.2)
	Female	31	6 (19.4)	30	18 (60.0)
Born in UK	No	83	22 (26.5)	93	66 (71.0)
	Yes	31	13 (41.9)	19	12 (63.2)
Previous TB	No	82	25 (30.5)	85	58 (68.2)
	Yes	30	9 (30.0)	27	20 (74.1)
	Unknown	2	1 (50.0)	0	
Site of disease	Pulmonary only	60	20 (33.3)	55	37 (67.3)
	Pulmonary and extrapulmonary	13	5 (38.5)	14	11 (78.6)
	Extrapulmonary only	41	10 (24.4)	43	30 (69.8)
Social risk factor (any) *	Never	48	8 (16.7)	47	35 (74.5)
	>5 years ago	19	6 (31.6)	19	11 (57.9)
	Within 5 years	47	21 (44.7)	46	32 (69.6)
Homeless	Never	77	19 (24.7)	70	49 (70.0)
	>5 years ago	14	7 (50.0)	16	10 (62.5)
	Within 5 years	23	9 (39.1)	24	17 (70.8)
	Unknown	0		2	2 (100)
Prison	Never	93	26 (28.0)	97	68 (70.1)
	>5 years ago	9	5 (55.6)	8	5 (62.5)
	Within 5 years	11	3 (27.3)	7	5 (71.4)
	Unknown	1	1 (100.0)	0	
Drug use	Never	96	27 (28.1)	89	65 (73.0)

	>5 years ago	2	2 (100.0)	4	3 (75.0)
	Within 5 years	15	6 (40.0)	18	9 (50.0)
	Unknown	1	0 (0)	1	1 (100.0)
Alcohol problems	No	91	22 (24.2)	92	66 (71.7)
	Yes	21	13 (61.9)	17	12 (70.6)
	Unknown	2	0 (0)	3	0 (0)
Mental health problems	No	94	28 (29.8)	94	67 (71.3)
	Yes	18	7 (38.9)	14	8 (57.1)
	Unknown	2	0 (0)	4	3 (75.0)
Immigration concerns	No	102	32 (31.4)	99	70 (70.7)
	Yes	9	2 (22.2)	9	5 (55.6)
	Unknown	3	1 (33.3)	4	3 (75.0)

* History of homelessness, imprisonment, drug use or alcohol problems, mental health problems

TABLE S3: Observation at two months (total doses observed).

	DOT		**VOT**	
	N doses observed	**%**	**N doses observed**	**%**
ITT				
Total scheduled	3922		6474	
Main	1774	45.2	5091	78.6
Sensitivity A	1774	45.2	4756	73.5
Sensitivity B	2300	58.6	5350	82.6
Restricted				
Total scheduled	2418		5893	
Main	1774	73.4	5091	86.4
Sensitivity A	1774	73.4	4756	80.7
Sensitivity B	2300	95.1	5350	90.8

TABLE S4: Observation at two months (primary outcome).

	DOT		**VOT**			
	N *	**%**	**N**	**%**	**aOR † (95% CI)**	**P**
ITT						
Total	114		112			
Main	35	30.7	78	69.6	5.48 (3.10-9.68)	<0.001
Sensitivity A	35	30.7	68	60.7	3.60 (1.91-6.79)	<0.001
Sensitivity B	49	43.0	85	75.9	4.44 (2.29-8.61)	<0.001
Restricted						
Total	56		101			
Main	35	62.5	78	77.2	2.52 (1.17-5.47)	0.019
Sensitivity A	35	62.5	68	67.3	1.44 (0.75-2.75)	0.27
Sensitivity B	49	87.5	85	84.2	0.84 (0.28-2.46)	0.74

* Number of patients who had ≥ 80% observations successfully completed in the first two months following randomization (the primary outcome).

† aOR, adjusted odds ratio. ITT analysis adjusted for time since start of treatment, age, sex; Restricted analysis additionally adjusted for current social risk factor (drug or alcohol problems, homelessness, prison, immigration concern), ever lost to follow up, no recourse to public funds, mental health problems

TABLE S5: Observation at two months (secondary outcome).

	DOT Proportion doses observed		VOT Proportion doses observed		Adjusted coefficient	
	Mean	**sd**	**Mean**	**sd**	**(95% CI)***	**P**
ITT						
Main	0.36	0.41	0.78	0.31	0.41 (0.32-0.51)	<0.001
Sensitivity A	0.36	0.41	0.73	0.31	0.36 (0.27-0.46)	<0.001
Sensitivity B	0.46	0.48	0.82	0.31	0.36 (0.25-0.46)	<0.001
Restricted						
Main	0.74	0.27	0.86	0.17	0.14 (0.07-0.21)	<0.001
Sensitivity A	0.74	0.27	0.81	0.20	0.08 (0.006-0.16)	0.034
Sensitivity B	0.94	0.12	0.91	0.15	-0.026 (-0.074-0.021)	0.27

sd, standard deviation; CI, confidence interval

*Linear regression coefficient ITT adjusted for time since start of treatment, age, gender; Restricted additionally adjusted for current social risk factor, ever lost to follow up, no recourse to public funds, mental health problems

TABLE S6: Trial outcome of DOT by DOT location.

Location	**Number of patients (N=114)**	**Primary outcome (≥ 80% of scheduled observations completed) N (%)**
Clinic	20	10 (50.0)
Community	9	6 (66.7)
Home	27	19 (70.4)
No initial engagement	58	0

Chi-square test for difference in proportions (clinic vs community vs home – excluding never started) P = 0.348

TABLE S7: Treatment outcome by trial arm.

Outcome*	**DOT**		**VOT**	
	N	**% (of 114)**	**N**	**% (of 112)**
Completed	83	72.81	90	80.4
Currently on treatment	11	9.65	8	7.14
Died – TB	0	0	0	0
Lost to follow up	3	2.63	5	4.46
Transferred out	5	4.39	2	1.79
Treatment stopped/ interrupted/ not started	9	7.89	7	6.25
Withdrawn from study – no data collection	3	2.63	0	0

*Final known treatment outcome extracted from patient records March 2017

TABLE S8: Side effects by trial arm.

	N reports		**N patients**	
Symptom	**DOT**	**VOT**	**DOT (N=114)**	**VOT (N=112)**
Stomach pain, nausea or vomiting	82	73	9	16
Eye problems	0	7	0	4
Pain or swelling in face or joints	0	27	0	5
Numbness, pain or tingling in hands or feet	0	21	0	4
Skin rash, severe itching or hives	39	55	2	6
Headache or dizziness	9	21	2	7
Fever or chills	0	2	0	1
Unusual tiredness or loss of appetite	25	18	5	4
Other pain	0	144	0	13
Not specified	29	0	3	0

TABLE S9: Patient satisfaction by trial arm.

Satisfaction*	**DOT (% of those with answer)**	**VOT (% of those with answer)**
Strongly agree	30 (52.6)	29 (44.6)
Agree	24 (42.1)	30 (46.2)
Neither agree nor disagree	1 (1.8)	1 (1.5)
Disagree	2 (3.5)	2 (3.1)
Strongly disagree	0	3 (4.6)

*How much do you agree or disagree with the following statement: “I am satisfied with the way my treatment is observed”?

TABLE S10: Costs per patient of DOT and VOT, by treatment duration.

	Cost per patient (£)						
Duration of treatment (months)	**5**	**6**	**7**	**8**	**12**	**15***	**24***
DOT							
3 obs. per week	2,850	3,420	3,990	4,560	6,840	8,490	13,440
5 obs. per week	4,750	5,700	6,650	7,600	11,400	13,050	18,000
VOT (incl. set-up)							
10 patients	4,620	5,500	6,370	7,245	10,745	13,280	20,875
25 patients	2,195	2,610	3,020	3,435	5,085	6,280	9,870
50 patients	1,385	1,645	1,900	2,160	3,200	3,950	6,200
100 patients	980	1,160	1,345	1,525	2,255	2,780	4,365
200 patients	780	920	1,065	1,210	1,785	2,200	3,445
VOT (excl. set-up)							
10 patients	4,420	5,300	6,170	7,045	10,545	13,080	20,675
25 patients	2,115	2,530	2,940	3,355	5,005	6,200	9,790
50 patients	1,345	1,605	1,860	2,120	3,160	3,910	6,160
100 patients	960	1,140	1,325	1,510	2,235	2,760	4,345
200 patients	770	910	1,055	1,200	1,775	2,190	3,435

*For durations >12months, costs falling in the second year are discounted at 3.5%

6.2 Chapter 3 sub-analyses: treatment observation and levels of engagement stratified by DOT and VOT groups

Factors affecting adherence amongst patients with TB allocated to DOT and VOT

		DOT				VOT			
		N (%)	**80% doses not observed N (%)**	**80% doses observed N (%)**	**p-value**	**N (%)**	**80% doses not observed N (%)**	**80% doses observed N (%)**	**p-value**
Age group	16-24	18 (15.8)	14 (77.8)	4 (22.2)	0.471	23 (20.5)	6 (26.1)	17 (73.9)	0.929
	25-34	43 (37.7)	32 (74.4)	11 (25.6)		41 (36.6)	13 (31.7)	28 (68.3)	
	35-44	31 (27.2)	21 (67.7)	10 (32.3)		19 (17.0)	6 (31.6)	16 (68.4)	
	45-54	14 (12.3)	8 (57.1)	6 (42.9)		16 (14.3)	4 (25.0)	12 (75.0)	
	55-65	8 (7.0)	4 (50.0)	4 (50.0)		13 (11.6)	5 (38.5)	8 (61.5)	
Sex	Male	83 (72.8)	54 (65.1)	29 (34.9)	0.108	82 (73.2)	22 (26.8)	60 (73.2)	0.179
	Female	31 (27.2)	25 (80.7)	6 (19.4)		30 (26.8)	12 (40.0)	18 (60.0)	
Born in UK	No	83 (72.8)	61 (73.5)	22 (58.1)	0.112	93 (83.0)	27 (29.0)	66 (71.0)	0.500
	Yes	31 (27.2)	18 (58.1)	13 (41.9)		19 (17.0)	7 (36.8)	12 (63.2)	
Previous TB	No	82 (72.6)	57 (69.5)	25 (30.5)	0.325	85 (75.9)	27 (31.8)	58 (68.2)	0.565

		DOT				VOT			
		N (%)	80% doses not observed N (%)	80% doses observed N (%)	p-value	N (%)	80% doses not observed N (%)	80% doses observed N (%)	p-value
	Yes	30 (26.6)	21 (70.0)	9 (30.0)		27 (24.1)	7 (25.9)	20 (74.1)	
Pulmonary disease	No	41 (36.0)	31 (75.6)	10 (24.4)	0.274	43 (38.4)	13 (30.2)	30 (69.8)	0.982
	Yes	73 (64.0)	48 (65.8)	25 (34.3)		69 (61.6)	21 (30.4)	48 (69.6)	
Known HIV positivity	No	103 (92.0)	75 (72.8)	28 (27.2)	0.229	93 (87.7)	28 (30.1)	65 (69.9)	0.841
	Yes	6 (5.4)	3 (50.0)	3 (50.0)		9 (8.5)	3 (33.3)	6 (66.7)	
Social risk factor (any)	Never	48 (42.1)	40 (83.3)	8 (16.7)	0.012	47 (42.0)	12 (25.5)	35 (74.5)	0.415
	Within 5 years	47 (41.2)	26 (55.3)	21 (44.7)		46 (41.1)	14 (30.43)	32 (69.6)	
	>5 years ago	19 (16.7)	13 (68.4)	6 (31.6)		19 (17.0)	8 (42.1)	11 (57.9)	
Homeless	Never	77 (67.5)	58 (75.3)	19 (24.7)	0.104	70 (62.5)	21 (30.0)	49 (70.0)	0.824
	Within 5 years	23 (20.2)	14 (60.9)	9 (39.1)		24 (21.4)	7 (29.2)	17 (70.8)	
	>5 years ago	14 (12.3)	7 (50.0)	7 (50.0)		16 (14.3)	6 (37.5)	10 (62.5)	

		DOT				VOT			
		N (%)	80% doses not observed N (%)	80% doses observed N (%)	p-value	N (%)	80% doses not observed N (%)	80% doses observed N (%)	p-value
Prison	Never	93 (81.6)	67 (72.0)	26 (28.0)	0.221	97 (86.6)	29 (29.9)	68 (70.1)	0.899
	Within 5 years	11 (9.7)	8 (72.7)	3 (27.3)		7 (6.3)	2 (28.6)	5 (71.4)	
	>5 years ago	9 (7.9)	4 (44.44)	5 (55.6)		8 (7.1)	3 (37.5)	5 (62.5)	
Drug use	Never	96 (84.2)	69 (71.9)	27 (28.1)	0.067	89 (79.5)	24 (27.0)	65 (73.0)	0.150
	Within 5 years	15 (13.2)	9 (60.0)	6 (40.0)		18 (16.1)	9 (50.0)	9 (50.0)	
	>5 years ago	2 (1.8)	0 (0.0)	2 (100.0)		4 (3.6)	1 (25.0)	3 (75.0)	
Alcohol	No	91 (80.5)	69 (75.8)	22 (24.2)	0.001	92 (82.1)	26 (28.3)	66 (71.7)	0.923
	Yes	21 (18.6)	8 (38.1)	13 (61.9)		17 (15.2)	5 (29.4)	12 (70.6)	
Mental health problems	No	94 (83.2)	66 (70.2)	28 (29.8)	0.445	94 (83.9)	27 (28.7)	67 (71.3)	0.284
	Yes	18 (15.9)	11 (61.1)	7 (38.9)		14 (12.5)	6 (42.9)	8 (57.1)	
Immigration concerns	No	102 (90.3)	70 (68.6)	32 (31.4)	0.568	99 (88.4)	29 (29.3)	70 (70.7)	0.345
	Yes	9 (8.0)	7 (77.8)	2 (22.2)		9 (8.0)	4 (44.4)	5 (55.6)	

		DOT N (%)	80% doses not observed N (%)	80% doses observed N (%)	p-value	VOT N (%)	80% doses not observed N (%)	80% doses observed N (%)	p-value
Lost to follow-up (ever)	No	91 (80.5)	61 (67.0)	30 (33.0)	0.412	82 (73.2)	20 (24.4)	62 (75.6)	0.028
	Yes	17 (15.0)	14 (82.4)	3 (17.7)		20 (17.9)	11 (55.0)	9 (45.0)	
	Unknown	5 (4.4)	3 (60.0)	2 (40.0)		10 (8.9)	3 (30.0)	7 (70.0)	
Health-related quality of life	Above average	73 (64.0)	47 (64.4)	26 (35.6)	0.129	60 (53.6)	17 (28.3)	43 (71.7)	0.617
	Below average	41 (36.0)	26 (35.6)	9 (22.0)		52 (46.4)	43 (71.6)	35 (67.3)	

Table 6: Factors affecting adherence in patients with TB allocated to DOT and VOT groups.

Table 6 shows low levels of adherence with DOT – overall 49% (56/114) of those assigned to DOT had more than 80% of scheduled observations completed. Higher adherence to DOT was seen in those with social risk factors and alcohol problems than other patient groups. (p=0.012) and alcohol use (p=0.003)

Overall adherence to VOT was much higher with 90% (101/112) of those assigned to VOT having >80% of scheduled observations completed. Adherence to VOT was similar in most groups but there was some evidence of lower adherence in those

who had previously been lost to follow up (p =0.028) and in those with alcohol use (p=0.029)

Initiation phase: Risk factors affecting level of engagement with DOT and VOT intervention

		DOT				VOT			
		N (column %)	**Did not engage (row %)**	**Engage (row %)**	**p-value**	**N (column %)**	**Did not engage (row %)**	**Engage (row%)**	**p-value**
Age group	16-24	18 (15.8)	8 (44.4)	10 (55.6)	0.07	23 (20.5)	3 (13.0)	20 (87)	0.869
	25-34	43 (37.7)	26 (60.5)	17 (39.5)		41 (36.6)	3 (7.3)	38 (92.7)	
	35-44	31 (27.2)	18 (58.1)	13 (41.9)		19 (17.0)	2 (10.5)	17 (89.5)	
	45-54	14 (12.3)	5 (35.7)	9 (64.3)		16 (14.3)	1 (6.3)	15 (93.8)	
	55-65	8 (7.0)	1 (12.5)	7 (87.5)		13 (11.6)	2 (16.4)	11 (84.6)	
Sex	Male	83 (72.81)	41 (49.4)	42 (50.6)	0.61	82 (73.2)	9 (11.0)	73 (89.0)	0.50
	Female	31 (27.2)	17 (54.8)	14 (45.2)		30 (26.8)	2 (6.7)	28 (93.3)	
Born in UK	No	83 (72.8)	46 (55.4)	37 (44.6)	0.11	93 (83.0)	8 (8.60)	85 (91.4)	0.34
	Yes	31 (27.2)	12 (38.7)	19 (61.3)		19 (17.0)	3 (15.8)	16 (84.2)	
Previous TB	No	82 (72.6)	42 (51.2)	40 (48.8)	0.60	85 (75.9)	10 (11.8)	75 (88.2)	0.22
	Yes	30 (26.6)	15 (50.0)	15 (50.0)		27 (24.1)	1 (3.7)	26 (96.3)	

		DOT				VOT			
		N (column %)	Did not engage (row %)	Engage (row %)	p-value	N (column %)	Did not engage (row %)	Engage (row%)	p-value
Pulmonary disease	No	41 (36.0)	22 (53.7)	19 (46.3)	0.66	43 (38.4)	4 (9.3)	39 (90.7)	0.88
	Yes	73 (64.0)	36 (49.3)	37 (50.7)		69 (61.6)	7 (10.1)	62 (89.9)	
Known HIV positivity	No	103 (92.0)	54 (52.4)	49 (47.6)	0.91	93 (87.7)	10 (10.8)	83 (89.3)	0.30
	Yes	6 (5.4)	3 (50.0)	3 (50.0)		9 (8.5)	0 (0.0)	9 (100.0)	
Social risk factor (any)	Never	48 (42.1)	33 (68.8)	15 (31.3)	0.003	47 (42.0)	3 (6.4)	44 (93.6)	0.49
	Within 5 years	19 (16.7)	9 (47.4)	10 (52.6)		19 (17.0)	3 (15.8)	16 (84.2)	
	>5 years ago	47 (41.2)	16 (34.0)	31 (66.0)		46 (41.1)	5 (10.9)	41 (89.1)	
Homeless	Never	77 (67.5)	46 (59.7)	31 (40.3)	0.02	70 (62.5)	6 (8.6)	64 (91.4)	0.45
	Within 5 years	23 (20.2)	8 (34.8)	15 (65.2)		24 (21.4)	4 (16.7)	20 (83.3)	
	>5 years ago	14 (12.3)	4 (28.6)	10 (71.4)		16 (14.3)	1 (6.3)	15 (93.8)	
Prison	Never	93 (81.6)	49 (52.7)	44 (47.3)	0.15	97 (86.6)	8 (8.3)	89 (91.8)	0.29
	Within 5 years	11 (9.7)	7 (63.6)	4 (36.4)		7 (6.3)	1 (14.3)	6 (85.7)	

		DOT				VOT			
		N (column %)	Did not engage (row %)	Engage (row %)	p-value	N (column %)	Did not engage (row %)	Engage (row%)	p-value
	>5 years ago	9 (7.9)	2 (22.2)	7 (77.8)		8 (7.1)	2 (25.0)	6 (75.0)	
Drug use	Never	96 (84.2)	52 (54.2)	44 (45.8)	0.12	89 (79.5)	7 (7.9)	82 (92.1)	0.31
	Within 5 years	15 (13.2)	5 (33.3)	10 (66.7)		18 (16.1)	3 (16.7)	15 (83.3)	
	>5 years ago	2 (1.8)	0 (0.0)	2 (100.0)		4 (3.6)	1 (25.0)	3 (75.0)	
Alcohol	No	91 (80.5)	53 (58.2)	38 (41.8)	<0.001	92 (82.1)	9 (9.8)	83 (90.2)	0.80
	Yes	21 (18.6)	3 (14.3)	18 (85.7)		17 (15.2)	2 (11.8)	15 (88.2)	
Mental health problems	No	94 (83.2)	50 (53.2)	44 (46.8)	0.12	94 (83.9)	7 (7.5)	87 (92.6)	0.02
	Yes	18 (15.9)	6 (33.3)	12 (66.7)		14 (12.5)	4 (28.6)	10 (71.4)	
Immigration concerns	No	102 (90.3)	50 (49.0)	52 (51.0)	0.31	99 (88.4)	10 (10.1)	89 (89.9)	0.32
	Yes	9 (8.0)	6 (66.7)	3 (33.3)		9 (8.0)	0 (0.0)	9 (100.0)	
Lost to follow-up (ever)	No	91 (80.5)	46 (50.6)	45 (49.5)	0.88	82 (73.2)	8 (9.8)	74 (90.2)	1.00

		DOT				VOT			
		N (column %)	Did not engage (row %)	Engage (row %)	p-value	N (column %)	Did not engage (row %)	Engage (row%)	p-value
	Yes	17 (15.0)	9 (52.9)	8 (47.1)		20 (17.9)	2 (10.0)	18 (90.0)	
	Unknown	5 (4.4)	2 (40.0)	3 (60.0)		10 (8.9)	1 (10.0)	9 (90.0)	
Health-related quality of life	Above average	73 (64.0)	39 (53.4)	34 (46.6)	0.47	60 (53.6)	5 (8.3)	55 (91.7)	0.57
	Below average	41 (36.0)	19 (46.3)	22 (53.7)		52 (46.4)	6 (11.5)	46 (88.5)	

Table 7: Factors affecting levels of engagement with DOT and VOT interventions

Table 7 shows only 49.1% (56/114) of patients assigned to DOT engaged in treatment observation for at least 1 week. Patients with any social risk factor within the last 5 years were more likely to initially engage with DOT (10/19, 53%) compared to those without a social risk factor (15/48, 31%). Patients with any social risk factor more than 5 years ago were also more likely to initially engage with DOT (31/47, 66%) compared to those without any social risk factor. Patients with a history of homelessness within the last 5 years were more likely to engage initially with DOT (10/14, 71%) compared to those without a history of homelessness. Patients who had been homeless more than 5 years ago were also more likely to initially engage with DOT (15/23, 65%) compared to those who had never been homeless. Patients

with a history of alcohol misuse were more likely to initially engage with DOT (18/21, 86%) compared to those without an alcohol misuse history (38/91, 42%).

Initial engagement with VOT was much higher with 90.2% (101/112) of those allocated to VOT having at least 1 week of VOT completed. VOT engagement was similar across groups although there was some evidence that those with mental health problems were less likely to engage than those without (71% vs 91% p=0.04)

Maintenance phase: Adherence amongst participants who initially engage with DOT or VOT

		DOT				VOT			
		N (%)	**80% doses not observed amongst those who initially engage N (%)**	**80% doses observed amongst those who engage N (%)**	**p-value**	**N (%)**	**80% doses not observed amongst those who initially engage N (%)**	**80% doses observed amongst those who engage N (%)**	**p-value**
Age group	16-24	10 (17.9)	6 (60.0)	4 (40.0)	0.48	20 (19.8)	3 (15.0)	17 (85.0)	0.89
	25-34	17 (30.4)	6 (35.3)	11 (64.7)		38 (37.6)	10 (26.3)	28 (73.7)	
	35-44	13 (23.2)	3 (23.1)	10 (76.9)		17 (16.8)	4 (25.5)	13 (76.5)	
	45-54	9 (16.1)	3 (33.3)	6 (66.7)		15 (14.9)	3 (20.0)	12 (80.0)	
	55-65	7 (12.5)	3 (42.9)	4 (57.1)		11 (10.9)	3 (27.3)	8 (72.7)	
Sex	Male	42 (75.0)	13 (31.0)	29 (69.1)	0.08	73 (72.3)	13 (17.8)	60 (82.2)	0.06

		DOT				VOT			
		N (%)	80% doses not observed amongst those who initially engage N (%)	80% doses observed amongst those who engage N (%)	p-value	N (%)	80% doses not observed amongst those who initially engage N (%)	80% doses observed amongst those who engage N (%)	p-value
	Female	14 (25.0)	8 (57.1)	6 (42.9)		28 (27.7)	10 (35.7)	18 (64.3)	
Born in UK	No	37 (66.1)	15 (40.5)	22 (59.5)	0.51	85 (84.2)	19 (22.4)	66 (77.7)	0.82
	Yes	19 (33.9)	6 (31.6)	13 (68.4)		16 (15.8)	4 (25.0)	12 (75.0)	
Previous TB	No	40 (71.4)	15 (37.5)	25 (62.5)	0.73	75 (74.3)	17 (22.7)	58 (77.3)	0.97
	Yes	15 (26.8)	6 (40.0)	9 (60.0)		26 (25.7)	6 (23.1)	20 (76.9)	
Pulmonary disease	No	19 (33.9)	9 (47.4)	10 (52.6)	0.27	39 (38.6)	9 (23.1)	30 (76.9)	0.95
	Yes	37 (66.1)	12 (32.4)	25 (67.6)		62 (61.4)	14 (22.6)	48 (77.4)	
Known HIV positivity	No	49 (90.7)	21 (42.9)	28 (57.1)	0.14	83 (87.4)	18 (21.7)	65 (78.3)	0.43
	Yes	3 (5.6)	0 (0.0)	3 (100.0)		9 (9.5)	3 (33.3)	6 (66.7)	
Social risk	Never	15 (26.8)	7 (46.7)	8 (53.3)	0.63	44 (43.6)	9 (20.5)	35 (79.6)	0.67

		DOT				VOT			
		N (%)	80% doses not observed amongst those who initially engage N (%)	80% doses observed amongst those who engage N (%)	p-value	N (%)	80% doses not observed amongst those who initially engage N (%)	80% doses observed amongst those who engage N (%)	p-value
factor (any)									
	Within 5 years	31 (55.4)	10 (32.3)	21 (67.7)		41 (40.6)	9 (22.0)	32 (78.1)	
	>5 years ago	10 (17.9)	4 (40.0)	6 (60.0)		16 (15.8)	5 (31.3)	11 (68.8)	
Homeless	Never	31 (55.4)	12 (38.7)	19 (61.3)	0.86	64 (63.4)	15 (23.4)	49 (76.6)	0.45
	Within 5 years	15 (26.8)	6 (40.0)	9 (60.0)		20 (19.8)	3 (15.0)	17 (85.0)	
	>5 years ago	10 (17.9)	3 (30.0)	7 (70.0)		15 (14.9)	5 (33.3)	10 (66.7)	
Prison	Never	44 (78.6)	18 (40.9)	26 (59.1)	0.70	89 (88.1)	21 (23.6)	68 (76.4)	0.87
	Within 5 years	4 (7.1)	1 (25.0)	3 (75.0)		6 (5.9)	1 (16.7)	5 (83.3)	
	>5 years ago	7 (12.5)	2 (28.6)	5 (71.4)		6 (5.9)	1 (16.7)	5 (83.3)	
Drug use	Never	44 (78.6)	17 (38.6)	27 (61.4)	0.54	82 (81.2)	17 (20.7)	65 (79.3)	0.17
	Within 5 years	10 (17.9)	4 (40.0)	6 (60.0)		15 (14.9)	6 (40.0)	9 (60.0)	

		DOT				VOT			
		N (%)	**80% doses not observed amongst those who initially engage N (%)**	**80% doses observed amongst those who engage N (%)**	**p-value**	**N (%)**	**80% doses not observed amongst those who initially engage N (%)**	**80% doses observed amongst those who engage N (%)**	**p-value**
	>5 years ago	2 (3.6)	0 (0.0)	2 (100.0)		3 (3.0)	0 (0.0)	3 (100.0)	
Alcohol	No	38 (67.9)	16 (42.1)	22 (57.9)	0.30	83 (82.2)	17 (20.5)	66 (79.5)	0.97
	Yes	18 (32.1)	5 (27.8)	13 (72.2)		15 (14.9)	3 (20.0)	12 (80.0)	
Mental health problems	No	44 (78.6)	16 (36.4)	28 (63.6)	0.74	87 (86.1)	20 (23.0)	67 (77.0)	0.83
	Yes	12 (21.4)	5 (41.7)	7 (58.5)		10 (9.9)	2 (20.0)	8 (80.0)	
Immigration concerns	No	52 (92.9)	20 (38.5)	32 (61.5)	0.73	89 (88.1)	19 (21.4)	70 (78.7)	0.18
	Yes	3 (5.4)	1 (33.3)	2 (66.7)		9 (8.9)	4 (44.4)	5 (55.6)	
Lost to follow-up (ever)	No	45 (80.4)	15 (33.3)	30 (66.7)	0.29	74 (73.3)	12 (16.2)	62 (83.8)	0.009
	Yes	8 (14.3)	5 (62.5)	3 (37.5)		18 (17.8)	9 (50.0)	9 (50.0)	

		DOT				VOT			
		N (%)	**80% doses not observed amongst those who initially engage N (%)**	**80% doses observed amongst those who engage N (%)**	**p-value**	**N (%)**	**80% doses not observed amongst those who initially engage N (%)**	**80% doses observed amongst those who engage N (%)**	**p-value**
	Unknown	3 (5.4)	1 (33.3)	2 (66.7)		9 (8.9)	2 (22.2)	7 (77.8)	
Health-related quality of life	Above average	34 (60.7)	8 (23.5)	26 (76.5)	0.007	55 (54.5)	12 (21.8)	43 (78.2)	0.80
	Below average	22 (39.3)	13 (59.1)	9 (40.9)		46 (45.5)	11 (23.9)	35 (76.1)	

Table 8: Factors affecting adherence amongst patients who engage with DOT and VOT

Table 8 shows that amongst patients who engaged with DOT 62.5% (35/56) went on to complete more than 80% of scheduled observations. Patients who engage DOT and report a better baseline health-related quality of life are more likely to adhere to TB treatment (26/34, 77%) than those who report a poor health-related quality of life.

In patients who initially engaged with VOT 77.2% (78/101) went on to complete more than 80% of scheduled observations. Maintenance of adherence was good across all groups but was significantly lower in those with a history of loss to follow up (9/18, 50%).

Multivariable analysis: assessing adherence amongst those who initially engaged with DOT and VOT

Table 11: Final multivariable analysis: assessing the association of initial engagement with improved adherence stratified by DOT and VOT groups after adjusting for confounders

		DOT			VOT		
		80% doses observed amongst those who engage N (%)	**aOR (95% CI)**	**p value**	**80% doses observed amongst those who engage N (%)**	**aOR (95% CI)**	**p value**
Age group	16-24	4/10 (40.0)	1		17/20 (85.0)	1	
	25-34	11/17 (64.7)	9.88 (1.25 - 78.45)	0.030	28/38 (73.7)	0.80 (0.17 - 3.67)	0.770
	35-44	10/13 (76.9)	10.22 (1.12 - 93.30)	0.039	13/17 (76.5)	0.65 (0.11 - 3.78)	0.627
	45-54	6/9 (66.7)	20.06 (1.55 - 260.27)	0.022	12/15 (80.0)	0.99 (0.15 - 6.36)	0.993
	55-65	4/7 (57.1)	8.65 (0.64 - 116.34)	0.104	8/11 (72.7)	0.69 (0.10 - 4.81)	0.708
Sex	Male	29/42 (69.1)	1		60/73 (82.2)	1	
	Female	6/14 (42.9)	0.43 (0.08 - 2.25)	0.318	18/28 (64.3)	0.36 (0.12 - 1.06)	0.063
Lost to follow-up (ever)	No	30/45 (66.7)	1		62/74 (83.8)	1	

		DOT			VOT		
		80% doses observed amongst those who engage N (%)	**aOR (95% CI)**	**p value**	**80% doses observed amongst those who engage N (%)**	**aOR (95% CI)**	**p value**
	Yes	3/8 (37.5)	0.15 (0.02 - 1.15)	0.068	9/18 (50.0)	0.18 (0.06 - 0.59)	0.004
	Unknown	2/3 (66.7)	1.11 (0.06 - 21.94)	0.943	7/9 (77.8)	0.75 (0.13 - 4.45)	0.754
Health-related quality of life	Above average	26/34 (76.5)	1		43/55 (78.2)	1	
	Below average	9/22 (40.9)	0.11 (0.02 - 0.59)	0.010	35/46 (76.1)	0.93 (0.33 - 2.62)	0.886

*adjusted for age, sex, lost to follow up and health related quality of life

Multivariable analysis

Table 11 shows the multivariable analysis examining the association of initial engagement with improved TB adherence in DOT and VOT groups after adjusting for confounders. Using backward stepwise logistic regression after adjusting for gender, age, a history of being lost to follow-up and health-related quality of life, adherence improves as age increases amongst those in the DOT group.

Patients in the VOT group with a history of being lost to follow-up were less like to adhere.

Patients in both the DOT and VOT groups with a poorer health-related quality of life we less likely to adhere.

6.3 Interview topic guides

VOT/DOT semi-structured interviews: end of treatment

Primary aim: to identify enablers and barriers of treatment adherence in TB patients

Semi-structured interviews exploring:

i) views on privacy and confidentiality between arms by different age groups;
ii) comfort in utilising technology for health purposes
iii) whether or not the allocated treatment observation arm fit into their daily lives;
iv) any drivers behind the refusal to receive VOT observation for any individuals who were initially randomised to the VOT arm;
v) any advantages to receiving in-person DOT from VOT observation team and if so for what purposes (for those who were allocated to VOT arm and received treatment observation via VOT);

Mean interview time: 25 minutes

Sample size: 30 participants:

Sampling frame determined by the intervention:

Group A) 5 randomised to VOT who continued on VOT

Group B) 5 randomised to VOT but switched to DOT

Group C) 5 randomised to VOT but who never started VOT

Group D) 5 randomised to DOT who continued on DOT

Group E) 5 randomised to DOT but switched to VOT

Group F) 5 randomised to DOT but who never started DOT

Section A - General Questions

Your TB nurse suggested that you may benefit from extra support to help you take your TB medicines regularly by having treatment doses observed – how did you feel about this?

Prompts – Did you think this was necessary?

– If so why.

– If not why not?

At the time did you think observation of treatment doses was a useful way of helping you take treatment regularly?

– If so why,

– If not why not?

How did you feel about being asked to be part of a study where you had a 50:50 chance of being offered either Directly Observed Therapy of Video Observed Therapy?

Prompts – did you have a type of observation you would have preferred

Prompts – did you have a preference for which type of observation you would have chosen Prompts – which type of observation would you have preferred

– VOT or DOT?

– Why did you prefer this?

How did you feel when you were selected to be in the VOT arm of the study?

How much time did it take for you to take your medicine each time (including the process of filming yourself and sending your video clip)?

How easy/difficult did you find it to take medicines regularly?

What did you feel about the support you were given to take your treatment?

Section B1-

1) **Did you feel you got enough training in how to do VOT?**
2) **Was it helpful to meet the person who viewed your VOT clips?**
3) **Did you worry about privacy and who might see your video clips?**
4) **Did you have any issues around sending your video clips each day?**
5) **You were asked to show us that your mouth was empty after taking pills – how did you feel about that?**
6) **Do you think using VOT helped you to take your medicines regularly?**

7) **Do you have a smart phone of your own – if so would you have preferred to use this rather than a study phone?**

8) **What else did you use the study phone for – (calls, texts, emails, apps, internet use)?**

    a. How useful was this?
    b. Did this motivate you to keep taking your treatment?

9) **Would you have found it useful to be able to have a live videoconference with the person who viewed your video clips?**

10) **How do you feel about returning the phone to the study?**

VOT/DOT semi-structured interviews: end of treatment

Primary aim: to identify enablers and barriers of treatment adherence in TB patients

Semi-structured interviews exploring:

vi) views on privacy and confidentiality between arms by different age groups;
vii) comfort in utilising technology for health purposes
viii) whether or not the allocated treatment observation arm fit into their daily lives;
ix) any drivers behind the refusal to receive VOT observation for any individuals who were initially randomised to the VOT arm;
x) any advantages to receiving in-person DOT from VOT observation team and if so for what purposes (for those who were allocated to VOT arm and received treatment observation via VOT);

Mean interview time: 25 minutes

Sample size: 30 participants:

Sampling frame determined by the intervention:

Group A) 5 randomised to VOT who continued on VOT

Group B) 5 randomised to VOT but switched to DOT

Group C) 5 randomised to VOT but who never started VOT

Group D) 5 randomised to DOT who continued on DOT

Group E) 5 randomised to DOT but switched to VOT

Group F) 5 randomised to DOT but who never started DOT

Section A - General Questions

Your TB nurse suggested that you may benefit from extra support to help you take your TB medicines regularly by having treatment doses observed – how did you feel about this?

Prompts – Did you think this was necessary?

– If so why.

– If not why not?

At the time did you think observation of treatment doses was a useful way of helping you take treatment regularly?

– If so why,

– If not why not?

How did you feel about being asked to be part of a study where you had a 50:50 chance of being offered either Directly Observed Therapy of Video Observed Therapy?

Prompts – did you have a type of observation you would have preferred

Prompts – did you have a preference for which type of observation you would have chosen Prompts – which type of observation would you have preferred

– VOT or DOT?

– Why did you prefer this?

How did you feel when you were selected to be in the VOT arm of the study?

How much time did it take for you to take your medicine each time (including the process of filming yourself, sending your video clip; as well as DOT face-to-face observation session and travel time to and back from your clinic appointment if you had observed treatment)?

How easy/difficult did you find it to take medicines regularly?

What did you feel about the support you were given to take your treatment?

Directions

Complete section B1 and B2; and then B3 (if patient did not start DOT) or B4 (if patient started DOT).

Section B1 -

11) Did you feel you got enough training in how to do VOT?

12) Was it helpful to meet the person who viewed your VOT clips?

13) Did you worry about privacy and who might see your video clips?

14) Do you have any issues around sending your video clips each day?

15) **You were asked to show us that your mouth was empty after taking pills – how did you feel about that?**

16) **Do you think using VOT helped you to take your medicines regularly?**

17) **Do you have a smart phone of your own – if so would you have preferred to use this rather than a study phone?**

18) **What else did you use the study phone for – (calls, texts, emails, apps, internet use)?**

   a. How useful was this?
   b. Did this motivate you to keep taking your treatment?

19) **Would you have found it useful to be able to have a live videoconference with the person who viewed your video clips?**

20) **How do you feel about returning the phone to the study?**

Section B2 -

Why do you think VOT did not work for you?

Is there anything that would have helped you continue with VOT?

After finishing with VOT did you then have your treatment observed face to face (DOT)?

Directions

- If did not start DOT go to section B3
- If started DOT go to section B4

Section B3 – Started on VOT switched to DOT but did not take up DOT

Why did you not start on DOT?

Section B4 – Started on VOT switched to DOT and started DOT

Did you find DOT suited you better than VOT?

What did you find was better about DOT than VOT?

What did you find was better about VOT?

VOT/DOT semi-structured interviews: end of treatment

<u>Primary aim: to identify enablers and barriers of treatment adherence in TB patients</u>

Semi-structured interviews exploring:

i) views on privacy and confidentiality between arms by different age groups;
ii) comfort in utilising technology for health purposes
iii) whether or not the allocated treatment observation arm fit into their daily lives;
iv) any drivers behind the refusal to receive VOT observation for any individuals who were initially randomised to the VOT arm;
v) any advantages to receiving in-person DOT from VOT observation team and if so for what purposes (for those who were allocated to VOT arm and received treatment observation via VOT);

Mean interview time: 25 minutes

Sample size: 30 participants:

Sampling frame determined by the intervention:

Group A) 5 randomised to VOT who continued on VOT

Group B) 5 randomised to VOT but switched to DOT

Group C) 5 randomised to VOT but who never started VOT

Group D) 5 randomised to DOT who continued on DOT

Group E) 5 randomised to DOT but switched to VOT

Group F) 5 randomised to DOT but who never started DOT

Section A – General Questions

Your TB nurse suggested that you may benefit from extra support to help you take your TB medicines regularly by having treatment doses observed – how did you feel about this?

Prompts – Did you think this was necessary?

– If so why.

– If not why not?

At the time did you think observation of treatment doses was a useful way of helping you take treatment regularly?

– If so why,

– If not why not?

How did you feel about being asked to be part of a study where you had a 50:50 chance of being offered either Directly Observed Therapy of Video Observed Therapy?

Prompts – did you have a type of observation you would have preferred

Prompts – did you have a preference for which type of observation you would have chosen Prompts – which type of observation would you have preferred

– VOT or DOT?

– Why did you prefer this?

How did you feel when you were selected to be in the VOT arm of the study?

How much time did it take for you to take your medicine each time?

How easy/difficult did you find it to take medicines regularly?

What did you feel about the support you were given to take your treatment?

Section C -

You were offered Video Observed therapy but did not take up this offer. Why did you not take up VOT?

Did you receive training in how to use VOT?

Did you feel you received enough training in how to take part in VOT?

How was your treatment supported after you did not take up VOT?

Did you find this support helpful?

– Why/Why not?

VOT/DOT semi-structured interviews: end of treatment

<u>Primary aim: to identify enablers and barriers of treatment adherence in TB patients</u>

Semi-structured interviews exploring:

i) views on privacy and confidentiality between arms by different age groups;
ii) comfort in utilising technology for health purposes
iii) whether or not the allocated treatment observation arm fit into their daily lives;
iv) any drivers behind the refusal to receive VOT observation for any individuals who were initially randomised to the VOT arm;
v) any advantages to receiving in-person DOT from VOT observation team and if so for what purposes (for those who were allocated to VOT arm and received treatment observation via VOT);

Mean interview time: 25 minutes

Sample size: 30 participants:

Sampling frame determined by the intervention:

Group A) 5 randomised to VOT who continued on VOT

Group B) 5 randomised to VOT but switched to DOT

Group C) 5 randomised to VOT but who never started VOT

Group D) 5 randomised to DOT who continued on DOT

Group E) 5 randomised to DOT but switched to VOT

Group F) 5 randomised to DOT but who never started DOT

Section A – General Questions

Your TB nurse suggested that you may benefit from extra support to help you take your TB medicines regularly by having treatment doses observed – how did you feel about this?

Prompts – Did you think this was necessary?

– If so why.

– If not why not?

At the time did you think observation of treatment doses was a useful way of helping you take treatment regularly?

– If so why,

– If not why not?

How did you feel about being asked to be part of a study where you had a 50:50 chance of being offered either Directly Observed Therapy of Video Observed Therapy?

Prompts – did you have a type of observation you would have preferred

Prompts – did you have a preference for which type of observation you would have chosen Prompts – which type of observation would you have preferred

– VOT or DOT?

– Why did you prefer this?

How did you feel when you were selected to be in the DOT arm of the study?

How much time did it take for you to take your medicine each time (including the DOT face-to-face observation session, and travel time to and back from your clinic appointment)?

How easy/difficult did you find it to take medicines regularly?

What did you feel about the support you were given to take your treatment?

Section D –

Does having face-to-face meetings help you take your treatment?

Where did you have your DOT sessions?

– How did you feel about this?

Did you miss any DOT sessions?

– Why was this?

Did you arrange to take any of the doses on your own – without observation?

– Why was this?

Directions

Thank them for their time and conclude interview

VOT/DOT semi-structured interviews: end of treatment

<u>Primary aim: to identify enablers and barriers of treatment adherence in TB patients</u>

Purposive sampling to identify heterogeneous groups of patients randomly allocated to DOT and VOT trial arms covering a range of levels of treatment adherence. Semi-structured interviews exploring:

i) views on privacy and confidentiality between arms by different age groups;
ii) comfort in utilising technology for health purposes
iii) whether or not the allocated treatment observation arm fit into their daily lives;
iv) any drivers behind the refusal to receive VOT observation for any individuals who were initially randomised to the VOT arm;
v) any advantages to receiving in-person DOT from VOT observation team and if so for what purposes (for those who were allocated to VOT arm and received treatment observation via VOT);

Mean interview time: 25 minutes

Sample size: 30 participants:

Sampling frame will be determined by the intervention:

Group A) 5 randomised to VOT who continued on VOT

Group B) 5 randomised to VOT but switched to DOT

Group C) 5 randomised to VOT but who never started VOT

Group D) 5 randomised to DOT who continued on DOT

Group E) 5 randomised to DOT but switched to VOT

Group F) 5 randomised to DOT but who never started DOT

Section A – General Questions

Your TB nurse suggested that you may benefit from extra support to help you take your TB medicines regularly by having treatment doses observed – how did you feel about this?

Prompts – Did you think this was necessary?

– If so why.

– If not why not?

At the time did you think observation of treatment doses was a useful way of helping you take treatment regularly?

– If so why,

– If not why not?

How did you feel about being asked to be part of a study where you had a 50:50 chance of being offered either Directly Observed Therapy of Video Observed Therapy?

Prompts – did you have a type of observation you would have preferred

Prompts – did you have a preference for which type of observation you would have chosen Prompts – which type of observation would you have preferred

– VOT or DOT?

– Why did you prefer this?

How did you feel when you were selected to be in the DOT arm of the study?

How much time did it take for you to take your medicine each time (including the DOT face-to-face observation session, travel time to and back from your clinic appointment, as well as the process of filming yourself and sending your video clip if you had VOT)?

How easy/difficult did you find it to take medicines regularly?

What did you feel about the support you were given to take your treatment?

Directions

Complete section D1 and D2; and then D3 (if patient did not start VOT) or D4 (if patient started VOT).

Section D1 -

Does having face-to-face meetings help you take your treatment?

Where did you have your DOT sessions?

– How did you feel about this?

Did you miss any DOT sessions?

– Why was this?

Did you arrange to take any of the doses on your own – without observation?

– Why was this?

Section D2 -

Why do you think DOT did not work for you?

Is there anything that would have helped you continue with DOT?

After finishing with DOT did you then have your treatment observed using VOT?

Directions

- If did not start VOT go to section D3
- If started VOT go to section D4

Section D3 – Started on DOT switched to VOT but did not take up VOT

Why did you not start on VOT?

Section D4 – Started on DOT switched to VOT and started VOT

Did you find VOT suited you better than DOT?

What did you find was better about VOT than DOT?

What did you find was better about DOT?

VOT/DOT semi-structured interviews: end of treatment

<u>Primary aim: to identify enablers and barriers of treatment adherence in TB patients</u>

Semi-structured interviews exploring:

i) views on privacy and confidentiality between arms by different age groups;
ii) comfort in utilising technology for health purposes
iii) whether or not the allocated treatment observation arm fit into their daily lives;
iv) any drivers behind the refusal to receive VOT observation for any individuals who were initially randomised to the VOT arm;
v) any advantages to receiving in-person DOT from VOT observation team and if so for what purposes (for those who were allocated to VOT arm and received treatment observation via VOT);

Mean interview time: 25 minutes

Sample size: 30 participants:

Sampling frame determined by the intervention:

Group A) 5 randomised to VOT who continued on VOT

Group B) 5 randomised to VOT but switched to DOT

Group C) 5 randomised to VOT but who never started VOT

Group D) 5 randomised to DOT who continued on DOT

Group E) 5 randomised to DOT but switched to VOT

Group F) 5 randomised to DOT but who never started DOT

Section A – General Questions

Your TB nurse suggested that you may benefit from extra support to help you take your TB medicines regularly by having treatment doses observed – how did you feel about this?

Prompts – Did you think this was necessary?

– If so why.

– If not why not?

At the time did you think observation of treatment doses was a useful way of helping you take treatment regularly?

– If so why,

– If not why not?

How did you feel about being asked to be part of a study where you had a 50:50 chance of being offered either Directly Observed Therapy of Video Observed Therapy?

Prompts – did you have a type of observation you would have preferred

Prompts – did you have a preference for which type of observation you would have chosen Prompts – which type of observation would you have preferred

– VOT or DOT?

– Why did you prefer this?

How did you feel when you were selected to be in the DOT arm of the study?

How much time did it take for you to take your medicine each time?

How easy/difficult did you find it to take medicines regularly?

What did you feel about the support you were given to take your treatment?

Section F -

You were offered face to face Directly Observed therapy but did not take up this offer. Why did you not take up DOT?

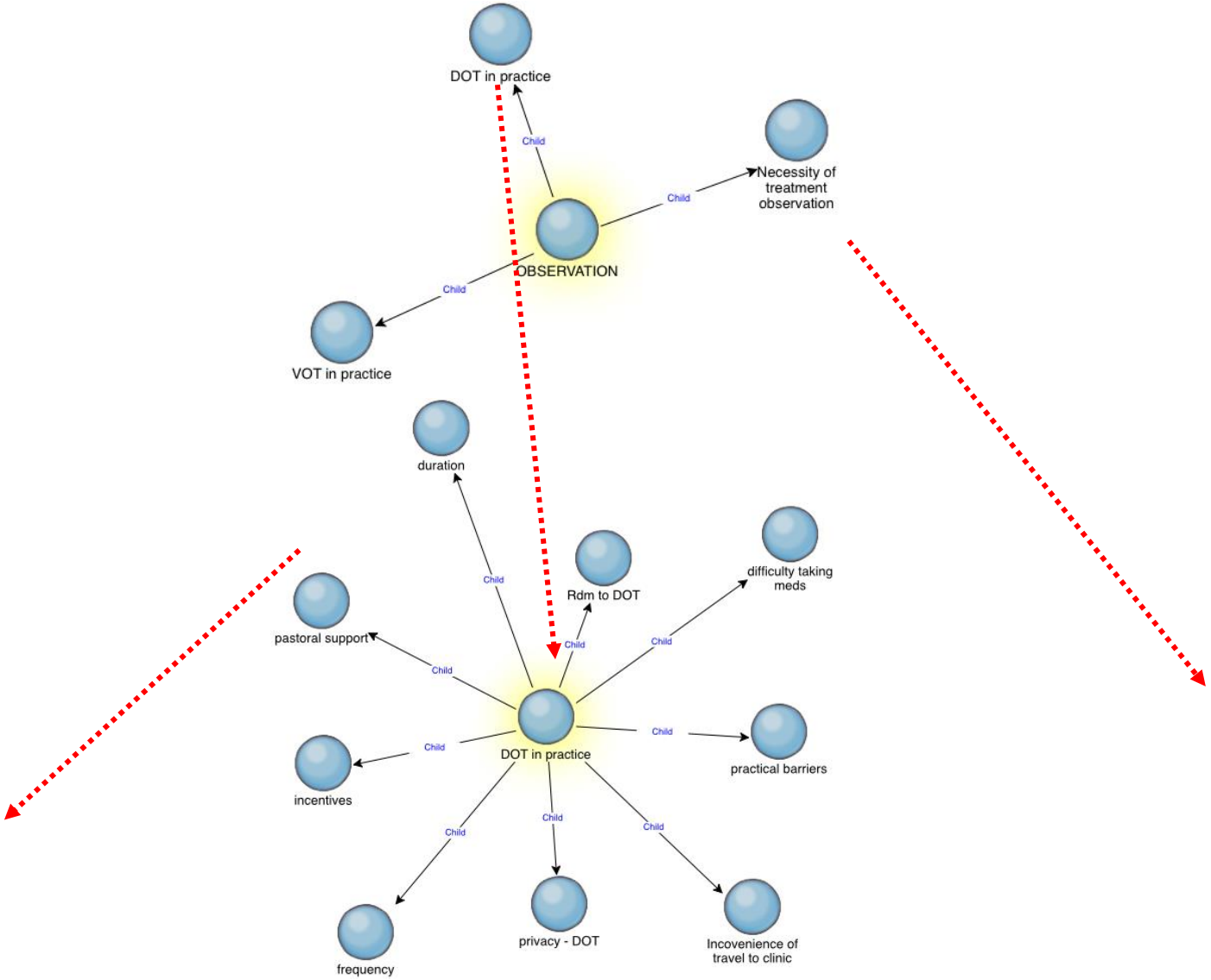
What would have made it easier for you to take up DOT?

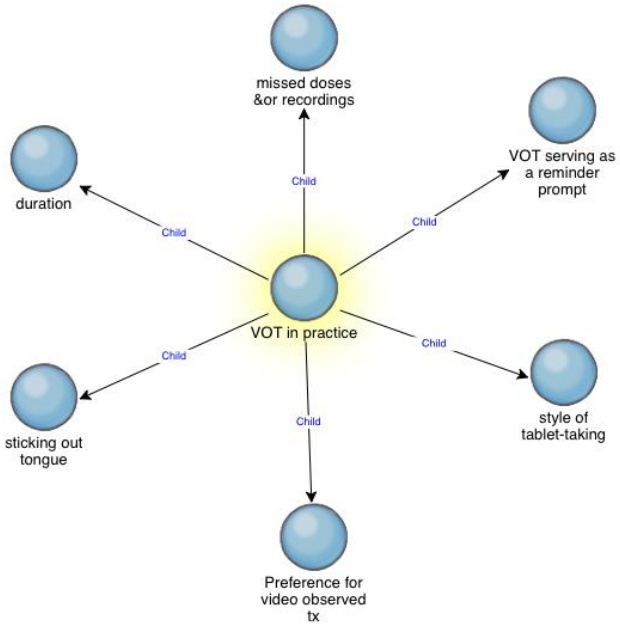
How was your treatment supported after you did not take up DOT?

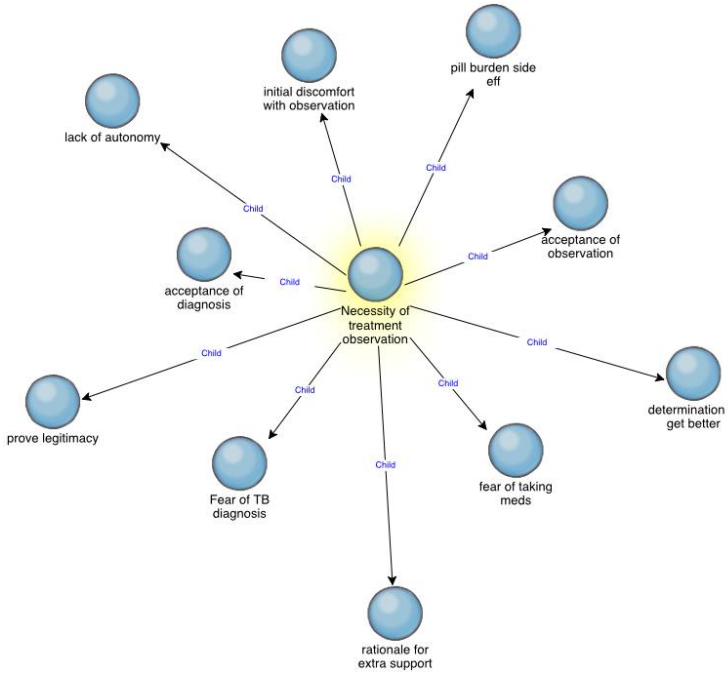
Did you find this support helpful?

– *Why/Why not?*

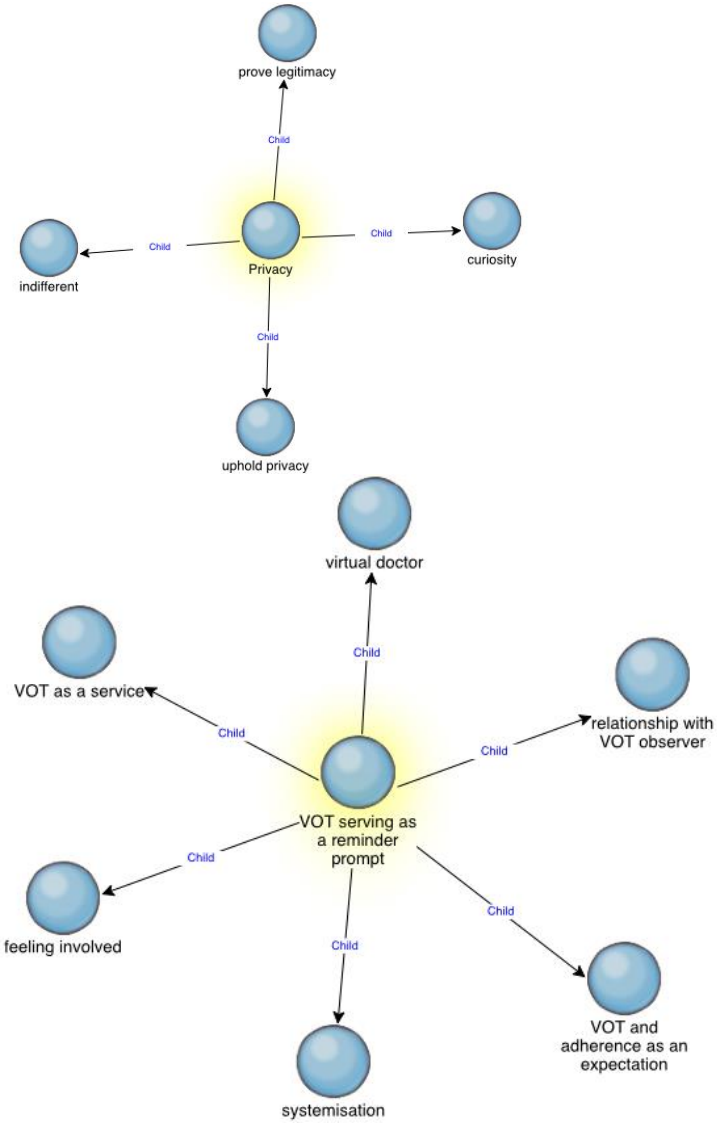
6.3 VOT trial qualitative interview coding tree

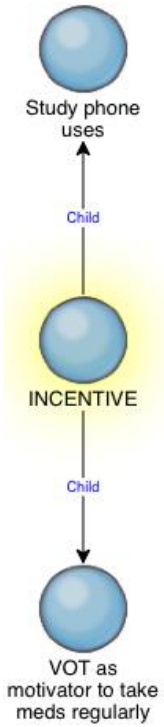



missed doses &or recordings
duration
VOT serving as a reminder prompt
VOT in practice
sticking out tongue
style of tablet-taking
Preference for video observed tx
Child


pill burden side eff
initial discomfort with observation
lack of autonomy
acceptance of observation
acceptance of diagnosis
Necessity of treatment observation
prove legitimacy
determination get better
Fear of TB diagnosis
fear of taking meds
rationale for extra support
Child


abilty to observe pt progress
reaction at being randomised to VOT
validation
INCENTIVE
re-gain autonomy
enabler
Privacy
Preference for video observed tx
manag unintentional adherence
rationale of switch from DOT to VOT
flex convenience
protect family's confidentiality
pref self administered
inconven travel to pharmacy
prove legitimacy
Child


prove legitimacy
indifferent
Privacy
curiosity
uphold privacy
virtual doctor
VOT as a service
relationship with VOT observer
VOT serving as a reminder prompt
feeling involved
systemisation
VOT and adherence as an expectation
Child


Study phone uses
INCENTIVE
VOT as motivator to take meds regularly
Child

Data extract	**Parent theme:** ***Sub theme:***
JH: No…and I think that was helpful for someone to come and be able to spend that time..ok so in terms of taking the medications you said it was a lot of tablets so having somebody come round was supportive..how did you find taking the tablets..did you find it was quite difficult.. FL: It was..yeah..very much..cos it was a lot of medication..it was a lot..so yeah..it was very difficult.. *(RDVOT 413 DOT-DOT)* SH: how easy or difficult was it to take medication regularly? AR: yeah cos what used to happen..they give me some of the tablets..the first thing I used to do was vomit..and then I told the nurse..I thought..I said to her it's a natural reaction..so what I'd do..Teresa her name was..I'll get you some other tablet fings at the same time..and I thought oh my God I'm already taking that many tablets..then anti-..shake..so what I used to do was take the tablets for TB..I used to take them straightaway..stopped vomiting..cos I used to do I used to vomit straightaway..I used to..mop..bucket..I used to keep the mop buke next to me cos I knew the moment..she'd go I used to vomit straightaway..but now.. *(RDVOT 710 DOT-DOT)*	DOT in practice *Difficulty taking medication* *Sickness* *Pill burden (new sub-theme)*
SH: how much time did it take you to take your medication each time? AR: Once the nurses turned up..oh my god..i used to be prepared anyway..got a glass of water with me..so when the nurses used to turn up..I'd take out my tablets and then I swallow my tablets..so I wouldn't say five minutes..not even a minute..in my mouth..take the water..gulp 'em down then done	DOT in practice *duration*

Data extract	**Parent theme:** ***Sub theme:***
(RDVOT 710 DOT-DOT)	
was it always three times a week or did you…did it start daily? FL: It started three days a week and THEN..because of how..she went back and told them that the pain that I was going through…also my mental health..like I said it was ALL too much for me so what they kept on doing was sending Rachel three times a week and the called me twice a week so they were covering up the full five days a week..so yeah..which I found helpful as well..so I wasn't alone *(RDVOT413 DOT-DOT)*	DOT in practice *Frequency (DOT visits per week)*
SH: what did you feel about the help and support you were given by the nurses when you took your treatment? AR: Yeah good..I'm probably repeating again..yeah can't knock 'em..cos in evry department..they used to..do food cos when I didn't have much money they used to do food vouchers…but I used to say to them I'm not gonna get there cos it's hard for me to walk to get the stuff they were gonna give me..and they'd say? We'll organise that we'll get the stuff to you..tehy used to bring like..not everyday..every so often..er..er. er..can't remember her name..we'll bring you up the stuff..you know when you can't even get down the stairs..we'll bring I up the stairs for you..can't knock 'em..can't knock 'em.. *(RDVO710 DOT-DOT)*	DOT in practice *Incentives*
SH: how did you feel when you were asked to be part of a study when you had a 50:50 chance of being offered directly observed therapy, the nurses coming to your home, or VOT when you were given a phone. Do you remember being asked about that?	DOT in practice *Inconvenience of travel to clinic* *Stigmatised (new sub-theme)*

Data extract	Parent theme: *Sub theme:*
AR: yeah..doctor said it's up to you..its' ok with me…cos I do find it hard to travel about..cos I've got to take a train and then another train..and then I've got to get a lift from my landlord.. SH: so for you..you.were fine either way..DOT or the phone..as long as you didn't have to go anywhere yourself..correct? AR: yeah..yeah..if I'm able to get transport then that's different..even then I have to go down the starirs because where I live it's like a flat..my landlord' normally parked outside then I jump in his van..drop me back off ..that way I'm ok..if I had to walk..or bus stop was round the corner…but it's hard for me *(RDVOT710 DOT-DOT)* I was working as well so for me.. so for me to go..cos in the end I would've had to continue the supervised..to my pharmacy..so I'd rather not go every morning to my pharmacy…if I can do it from home..that's better for me. *(RDVOT070 DOT-DOT)* JH: and yeah..how long would that process take..having to go to the pharmacy..? AA: The thing is I'll have to wake up..Then I'll have to go to the pharmacy without having any breakfast because I had to take the medication empty stomach..so I'll come back from the pharmacy I'll have to wait another…30 to 45 minutes till I can have something to eat..then I can go about my day..it was.. the pharmacy for me was about 15 to 20 minutes walk especially with the illness and the symptoms it was quite difficult so once they actually gave me the phone I got used to the whole thing..recording… *(RDVOT070 DOT-DOT)*	

Data extract	Parent theme: *Sub theme:*
JH: do you think that was reason DOT didn't work for you as it was more time-consuming..what would you say was the reason that having face-to-face observation wasn't working? AA: Face-to-face observation was working it was just..I didn't want to go in there everyday..and plus there were people around and it was supervised as well..I had to take it in front of them when there were people around…there was a lot of medication..so it was uncomfortable..cos I had to take about eight..nine tablets which is about four different antibiotics and I did find it quite uncomfortable especially waiting…sometimes they will be serving someone else and I will be waiting around..and plus I knew I'd got the illness..it just plays around in your mind…here I think it's more private..and I do it in my own personal time..and I can keep everyday the same time..dosage..everything I can do that without no issue..so yeah it was very helpful..for me..coming on a personal level. *(RDVOT070 DOT-DOT)* but to you to the clinic I have to go everyday far away..so to me it's better to be the phone *(RDVOT193 DOT-DOT)*	
What did you find was better about DOT than VOT? FW: re-phrased question: what do you think was better about the nurse coming? JI: it's alright cos nurse have to come to be like…she used to come three…four weeks later anyway to come and give you medication….my medications only used to come from the hospital…so when they give you three four weeks…at the end of the medications she comes anyway to see how you are…and it's nice sometimes when they come…when you talk to the person….and you sit down have a cup of tea with them…she used to come have a cup of tea	DOT in practice *Pastoral support*

Data extract	Parent theme: *Sub theme:*
and…make you comfortable…but like sometimes…every day comfortable…it's no…what they say it get too much innit…it's like when you're married…it's like everyday [laughs]….so we meet people less on certain times it's better…anyway…cos if you like meet person everyday…you just lose…the…what's the…what can you say…you get fed up innit…like sometimes they….then you get more friendly and talking then they start picking issues innit…and like…like a marriage innit…I been married a long time so..[laughs]… *(RDVOT115 DOT – DOT)*	
LP: To come everyday..to be observed everyday..because you only came once a week isn't it? MS: yeah I've been doing that since I come out of hospital..I haven't really seen a nurse..I mean..I can't..I understand the medical point of view but at the same time..I'm a working guy you know..I've got..a little business where..I can't afford to..come to the hospital everytime..I had to make that clear to Thomas..just to like..I just CAN'T keep coming to the hospital every week just to pick up tablets..you know..we tried to make arrangements whether I come back on a week basis or a couple of week basis ..you know..I just can't keep coming to the hospital just to pick up tablets you know..just a whole day wasted for me..so as far as that's concerned I haven't really seen anyone on a day-to-day basis..I've just been going through this treatment..taking my treatment..erm feeling a HELL of a lot better since ..I must admit..without a doubt. *(RDVOT437 DOT-DOT)* I was working as well so for me.. so for me to go..cos in the end I would've had to constinue the supervised..to my pharmacy..so I'd rather not go every morning to my pharmacy *(RDVOT070 DOT-DOT)*	DOT in practice *Practical barriers*

Data extract	Parent theme: ***Sub theme:***
JH: do you think that was reason DOT didn't work for you as it was more time-consuming..what would you say was the reason that having face-to-face observation wasn't working? AA: Face-to-face observation was working it was just..I didn't want to go in there everyday..and plus there were people around and it was supervised as well..I had to take it in front of them when there were people around…there was a lot of medication..so it was uncomfortable..cos I had to take about eight..nine tablets which is about four different antibiotics and I did find it quite uncomfortable especially waiting…sometimes they will be serving someone else and I will be waiting around..and plus I knew I'd got the illness..it just plays around in your mind…here I think it's more private..and I do it in my own personal time..and I can keep everyday the same time..dosage..everything I can do that without no issue..so yeah it was very helpful..for me..coming on a personal level. *(RDVOT070 DOT-DOT)* Did you find DOT suited you better than VOT? JI: Phone it was like…at least it give you privacy like ….if nurse coming you know you're in your home…innit…you are with the way you are comfortable…so you have to run clear up [laughs] before the person come…so if the phone you can go sit in a corner…. They can't see what mess I made over there [laughs] Fw so…[laughs] which one? JI: phone is better *(RDVOT115 DOT-DOT)*	DOT in practice *Privacy*
I was fine..didn't have a problem with that..because one of the nurses said to me..we're gonna come everyday..and I said that's fine..and she said to me "do you prefer the morning or the afternoon?" ..just make sure he doors were both open..	DOT in practice *Favourable opinion*

Data extract	Parent theme: ***Sub theme:***
(RDVOT710 DOT-DOT) Yeah..face-to face fine..not a problem *(RDVOT710 DOT-DOT)*	
LP: At that time..was there a type of observation that you would have preferred..would you have like to get..to do the videos.. MS: Listen sweetheart at the end of the day..that malarkey was just nonsense..cos if I've got a disease and I'm being treated for it..and on a regular basis..it shouldn't..bottle down to a roll of a dice if you see what I mean..cos..and now they're throwing me back out to nature..with other people..so as far as I'm concerned..that is just nonsense..you either do it or you don't..and at that time I was in the prime position..and you're telling me you've got to throw as dice to find out whether I'm entitled to something or not..that..that aspect was absolute nonsense as far as I' concerned..why even bother doing something like that I just don't know.. *(RDVOT437 DOT-DOT)* when they first introduced it to me…it was like if..erm..it wasn't a very big thing..it was like..wrm..we'll put you for this thing..random..programme *(RDVOT070 DOT-DOT)*	DOT in practice *Indifferent re rdm*
AA: To be honest..I didn't really think about it too much cos at that time I was more concerned about my illness and how to treat it..cos I knew I would be on the medication programme *(RDVOT070 DOT-VOT)*	DOT in practice *Rdm to DOT*

Data extract	Parent theme: ***Sub theme:***
	Re-gain sense of agency
SH: Did you miss any DOT doses? AR: Yeah..what happened yeah.. there was a couple of times where I went to my friend's house..i thought I'd be back before and do it..in the evening but I ended up staying there a couple of days..eh..so I missed couple of days *(RDVOT710 DOT-DOT)* SH: so when you missed the DOT appointment did you arrange to take the medication on your own without observation or did you miss the medication? AR: yeah..no..what it was was like..the nurses would come everyday..except? Friday..and there was a couple of days I did miss..but I told them I thought I'd be back..what it was..can't lie..I ended up staying there longer than I planned to SH: so when you missed the observation you didn't take the medication so you you missed the medication, is that right? AR: yeah *(RDVOT710 DOT-DOT)*	DOT in practice *Reported missed doses*
..the nurse..we came..and I told you should've..and she said what you should do if you're ever gonna do that again you should take your medication with you and then if you're not at your..at least you've got your medication with you..make sure you've got your medication and complete your course..	DOT in practice *Reported missed doses* *DOT observer response*

Data extract	Parent theme: ***Sub theme:***
(RDVOT710 DOT-DOT)	
LP: it turned out you didn't get the phone.. you fell into what was called the DOT arm where you would be directly observed..did you actually spend any time going to the clinic or having the nurse coming to you to observe you taking your meds or did you go into self [sic] medicating..? MS: No one..no nurse came to me and erm..directly at my premises..no..but every week I went to go and see my GP..advisor..so to so..and then every couple of months I would go to see the doctor..I actually missed an appointment yesterday..I thought it was today…I should've gone..[sniff] ..oh well..[SMALL CHUCKLE] *(RDVOT437 DOT-DOT)*	DOT in practice *Reported missed doses* *Self-administered*
SP: Yes [INTERRUPTS] it does help me *(NR913 MDR non-rdm to VOT)* NN: It's not a thing it's necessary..it's absolutely..I..expected it.. (RDVOT193 VOT-VOT) this is what I NEED to do..to do it like camera and everything..and stuff like that *(RDVOT193 VOT-VOT)*	Necessity of treatment observation

Data extract	Parent theme: *Sub theme:*
Chelsea hospital eleven month ago..errrm..it was red colour when I do pee and I was scared before first experience was take medication with the..you know..I do to in front of the nurse..I had to..the nurse had to look I had take the medication..if not the nurse still sitting down..my medication is finished..that my experience.. *(RDVOT193 VOT-VOT)* but once the whole thing was explained to me..that I thought about how it's gonna help me..in person..then I thought you know what..it's actually a really good programme. *(RDVOT070 DOT-VOT)* Yes, I think it was necessary because I might the dosage and medicnes and the fact that I HAD TO BE OBSERVED I THOUGHT WAS NECESSARY SH: At the time did you think observatuion of your treatment doses was a useful way to take treatment doses? Yes I beelev so because at the atime because including the infusion (IV line medication) in the first 6 months because I WANTed to observethe effect sand results and side effects as well *(NR914 MDR non-rdm to VOT)* FW: And at the time you thought treatment observation was a useful way to help you take medication regularly? JI: Yeah…first I thought it was childish…because I mean….like….I'm an old person….I'm…sick…so I've got to take my medication….but…as a long [???]…I've got to take my medication because sometime you get fed up because it was 12…14 tablets a day…and	

Data extract	Parent theme: *Sub theme:*
sometimes you get fed up because it makes you drowsy… you get a [affected?] your mood changed…so in a way it's a good because sometimes….maybe some time…I...would've said fuck it…sometimes…you know how you get fed up…so you say I don't wanna take it today …leave it…. *(RDVOT115 DOT-VOT)* AI: Being observed, yeah it's a good thing like to be honest instead of like going to the hospital every single day it's better it's like their monitoring me every single day they're monitoring how I'm taking my medication because no one like to take medicine so it's like you're under the impression (sic) that you have to take the medicine because if you don't take it next day they let me know why it's important for me to take the medicine…it's good to be observed and I'm really happy they did it like…really..carefully and they were keen to make me feel better about this and I'm happy to be part of this… *(RDVOT078 VOT-VOT)* FW: that's good. At the time did you think observation of treatment doses was a useful way of helping you take your treatment regularly if so why? AI: of course I think it's really very helpful because like I said no one wants to take medicine but if I didn't have to take some videos I would've missed some days…like I was in Manchester but I didn't want to make excuse but I really didn't like it because it's too hard when you take the medicine because you feel really dizzy and everything but because of these things I had to take it I being monitored…that was in my head…yes I have to send the videos and there is no way you can…the important thing of this app is you can't change data and you can't even watch it .. you have to take it so it's a good thing…it's like a prison inside..but it's fun *(RDVOT078 VOT-VOT)*	

Data extract	**Parent theme:** ***Sub theme:***
Because I got MDR-TB *(NR193 MDR non-rdm to VOT)* the doctor said you need to take it..I accept what the doctor say..I'm here taking it. *(RDVOT367 VOT-VOT)*	Necessity of treatment observation *Acceptance of diagnosis*
NN: No..it's good..cos you know I used to it..I wanna get better..that's it..there's no point you like sending video and then if you not happy..you have to get better and have to be happy as well to take medication..that is the thing *(RDVOT193 VOT-VOT)* MK: yeah I feel I appreciate it..to be recovered..you know.. *(RDVOT367 VOT-VOT)* yes..of course..this is treatment for my HEALTH *(NR913 MDR non-rdm to VOT)*	Necessity of treatment observation *Determination to get better*

Data extract	**Parent theme:** ***Sub theme:***
second thing is when I take medication when I do pee-pee it's red I was so scared..screaming so I ask the doctor..the doctor said it's beautiful so the medication is working (RDVOT193 VOT-VOT)	Necessity of treatment observation *Fear of taking meds*
NN: Yes it is ..because I'm scared..it's gonna die or something..because that is dangerous you know.it's TB..it's dangerous so I need someone to support with that..with the TB medication and stuff like that *(RDVOT193 VOT-VOT)*	Necessity of treatment observation *Fear of TB diagnosis*
To be honest..at first.. cos I didn't understand the whole programme of it..I was a bit uncomfortable with it cos I thought I would probably have to go and visit a few more different institutions..hear my illness with a few more different people..at first. *(RDVOT070 VOT-VOT)*	Necessity of treatment observation *Initial discomfort with observation*
MK: I know it's boring to take all these tablets..but I don't have a choice. *(RDVOT367 VOT-VOT)* MK: I know it's boring..boring..when someone is sick you don't have choice..you have to take it..you know..you have to stuck on it beause..no one need to suffer..you know..I don't want to suffer you know..I want to recover a soon as possible you know..so… *(RDVOT367 VOT-VOT)*	Necessity of treatment observation *Lack of autonomy*

Data extract	Parent theme: ***Sub theme:***
FW: Is there anything you'd like to tell me about your experiences being observed taking treatment? JI: I mean…I…I think it was good…you need to observe…I'm fifty-two yeah…I'm fifty-three I'm just gone now….I was thinking on that age they have just trusted me…that…I would take my tablets…I would take my life seriously…at the that age…young person…you need somebody to…to look at the them to take medication….because…as I said sometimes I used to get fed up…that I don't wanna take it…cos like…it's too many tablets….and look at the facts….can I like explain you the facts of your own body…goes with different kind temperatures…when you take them tablets…so it does make you like…why am I taking it…I don't wanna take it today I feel like sometimes….my mouth is dried….like…I should finish in two weeks…they cleared me yesterday…they said wherever I go just finish that course….but like it dries your mouth….and keep making you thirsty and you feel like your body's like burning inside…like temperature…like body's temperature is hot…so it makes you fed up…so if I…like I said….if I felt no one was watching me...maybe someday I would've say you know I don't wanna take them…so it's bad fing in a way… *(RDVOT115 VOT-DOT)*	Necessity of treatment observation *Pill burden; side effects*
AI: Ok...to be honest if you ask anyone they will ask for the direct doctor because that would be more trustworthy *(RDVOT078 VOT-VOT)*	Necessity of treatment observation *Prove legitimacy*

Data extract	**Parent theme:** ***Sub theme:***
MA: I didn't really mind..because the video recordings show that I'm taking my medications..so if I miss a dosage or something then they would obviously inform me *(RDVOT415 VOT-VOT)*	
they didn't leave me for one minute..every five minutes..a different nurse would come round ask me "are you ok?" "Do you need some water"…do you need this..do you need that..do you want something to eat.. *(RDVOT710 DOT-DOT)* NN: Yeah.. I feel great because you know that..they support me and everything like..taking medication..you have to take medication and everything.that..so I feel good.. *(RDVOT193 VOT-VOT)* NN: Useful..excellent it's like..happy very happy..everyone support me.it's like the team..medication..good team you know nurses ..always saying "are you ok?" stuff like that ..I'mjust so happy.. *(RDVOT193 VOT-VOT)*	Necessity of treatment observation *Rationale for extra support*
I didn't even wanna be there.. no we have to..I mean that way..I can't knock 'em *(RDVOT710 DOT-DOT)*	Necessity of treatment observation *Rationale for extra support* *Escapism*

Data extract	**Parent theme:** ***Sub theme:***
SM: Yeah yeah yeah [sighs] I felt it was necessary because.I mean myself personally I was very sick and I don't think I would've taken the medications regularly..I wasn't going to be compliant to be honest..you know *(NR903 MDR non-rdm to VOT)* I've been down with some of my medication..stopping my medication for no reason..so this opportunity..this gave me an opportunity to take my medication whenever I had to take it..I felt good *(RDVOT046 VOT-VOT)* and as I was told when I started the TB medication..i couldn't miss any..not even for a day..I couldn't ..so I think the doctor thought it would be good for me..if I had that extra support…after the history HE has with me..he didn't want me to go through the stopping of this medication as well..so he suggested it in goodwill..so..yeah *(RDVOT046 VOT-VOT)*	Necessity of treatment observation *Rationale for extra support* *Non-adherence*
i think it varies on people..I think for me..even if I would've taken it home…like the VOT programme I know I would taken it cos I was pretty bad…my health..my symptoms..so I know I would taken it..but if you look at it from other peoples' point of view some people are different so I imagine…I also had a very bad addiction to substances and stuff…so if you look at it from that angle..I think it's probably not a very good idea to just give it to them..especially if you have other things..as a priority in your mind..that way I think VOT did a really good job..it's really good programme	Necessity of treatment observation *Rationale for extra support* *Non-adherence* *Addiction issues*

Data extract	Parent theme: *Sub theme:*
(RDVOT070 DOT-VOT)	
yeah like I said..i have high blood pressure? [inaudible] I had stitches in my knee..and apart from that..I [inauditble] so anything that they can do for me..then I'm grateful.. *(RDVOT710 DOT-DOT)* JN: Ermm..it's not about the TB medication..there's other medications I'm on..the doctor has seen me go through the downfall of the other medication. *(RDVOT046 VOT-VOT)*	Necessity of treatment observation *Rationale for extra support* *Non-adherence* *Comorbidities – coinfection*
AA: the only think I can think of is…if they had prescribed the..for example the six weeks medication..or a month's medication in advance then I could take it home and do it but then there is the issue of..what if you miss a dose then *(RDVOT070 DOT-VOT)* when I was in the hospital..I got TOOO much medication..the doctors didn't think it would be ideal for me to go home without bunch of medication..a month or two month..then I wouldn't have taken it..straightaway I wouldn't have taken it. *(RDVOT046 VOT-VOT)*	Necessity of treatment observation *Rationale for extra support* *Non-adherence* *Surplus meds dispensed*
yeah it's easy to forget *(NR903 MDR non-rdm to VOT)*	Necessity of treatment observation *Rationale for extra support*

Data extract	Parent theme: ***Sub theme:***
	Non-adherence *Unintentional*
they obviously felt that there's something ..you know problems with me and they felt that they needed to assist me. *(RDVOT710 DOT-DOT)*	Necessity of treatment observation *Rationale for extra support* *Recognition of flaws*
when I got home from the hospital..I thought it would be like a one day [treatment?] [inaudible]..the doctor's diagnosed you with TB..it was very helpful they way they treated me..very very helpful..I cam't knock 'em..I can't. *(RDVOT710 DOT-DOT)*	Necessity of treatment observation *Rationale for extra support* *Support for longer term regimen*
so the process was very quick all I had to do was erm wake up in the morning…give them my patient number and record the patient video and send it..that's all. *(RDVOT070 DOT-VOT)* JH: so that sounds a lot quicker than pharmacy AA: Oh my God! It was SO much better…I could wake up…straight up [PACE QUICKENS] I could take my medication straight away rather than getting dressed..getting ready…going out..and..it's a long process.. *(RDVOT070 DOT-VOT)*	Observation *VOT in practice* *Duration*

Data extract	Parent theme: *Sub theme:*
30 to 45 seconds]..all I had to do was pretty straight forward.. *(RDVOT070 DOT-VOT)* LP: And how much time did it take for you to video yourself taking your medicine each time, including preparing everything, including preparing the water and tablets? SM: Not much time..the video clip lasted for about five seconds..isn't it? [LAUGHTER] because the preparation wasn't really bad..the medication was in a dossette box which was very easy..and it was just a matter of getting a glass of water or whatever I use to take it..all-in-all about less than five minutes preparation to be honest..but the video itself was about five seconds *(NR903 MDR non-rdm to VOT)* SP: Alright..how much time did it take for you to take your medicine each time, including filming and sending? SH: the morning one is a little bit longer..like sending..about a minute..one minute..and evening one there is not much variation..like six..ten tablets or seven ten tablets so.. half..thirty seconds.. SH: Thirty seconds..does that include filming it and sending the video clip? SP: I'm talking about recording it..i don't know sometimes they said to me..when you record the video and it will take time to received it..it depend the network..sometimes it takes half and hour sometimes it takes longer	

Data extract	Parent theme: *Sub theme:*
SH: But the filming process for you takes shorter? SP: Yes *(NR913 MDR non-rdm to VOT)* He says in the morning I take 4 tablets and they take 1 minute and the half a dose in the evening which is 2 tablets and in the night I take 6 tablets which is 30 seconds..so it's about 1 minute and 50 seconds SH: And does that include sending the clips as well? Yeah *(NR914 MDR non-rdm to VOT)* How much time did it take for you to take your medicine each time (including the process of filming yourself, sending your video clip; as well as DOT face-to-face observation session and travel time to and back from your clinic appointment if you had observed treatment)? JI: 5 mins FW: and the self-medication. So how long did it take taking tablets on your own without the phone? JI: I mean…what I did I put the phone here …I put the glass of water…I put my tablets here…took my tablets…I put the phone here…it would've taken me the same time even without the phone…the phone is just like a recording then isn't it…its' just there right isn't it…all I…I just hold it in my hand because I just..I just put it in the thingy then I just take the tablets…and then that's it…and then I just send it FW: so around the same the same time for both using the phone and the same time for taking the tablets on your own.	

Data extract	**Parent theme:** ***Sub theme:***
JI: Yes *(RDVOT115 VOT-DOT)* AI: It start from sometime between forty seconds. *(RDVOT078 VOT-VOT)* it's really short..maybe 30 seconds..but before I take medication first time with the video..because the medication is too big like this so I have to crush it..to do it like ..10 minutes *(RDVOT193 VOT-VOT)* JH: ..So if we talk a bit about the filming process..how much time does it take or did it take to do the filming..is it straightforward or how long would you say it took? JN: with me it's straightforward I swallow my medication at once..I don't just take one tablet..i take all of it at once..it's straightforward I just put on the phone press record..get ready my medication..swallow and that's it JH: so it's over and done with in? JN: Five minutes?..less than five minutes..five minutes.yeah.. JH: perfect..and you just get one with your day.. JN: Yeah *(RDVOT046 VOT-VOT)*	

Data extract	**Parent theme:** ***Sub theme:***
MA: Well in the beginning I took a lot of time but..now it's like 4 minutes *(RDVOT415 VOT-VOT)* MK: Err it's about two minutes from time..to do the whole thing..sometimes two and a half..or three…sometimes even less.. *(RDVOT367 VOT-VOT)*	
so sometimes I would forget..they actually reminded me through text..the support worker would actually phone me and say..ahh you haven't taken your dose or..you haven't recorded [LAUGHS] I remember a couple of times I forgot my dose or I forgot to record it so the I would text her.. *(RDVOT070 DOT-VOT)* LP: And did you have any issues with sending your video clips everyday? SM: [3-4 second pause] Yeah at times when I used to take them late ..when I started working I would say early in the mornings it was difficult..because I was supposed to take them before food..some of them so they really made me sick [coughing] but then I started to take them with food actually..so at work when you take them before you actually..after handover you tend to forget..and then you realise later *(NR903 MDR non-rdm to VOT)* SP: Yeah of course I used to miss..a couple of months ago I missed some clips..that reason [laughs] I can't tell you but sometimes in the weekend I go out so I don't take this mobile outside because you know because last time I take the phone outside and I damaged the phone	VOT in practice *Missed doses or recordings*

Data extract	Parent theme: *Sub theme:*
(NR913 MDR non-rdm to VOT) FW: How easy/difficult did you find it to take medicines regularly? JI: I mean…as I said…sometime you get…because you're taking medications everyday…it's a lot of medication plus…it gives you…what's the word for it..sometime side effects…you don't feel..alright….I still get burns in my chest….like….because it's heavy…so sometimes you do get fed up you don't wanna take it….you're taking that many tablets…if affects your body from inside…like…because all the tablets…are like hot…and powerful…so sometimes you don't get like…like if the phone wasn't there….so maybe I would've missed few days…I'm not gonna lie….if the nurse wasn't there…and the phone wasn't watching me…I would've say a few days…yeah I don't feel like taking tablets today…it does help you that way *(RDVOT115 VOT-DOT)* if I didn't have to take some videos I would've missed some days *(RDVOT078 VOT-VOT)* there is no way I shouldn't miss it and because of this part I never missed I guess I missed once or twice.. it's not because…I fell asleep and she understood… *(RDVOT078 VOT-VOT)* JN: With the TB I've never…I missed recording..but I've never missed a dose *(RDVOT046 VOT-VOT)*	

Data extract	**Parent theme:** ***Sub theme:***
SH: anything else you want to say about treatment It was quite a good experience and I do support this kind of study *(NR914 MDR non-rdm to VOT)* I preferred a phone *(RDVOT193 VOT-VOT)* I wanted the phone..I wanted the phone because I don't think I would have…err..ok I don't think I would've been comfortable with someone sitting there watching me take my medication. *(RDVOT046 VOT-VOT)*	VOT in practice *Preference for video observed treatment*
LP: Well it is..it's just that doing the videos is something new. On that note which type of observation would you have preferred, did you like the videos or would you have liked a face-to-face or taking your medication by yourself..did you have a preference..would you have preferred something diffierent? SM: No the video was good..at least you could see me how..how..what can I say..my progress you could physically see *(NR903 MDR non-rdm to VOT)*	VOT in practice *Preference for video observed treatment* *Ability to observe patient progress*
JH: Ok. So the idea was ok but you felt there were practical things that would prevent that from happening..in terms of having to.. you were working..so finding a way round that. When the study was introduced to you by the nurse or one of my colleagues and it was put to you that it's a randomised trial so there's a 50:50 chance of..to get the phone. How did you feel there was a 50:50 chance of getting the phone?	VOT in practice *Preference for video observed treatment* *Enabler*

Data extract	Parent theme: *Sub theme:*
AA: To be honest..I didn't really think about it too much cos at that time I was more concerned about my illness and how to treat it..cos I knew I would be on the medication programme..but erm..when they first introduced it to me…it was like if..erm..it wasn't a very big thing..it was like..wrm..we'll put you for this thing..random..programme..if they select you..you get..you get selected..so I was like out my name down I'll fill out the form..I'll give you the consent..and actually when I thought..the whole thing went through and they came back to me and you've been selected..and they'lll give you a phone..and I thought about it..and I thought [PACE QUICKENS, SMILES] ..ok I think this will be a very brilliant thing for me because doing it from home rather than..cos it was really hard for me going to..going to the pharmacy every morning..and breakfast.. *(RDVOT070 DOT-VOT)* JH: How..how long was it..you continued to go to the pharmacy for a bit..and how long was it before you were then given the phone? AA: They actually posted it pretty quick..cos erm..cos I was actually them..is there anyway of actually bringing the medication home cos I can take it from home cos I work and for me to get to the pharmacy is very hard so that's when they actually put me through for that programme..and you know what..I think that actually happened within 3 weeks so actually pretty quick [LAUGHS] I was quite chuffed about that *(RDVOT070 DOT-VOT)* JH: And did you feel you were supported and how did you feel about the support you were provided with from your nurse or from the person who was observing you films when they were coming through?	

Data extract	Parent theme: ***Sub theme:***
AA: I think they were very supportive…they saw me once..at the start they saw Me..i think..at least every 2 weeks and then they saw me after a month and then..it went back to..once I got the medication..and once I was in the whole process of it..they saw me every few months..I had to go there every 6 weeks to go my medication and prescription so what they did they would erm..transfer it over to the pharmacy..all I had to do was go to the pharmacy and pick up the dose and take it home and carry on with the recording programme… *(RDVOT070 DOT-VOT)* JH: if VOT..if using the phone hadn't have been an option what would have helped you continue with the DOT do you think? Would there would've been something that would've helped you do that? AA: the only think I can think of is…if they had prescribed the..for example the six weeks medication..or a month's medication in advance then I could take it home and do it but then there is the issue of..what if you miss a dose then..and things like that..i think it varies on people..I think for me..even if I would've taken it home…like the VOT programme I know I would taken it cos I was pretty bad…my health..my symptoms..so I know I would taken it..but if you look at it from other peoples' point of view some people are different so I imagine…I also had a very bad addiction to substances and stuff…so if you look at it from that angle..I think it's probably not a very good idea to just give it to them..especially if you have other things..as a priority in your mind..that way I think VOT did a really good job..it's really good programme *(RDVOT070 DOT-VOT)*	
and I can keep everyday the same time..dosage..everything I can do that without no issue..so yeah it was very helpful..for me..coming on a personal level. *(RDVOT070 DOT-VOT)*	VOT in practice *Preference for video observed treatment*

Data extract	Parent theme: ***Sub theme:***
it saves a lot of time..a lot of effort..erm I think in a way it's..more efficient…cos the thing is I'll get to wake up in the morning and take the medication first thing in the morning..rather than worry about anything else..and going to the pharmacy and getting ready..it's like..that way it's more efficient…erm..plus you get more..reminders if you forget..so all in all I think it was good for me *(RDVOT070 DOT-VOT)* LP: Did you feel you had enough training in how to film yourself? SM: Oh yeah yeah it was very easy you know..Gloria came and taught me how to do it..even when I was stuck at home the kids they knew the technology it was..very easy [LAUGHTER]..yeah it was fine I got the support everywhere.. *(NR903 MDR non-rdm to VOT)* SP: Because there's no time..sometimes I have to take the medicine like in the morning sometimes I take in the afternoon there's no maximum time to take..at night..if I forgot oor something..you know sometime I have to go with my Mum sometime out so I'll take sometime medicine early..like 10..11 o'clock in the morning..and sometime I have to go to the hospital..like today I go to appointment 12 o'clock so I just came half-past one I just take the medicine..sometime the medicine is strong so they affect me in my liver so they took..so I go to appointment today so had blood test today so I has to take the medicine today..the TB nurse contact me to start medicine today or tomorrow SH: So do you mean that you think it's flexible to have the phone? SP: Yeah..yeah..yeah	*Flexibility / Convenience*

Data extract	Parent theme: *Sub theme:*
(NR913 MDR non-rdm to VOT) so..if I go outside sometime I will go around with my female family outside..and I take that mobile and I will call them with one of the lady done there and I can tell them I can take the medicine..otherwise I can take the medicine regularly and keep in touch with nurse or Joe or whatever *(NR913 MDR non-rdm to VOT)* JI: I mean…I think it's a good idea….it saves you money…time…otherwise what they wanted to do..the nurse wanted to come everyday visit to make sure you were taking your medication so that way the nurse can do something about it so just do a visit at home...the phone thing is better…just record it and send it to them. It saves the money and time for both the people. *(RDVOT115 VOT-DOT)* How did you feel about being asked to be part of a study where you had a 50:50 chance of being offered either Directly Observed Therapy or Video Observed Therapy? JI: I would do the video therapy…because as I said…it would save your time…the nurse and the hospital money and your time. FW: the 50:50 chance thing. What about that? Half a chance of it being one option JI: If it was one option…It I didn't have no option then I would have to go to the nurse. If I got the option then I would take the phone option…because it saves my time cos I then I have to go travel…or the nurse has to come…first…in the beginning when I first started taking tablets I was so sick I couldn't even stand up….so then the nurse would've had to come everyday…so…otherwise I would've have to go to the hospital so I would feel the phone fing is a	

Data extract	Parent theme: ***Sub theme:***
lot better….than travelling cos that way you're saving your money…because when you're sick you're not working anyway so it helps…the phone thing is the best idea anyway…technology work for you… *(RDVOT115 VOT-DOT)* like you don't have to call your doctors all the time I can send a text to them and let them know my situation *(RDVOT078 VOT-VOT)*	
LP: And what else did you use the phone for..did you use the phone for something else.? SM: For phoning me on the phone [LAUGHTER] I was using it..I was told I could use the phone..it was a bonus [LAUGHTER] it was really a bonus..it was very very useful..I miss the phone now..I miss it [LAUGHTER].. *(NR903 MDR non-rdm to VOT)*	VOT in practice *Preference for video observed treatment* *Incentive* *Study phone uses*
I prefer to use this phone..the study phone because you know hospital..use this number..you know the helping me..this phone..that one phone..only for music..take picture..this one for you doctor..for message for the key worker because I said to the..this one is for doctor *(RDVOT193 VOT-VOT)* JN: I use it just for filming when I'm taking my medication and sometimes when I have to talk to Joe or Gloria..and that's all I use it for..	VOT in practice *Preference for video observed treatment* *Incentive* *Study phone uses*

Data extract	**Parent theme:** ***Sub theme:***
(RDVOT046 VOT-VOT) so I prefer it to be on the other phone so I know I can leave it at home..I know I can keep it in a safe place for myself..it's my thing..it's only for me..ME..you know.. *(RDVOT 046 VOT-VOT)* JN: Keeping that side private from my everyday life..hmm *(RDVOT 046 VOT-VOT)*	*Compartmentalising TB care and external services*
I'm usng it for PHONE, EMAIL, TEXTING AND APPS Sh: how useful is this? Its Quite useful SH: MOTIVATE? Yes it did motivate me *(NR914 MDR non-rdm to VOT)* SH: RETURN THE PHONE To be honest I'm ok but I've given the number to lots of different provider and contacts but it's ok *(NR914 MDR non-rdm to VOT)*	VOT in practice *Preference for video observed treatment* *Incentive* *Study phone uses* *Internet/ apps e.g. Whatsapp, Facebook, streaming/downloading*

Data extract	Parent theme: *Sub theme:*
I'm gonna give you phone and you can call any time you like..you can call anyone you like….unlimited minutes…unlimited texts…unlimited internet so you can watch movies and everything so it..it's looks attractive, no? *(RDVOT078 VOT-VOT)* EG: …what else does he use the phone for? Translator: he uses it for internet to access his Facebook account..yes he thanks you very much..he wants to know whther you can give him some control over when he has exceeded his limit *(RDVOT510 VOT-VOT)* Last week I was in Hampstead hospital because of my liver a little bit damaged so that time I used whatsapp for a long amount of time because there was no TV or any kind of stuff..i used some sports video and watch movie and stuff like that so I use the whatsapp *(NR913 MDR non-rdm to VOT)* What else did you use the study phone for – (calls, texts, emails, apps, internet use)? JI: Yeah I did make phone calls…I did watch films on…it was…cos I couldn't go now where in them days so mostly I was sitting home…so like… sometimes... when I would [couldn't] come out the …downstairs to watch TV so I was just watching it…on the…phone…on the thing…so…it was good…cos it didn't cost you nothing anyway…end of the day the was doing a study to help other people….it's a very nice thing	

Data extract	**Parent theme:** ***Sub theme:***
(RDVOT115 VOT-DOT) NN: It's not about that..sometimes I'm bored at home..so just yeah. *(RDVOT193 VOT-VOT)* MK: Nowadays if I had my phone I would have preferred to film myself..you know..with my phone..but at the moment I don't have phone..so I have to get one. *(RDVOT367 VOT-VOT)*	
MA: Yes it really does *(RDVOT415 VOT-VOT)* I was showing off..this is a phone I was given from the hospital..everybody was like "really..really?!" [LAUGHTER] "so that means you are so special" and I said "oh yeah yeah…it's only given to special people" [LAUGHTER]…yeah..i really appreciate it..i'm very grateful..for the phone and for everything *(NR903 MDR non-rdm to VOT)*	VOT in practice *Preference for video observed treatment* *Incentive* *Phone as a motivator to take medication* *Feeling superior*

Data extract	**Parent theme:** ***Sub theme:***
if you have a chance and you can afford to give phone it will help patient to feel important…that's what I felt…I don't have anything…they're giving me phone…they're really caring about my situation and everything…so yeah…that's what I felt *(RDVOT078 VOT-VOT)*	
it's goning to save lives..it's a lifesaver to be honest…hmmm.. *(NR903 MDR non-rdm to VOT)* "we can give you a bit..just a little bit"..I think it's been helpful..it's been great..because I know I take it on Wednesday the following week..[HAND GENTLY THUMPING TABLE] it has to end and I have to go and pick it…it motivates me to come to the clinic rather than having a bunch of them lying there sometimes I don't take it..so..it's been great what they do with me..[LAUGHS] *(RDVOT046 VOT-VOT)*	VOT in practice *Preference for video observed treatment* *Incentive* *Phone as a motivator to take medication* *Life-saver*
and actually when I thought..the whole thing went through and they came back to me and you've been selected..and they'lll give you a phone..and I thought about it..and I thought [PACE QUICKENS, SMILES] ..ok I think this will be a very brilliant thing for me because doing it from home rather than..cos it was really hard for me going to..going to the pharmacy every morning..and breakfast.. *(RDVOT070 DOT-VOT)* The thing is I'll have to wake up..Then I'll have to go to the pharmacy without having any breakfast because I had to take the medication empty stomach..so I'll come back from the	VOT in practice *Preference for video-observed treatment* *Inconvenience travel to pharmacy*

Data extract	Parent theme: ***Sub theme:***
pharmacy I'll have to wait another…30 to 45 minutes till I can have something to eat..then I can go about my day.. *(RDVOT070 DOT-VOT)*	
if I forgot or something..you know sometime I have to go with my Mum sometime out so I'll take sometime medicine early..like 10..11 o'clock in the morning..and sometime I have to go to the hospital..like today I go to appointment 12 o'clock so I just came half-past one I just take the medicine *(NR913 MDR non-rdm to VOT)*	VOT in practice *Preference for video-observed treatment* *Managing unintentional non-adherence*
SH: vot, dot, self-adminstered. Which prefer I prefer to take it myself or keep a record by myself but because of the observation I would have preferred to be face-to-face SH: ASKS FOR CLARIFCATION: face to face on phone I prefer self-administered SH: why Because it's my own medication so it would be better if I take it myself SH: so given that how di you feel to be selected to take part in the VOT study to take your medication in that way? To be honest I KIND OF DID FOR THEIR OWN BENEFIT AND I thought why noT, it was because it for a study	VOT in practice *Preference for video-observed treatment* *Preference for self-administration*

Data extract	**Parent theme:** ***Sub theme:***
Sh: I see was that to be nice to the staff yes to be nice to the staff they said *(NR914 MDR non-rdm to VOT)*	
I was a bit worried when I was actualy taking the footange and submitting I knew who I was sendng it to but I was a bit uncomfortable *(NR914 MDR non-rdm to VOT)* SH: was it helpful to meeting person who viewed VOT clips? It's a good idea that I met the person I was sending the clips to.because I knew exactly who the footage was going to SH: Privacy I mentioned this initially..i didn't want it to be be public and the fact that they told me it would only go to that person and that it would be deleted eventually I was ok with that *(NR914 MDR non-rdm to VOT)* I didn't tell them that I got TB and whatever…I just say..”doctor want me to take medication with the camera”..that's it! *(RDVOT193 VOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Privacy*

Data extract	**Parent theme:** ***Sub theme:***
JN: Erm..no because I was told it was for a study..so I assume whoever's doing the study could watch them..erm I don't have a problem..I'm comfortable..I agreed to do the study..as long as whoever it watching them is going to help someone then I'm fine with it *(RDVOT046 VOT-VOT)* it would have made a difference because this is my personal phone..that I go with everywhere..my friends..so sometimes you can have friends who are nosey.. *(RDVOT046 VOT-VOT)* MK: No I'm not worried about.. *(RDVOT367 VOT-VOT)* MA: No..because I was told…it was encrypted as well…all the videos that are sent was encrypted.. *(RDVOT415 VOT-VOT)*	
Actually yes, when I was in my friend house..when they asking me "what are you doing?!" I was like.."I'm taking medication.." and they was "why you do camera..and stuff.." *(RDVOT193 VOT-VOT)* "how come you take medication with the camera on?"..they kept asking me.. *(RDVOT193 VOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Privacy* *Curiosity*

Data extract	**Parent theme:** ***Sub theme:***
why you have that kind of app on your phone..why you are using it for..you know that kind of.. *(RDVOT046 VOT-VOT)*	
Did you worry about privacy and who might see your video clips? JI: Not really…I don't think…cos at the end of the day I'm sick so what's wrong with me take my medication…no…I mean I didn't find nothing wrong with it….I mean how could you find [anything] wrong with it….maybe people feel….I didn't feel nothing wrong with it *(RDVOT115 VOT-DOT)* AI: To be honest there is nothing…what ever you people are doing is to help us…so I…why it wasn't anything private…I was taking medicine..and …if you are showing that video to someone it's for a good cause…that's what I believe *(RDVOT078 VOT-VOT)* JH: Were you worried at all about privacy..apart from who might look at the films..apart from who you're sending the clips to JN: Erm..no because I was told it was for a study..so I assume whoever's doing the study could watch them..erm I don't have a problem..I'm comfortable..I agreed to do the study..as long as whoever it watching them is going to help someone then I'm fine with it *(RDVOT046 VOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Privacy* *Indifferent*

Data extract	**Parent theme:** ***Sub theme:***
she wasn't going to believe me…she said "no you have to show me" I guess…I know… she was doing her job so I was like ….no I took it so one day I just put it…there was like a box and I couldn't find it…and what I wanted to do…I used to take medicine before I go to sleep so it wouldn't affect me that much I would just go to sleep for long so I just took it in my hand I just had it ...she said "no don't do this" I said "why, don't you trust me"… she said " no I do but we need to see what kind of medicine you are taking" so this is something…it's annoying but it's helpful [laughs quietly] *(RDVOT078 VOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Privacy* *Prove legitimacy*
here I think it's more private..and I do it in my own personal time. *(RDVOT070 DOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Privacy* *Uphold privacy*
FW: And how did you feel. Tell me more a little about how you felt? About being part to be selected to be part of the JI: I mean…I wasn't like...some people are shy….they don't wanna be on the thingy…people knowing their business…but if they…when they explained at the beginning…like it was helping other people… *(RDVOT115 DOT-VOT)*	

Data extract	**Parent theme:** ***Sub theme:***
MA: Erm..basically I wanted to choose..this one..because..I knew my mum wouldn't want people coming to the house.. *(RDVOT415 VOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Privacy* *Protect family's confidentiality*
AA: Erm to be honest..I was actually very focused about my treatment because they explained to me how serious it was..so at that time I took some time off from work and I actually focused on my treatment because..when I actually got diagnosed it was at a very bad stage..so I thought you know what I'm gonna worry about my health than anything else *(RDVOT070 DOT-VOT)*	VOT in practice *Preference for video-observed treatment* Rationale switch from DOT to VOT Adherence – "agency-centric"
I'm not disrespecting the doctor but they're the people who are the decision-maker if there is any chance for the patient to help them we should do it. *(RDVOT078 VOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Re-gain autonomy*
NN: Well..I was like surprised I never heard that before..so that it [SMILING] *(RDVOT193 VOT-VOT)* Happy..very happy.. *(RDVOT046 VOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Reaction at being randomised to VOT*

Data extract	**Parent theme:** ***Sub theme:***
MK: err..I feel glad you know..I was happy.. *(RDVOT367 VOT-VOT)*	
I feel a little bit confident *(NR913 MDR non-rdm to VOT)*	VOT in practice *Preference for video-observed treatment* *Reaction at being randomised to VOT* *Confident*
How did you feel when you were selected to be in the VOT arm of the study? FW: And how did you feel. Tell me more a little about how you felt? About being part to be selected to be part of the JI: I mean…I wasn't like...some people are shy….they don't wanna be on the thingy…people knowing their business…but if they…when they explained at the beginning…like it was helping other people…like..it was more a study fing to see how it works for other people…I didn't mind…because if it helps…because that's how you learn…anyway…innit…we learn things from the past and then we learn things to go in the future..innit..I mean if they didn't design it how would the next people know…so in a way I didn't mind…I mean..I never mind doing study fings…if it helps someone in the future….I mean…that's the way they make the medications anyway. *(RDVOT115 VOT-DOT)*	VOT in practice *Preference for video-observed treatment* *Reaction at being randomised to VOT* *Contribution to science; civic duty*

Data extract	**Parent theme:** ***Sub theme:***
I felt like if there is a new discovery going on… if there's a new experiment if we don't help to participate there won't be anyway to solve these kind of issues *(RDVOT078 VOT-VOT)* and I realised if I do that maybe because of me maybe ten people will join…and there is some positive feedback …and that's how technology goes faster it's a good thing *(RDVOT078 VOT-VOT)*	
we know we don't have enough doctors and they are trying really hard *(RDVOT078 VOT-VOT)*	VOT in practice *Preference for video-observed treatment* *Reaction at being randomised to VOT* *Contribution to science; civic duty* *Resource scarcity*
SM: Yes..it was fine..hmm *(NR903 MDR non-rdm to VOT)*	VOT in practice *Sticking out tongue*

Data extract	Parent theme: *Sub theme:*
SH: And you were asked to show us that your mouth was empty after taking the pills how did you feel about that SP: yeah I feel a little bit down because there was a lot of medication..the medication smell it always stay in my mouth for another twenty minute half an hour so if I feel a little bit bad I chew some chewing gum to refresh my mouth *(NR913 MDR non-rdm to VOT)* I feel normal..I don't make any..there's nothing about that..I feel normal *(NR913 MDR non-rdm to VOT)* FW: so tell me more about what you feel about it? JI: To tell you the truth…one time…I was in a prison…I'm not gonna lie to you…so that happened to me in a prison….so they told me when you take the medication…[they said] open your mouth…so didn't I…I got used to it before….that's why I didn't felt nothing about that….it's a good idea…that's the whole idea…it's about the phone thing or the nurse coming…because that…to see you taking your medication….so other[wise]…if you just gonna…take your medication…and just swallow don't swallow it's not worth taking your medication is it? *(RDVOT115 VOT-DOT)* AI: [pauses for 2-3 seconds] First it was a bit uncomfortable it's like you're seeing…[mumbles; gestures]….keeping your tongue out..but they wanted to make sure that I'm taking the medicine *(RDVOT078 VOT-VOT)*	

Data extract	Parent theme: *Sub theme:*
like yeah…I did it..it was a bit uncomfortable for…at the beginning…but it was a bit fun…[laughs] you see I was like “AAAAAHHHH!!!” you see [laughter] *(RDVOT078 VOT-VOT)* NN: it’s ok..because you know of course like after taking video I have to everything like showing..you know that you’re taking medication.. *(RDVOT193 VOT-VOT)* NN: [INTERUPTS] Not at all..not at all..I’m happy with that because..we showing everything you know..but “you take medication?”..”Yes”..”Ah-haaa” [laughter] *(RDVOT193 VOT-VOT)* I could either use the small pot..which will show exactly what was going on in the pot..or I could use my tongue..put out my tongue put the tablets on..so..I..I..I chose to use the pot..most of the time I used the pot..there were some times I did have my pot so I have to use my tongue..[SPEAKING RYTHMICALLY] ..but it was ok..as I went on doing it..I started feeling comfortable with it..yeah..so.. *(RDVOT046 VOT-VOT)* MA: I felt it was fine..because I have swallowed the medication *(RDVOT415 VOT-VOT)*	

Data extract	**Parent theme:** ***Sub theme:***
You were asked to show us that your mouth was empty after taking pills – how did you feel about that? JI: I mean…it was a little bit like funny at the moment …and I could like understand…because what they was….one day he was explaining me was that some of the people put the tablets under their tongue and then they take them out later on…so in a way it's bad…cos …that way it's like not seeing you swallow it…that's the whole idea… is like the nurse suppose to come look at you taking your tablets…so you take your medication…so that's what I think otherwise you could've just taken them out. *(RDVOT115 VOT-DOT)* sometimes I realised I'm putting myself into other peoples……maybe some people…they swallow it they just keep it over there …they just..and throw it away [gestures spit into hand and throw away]…because I watch a lot of movies these things happens….and that's how you learn from things… *(RDVOT078 VOT-VOT)*	VOT in practice *Sticking out tongue* *Awareness of intentional non-adherence*
plus the programme helped me in that sense because if I had to take my medication at a certain time everyday..so sometimes I would forget..they actually reminded me through text..the support worker would actually phone me and say..ahh you haven't taken your dose or..you haven't recorded [LAUGHS] I remember a couple of times I forgot my dose or I forgot to record it so the I would text her..	VOT in practice *VOT serving as a reminder / prompt*

Data extract	Parent theme: *Sub theme:*
(RDVOT070 DOT-VOT) For me.. I found that very helpful to me and very supportive cos erm..I knew I had to take the medication..and it felt like I was gaining extra support..encouragement and help..just..you know what I mean..it's just..I knew I had to take my medication everyday and it felt like..at least they..some of those people they understand my situation..cos I would get to talk to them as well..and tell them look if there's any issues I'll be able to erm..acknowledge my issues and knowledge and problems..then work around it..I found it to be very useful..and supportive……they weren't very intrusive or anything like that…so the processwas very quick all I had to do was erm wake up in the morning…give them my patient number and record the patient video and send it..that's all. *(RDVOT070 DOT-VOT)* plus you get more..reminders if you forget..so all in all I think it was good for me *(RDVOT070 DOT-VOT)* yeah sometime before like..when I first take medication and then I fall asleep and then I remember..and I say "Oh medication!" and then I say "not yet" I say "ok" and I have to wake up take medication and then do video sometimes before..but now everytime I did take medication now that's it..it's very easy..but ..it's easy to take medication *(RDVOT193 VOT-VOT)* MA: Not really..each time I look at the phone I just have to remember to take..[sic] my medicines *(RDVOT415 VOT-VOT)*	

Data extract	**Parent theme:** ***Sub theme:***
JN: it is helpful because it make me feel involved..you know..it makes me feel like..you know I have to do this..it's not the same waking up in the morning and just putting your medication there and just take it..you know..so with the video thing..it makes me feel erm..it makes me feel involved in a way..I'm involved in this..i have to do this..and it make me feel good about taking my medication.. *(RDVOT046 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Feeling involved*
JN: Ermm I think it's good I met the person and she told me she would be one of THE people who would be viewing the videos..and it made me comfortable..she made me comfortable when she was showing me what to do. *(RDVOT046 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Comfort*
LP: Was it helpful to meet the person who was looking at your clips..like meeting Gloria..Sara? SM: Yeah it was..it was..[LAUGHTER] behind the scene..it was very helpful honestly..it builds you confidence and you feel loved as well when you meet people.. *(NR903 MDR non-rdm to VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Confidence-building*

Data extract	**Parent theme:** ***Sub theme:***
I think it was very helpful..me as a person..to at least know the person who is going to be watching me [VOICE BECOMES SLIGHTLY HIGH-PITCHED] ..actually we had a connection when she showed me whatever was going on..so it was good..it was good that I met her and that she would be part of some of the people who was going to be watching the videos..so yeah *(RDVOT046 VOT-VOT)* *I actually know her..I've met her..so there's a difference..it makes a big difference..* *(RDVOT046 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Familiarity*
AI: Because…you don't know…sometime s I felt like…is she actually doing it or is it the computer? That's human nature. Cos when I was texting her the replay was like "thank you for your message" every time and then I realised it's not an automatic message…message comes every time you send a text and later she replied "ok I will discuss with the doctors and I'll let you know" so I spoke to her on the phone…so it wasn't the robot *(RDVOT078 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Familiarity* *Trust* *Automation of VOT*
Because whenever I meet them they ask me they're always sending me the..whenever I record the clips..they always text back..so whenever I do the mistake they will explain me why did you take..this is the medicine..you mistake this and that..this can of messages they give to me and I was accept and I was answer back *(NR913 MDR non-rdm to VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Feedback on clips*

Data extract	Parent theme: ***Sub theme:***
Was it helpful to meet the person who viewed your VOT clips? FW: changed question to: “did you ever meet the person you were sending your clips to?” JI: Yes. The first time he did came, yes. The first time I got the phone he said…made me sign a few papers and things…sat down with me for an hour or so…so yeah…so then he was phoning every two...three days, like. FW: and was that helpful for you? JI: It was nice to talk to… and they was like happy with your clips…they was…sometimes it was dark and so they would like tell you today your clip didn’t come clear because of the light everything…so we couldn’t see the tablets…or blah blah…if there was a problem…he was telling me…so I just trying to sort it out….so it was nice just to know someone care… *(RDVOT115 VOT-DOT)*	
AA: For me.. I found that very helpful to me and very supportive cos erm..I knew I had to take the medication..and it felt like I was gaining extra support..encouragement and help..just..you know what I mean..it’s just..I knew I had to take my medication everyday and it felt like..at least they..some of those people they understand my situation..cos I would get to talk to them as well..and tell them look if there’s any issues I’ll be able to erm..acknowledge my issues and knowledge and problems..then work around it..I found it to be very useful..and supportive……they weren’t very intrusive or anything like that *(RDVOT070 DOT-VOT)* SM: Oh yeah yeah..everybody was very caring to be honest..right from admission everybody was very supportive and very caring…hmm…very very caring	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Feeling supported*

Data extract	Parent theme: *Sub theme:*
(NR903 MDR non-rdm to VOT) Yeah really thankful to you guys and the nurses at the hospital..because of you guys I'm feeling much better for that..If I'm really painful and all that because of lots of medications but you guys help..lots of support..I'm feeling much better now.. *(NR913 MDR non-rdm to VOT)* What did you feel about the support you were given to take your treatment? JI: I was happy with it….I was happy with it…I mean that was the best thing they could do…I mean there was no complain about it. FW: Tell me a bit more about the support. What kind of support? JI: Only the support…it's like they were checking me everyday. When I send the clip they were phoning me back…you know if everything w as alright…that kind of things…you know they was just talking to me….so it was like…kind of therapy…sometimes you need to talk to somebody…so….that's all I needed…there was nothing else I needed…yeah because like….I was happy…but it was all this medication….I can't see any complaints about this….I mean if there was any time I would help I would have….there's no problem with that kind of thing *(RDVOT115 VOT-DOT)* I always connected with Gloria and she explained to me how why it's important and why I shouldn't miss it….I guess I've been a very important student. *(RDVOT078 VOT-VOT)*	

Data extract	**Parent theme:** ***Sub theme:***
JN: I feel good about it..because I know sometimes I miss but it feels good sometimes when someone actually asks you: “how come we didn’t see your video two days ago?” “are you ok?” “we haven’t received your video”..it feels good..at least someone is there..someone care to know we haven’t seen your videos..it feels good.. *(RDVOT046 VOT-VOT)* MK: Yeah.. with the help you give me..with the nurse in the hospital..you and your colleague you look after me..so I’m very glad about it *(RDVOT367 VOT-VOT)* MK: Ahh..you know I thank you guys and the hospital..tehy’re doing their best to help me out because of my sickness..and I’m very much happy for you to look after me..and thanks you very much for that.. *(RDVOT367 VOT-VOT)*	
SH: live vido conference To be honest it doesn’t make much difference because the peurpose forme to submit and other person to receive but would have preferred if it was live but as long as they received the clip it doesn’t make a difference *(NR914 MDR non-rdm to VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Live video-conferencing*

Data extract	Parent theme: ***Sub theme:***
NN: It's up to you actually..because..it's not..I'm just taking medication so..what is the best just taking video this one or taking face-to-face this one…just like err. I wanna say "thank you for the video call it was lovely" so make it exciting for when I do video *(RDVOT193 VOT-VOT)*	
But it's better if you record it and she can send it…like she can have freedom to watch it later and observe it and I can have the freedom to do when ever I like. *(RDVOT078 VOT-VOT)* It's up to you actually..because..it's not..I'm just taking medication so..what is the best just taking video this one or taking face-to-face this one *(RDVOT193 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Live video-conferencing* *Choice between asynchronous and synchronous*
JH: Ok..so you do your filming…you send the clips and you get a text to say thank you..or is everting ok..we've not seen a clip..any other extras..because the app just let's you do the film and send the film..but if there had been some form of..video conference..some kind of Skype element would've allowed you to have real-time conversations with the observer..would that have been helpful or.. JN: Ermm. I think so..I think if there was a way if I could maybe talk to you on the day..you know I've missed some recordings..if they had that problem of video chatting probably..it would like oh..I'm talking to Joe face-to-face ..because I've met you before..I knoew how it felt..so it would be easier for me to talk to you rather than watching..or texting you..cos sometimes I would get a	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Live video-conferencing* *Communicate missed doses*

Data extract	**Parent theme:** ***Sub theme:***
text and I won't reply yet..so I think if there was a video chatting..an instant straightaway thing it would be more helpful..yeah.. *(RDVOT046 VOT-VOT)*	
MA: Maybe..I'm not sure about that..it would be quite useful..but it would be more time-consuming for you though..you would have to watch..for example you would have face-to-face communication after taking it.. *(RDVOT415 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Live video-conferencing* *Empathy for services*
For me it would be difficult because as I say because of the other issues I mentioned you before about eye contact. *(RDVOT078 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Live video-conferencing* *Intimidation*

Data extract	Parent theme: ***Sub theme:***
I don't mind to do that..but there is time..before I told you there's no specific time when I take the medicine in the morning or afternoon..even at night sometime I take video at ten..and then I take half eleven..there's no time *(NR913 MDR non-rdm to VOT)* Would you have found it useful to be able to have a live videoconference with the person who viewed your video clips? JI: No…then…it wouldn't have be….sometime it would happen…sometime I take my medication…late…but then they got the time nine to five…whatever…but it you do it like you stuck to the time… it's twelve o'clock you have to go take your medication….sometime you want to take it late…because of the side effects…them fings…I used to take it late…because the nurse told me…take it late…because you get pain them fings in the night time….so like would be like…urghhh…so… life would be like I have to stick with their time table…so like…I need more freedom so I can take it before twelve o'clock in the night in the night so I can take it *(RDVOT115 VOT-DOT)* But I don't think with other people….that it don't save the time you are looking for…if you have to do live…she'll just…she have to…every single time she has to be with you…like you know…she has to say ok whatever…you do it… she has to…she can't…there is no timetable…I can do anytime I like…there is a freedom. But if you do that there has to be a timescale…and that's a problem…cos you have to fit two people at the same time…maybe I'm busy with something now and she's free now and she wants to come "ok, let's do the video now and take the medicine and I'd be like no hang on I'm busy now I'm watching movies now *(RDVOT078 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Live video-conferencing* *Limit flexibility*

Data extract	**Parent theme:** ***Sub theme:***
if they had that problem of video chatting probably..it would like oh..I'm talking to Joe face-to-face ..because I've met you before..I knoew how it felt..so it would be easier for me to talk to you rather than watching *(RDVOT046 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Live video-conferencing* *Rapport established at treatment initiation*
SM: Uh-hm Uh-hm..oh yes yes yes..just to communicate on how we are feeling ..because at times I really felt rough..with the treatment you know when I was getting the injections..and whatever..oh it was horrible..yeah..the side effects *(NR903 MDR non-rdm to VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Relationship with VOT observer* *Live video-conferencing* *Reporting side effects*
AA: I fixed in my times…cos erm I think it was easier for me to do that..first thing in the morning and then just get it out of the way…rather than..cos the the thing is they expected me to take the medication on an empty stomach so that woukd have been the best thing for me to wake up and take the medication and lie down for 30minutes…40 minutes until the medication has been absorbed..then I can go and have my breakfast.. *(RDVOT070 DOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Systemisation*

Data extract	**Parent theme:** ***Sub theme:***
NN: The preparation only like 5 minutes I have to like take banana..I have to take water..i have to prepare the video [speaking rhythmically] I have to make sure the video is on correct..make sure everything is see..5 minutes.. *(RDVOT193 VOT-VOT)* SH: But when you were first given the phone how did you feel about filming yourself and doing VOT? SP: Yeah it's one year ago I just started that VOT with you and I was a little surprised because I never had this kind of video before so then I became used to it..so..it's better..I just have to send one time *(NR913 MDR non-rdm to VOT)*	
I have to prepapre myself first..I have to take banana [LAUGHS] and then I have to click the video *(RDVOT193 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Systemisation* *Pre-planning*
SH: Do you think that VOT helped you to take your medicines regularly? SP: Yes I do yeah SH: In what way?	VOT in practice *VOT serving as a reminder / prompt*

Data extract	Parent theme: ***Sub theme:***
SP: This is not priority to do that video..my doctor..nurses they satisfy so when you taking the video taking the medicine.. regularly..[that's why they are with you?] *(NR913 MDR non-rdm to VOT)* you know doctor is with me all the time… I went to Manchester for example I am having problem…I can show to the doctor what kind of situation I'm facing through this video which is really helpful…I was taking the medicine I was showing her she advised me how to deal with it what to do so doctor is with me all the time so this is something really good.. *(RDVOT078 VOT-VOT)* It doesn't have to go to doctor every single day if you have a chance to do that every day. He's still monitoring…she's still monitoring…everything is under control…it's our part to participate to solve the problem so I guess I'm trying to do my part of course they are not ignoring me they are monitoring did I take the medicine or not …it's time-saving and she can handle a hundred patients at the same time…so I think it's a good thing…I'm sorry *(RDVOT078 VOT-VOT)*	*Virtual doctor*
I believe they should carry on the programme as a standard treatment plan for people..it would make things a lot more easier for people.. *(RDVOT070 DOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *Virtual doctor* *VOT as a service*

Data extract	Parent theme: *Sub theme:*
it's really sad that whatever you have been doing is coming to an end..but I hope and I pray that you get the funds..to help others who are in the situation as mine..and I think it will help to save a lot of lives *(NR903 MDR non-rdm VOT)*	
SH: Ok..how easy or difficult did you find it to take your medicines on time each day regularly? SP: what do you mean? SH: You've taken medicine for about a year? How have you found it..has it been easy..difficult to take regularly for such a long time? SP: Yeah I do I feel a little bit harder..because I already got every Monday and Wednesday I got appointment at Charing Cross so they suggest all that things..even she always meet me at when I was admitted at Hammersmith hospital and..he tried to explain me all that things..how to take the medicine regularly because I have MDR-TB so make sure you have to take regularly and keep sending it with me all day and I will show you how to take the medicine.. SH: and how did that feel? SP: Oooh I'm feeling..I can't explain but it's ok SH: Do you find it easy or difficult? SP: A little bit difficult but eh..I try my best SH: Do you know what is difficult about it? SP: Not much *(NR913 MDR non-rdm to VOT)*	VOT in practice *VOT serving as a reminder / prompt* *VOT and adherence as expectation*

Data extract	Parent theme: ***Sub theme:***
LP: How easy or difficult was it for you to take meds everyday..regularly more than once a day? SM: [3-4 second pause] [long intake of breath] it wasn't easy..the fact that you are taking these drugs plus it was like two years..and I was thinking like "Oh my God" [LAUGHTER] for two years..am I going to survive? You know I didn't have that hope that I would be better because of the nature of the condition..I just thought maybe…you know..I don't know…I just didn't think it was going to end [hmmm] *(NR903 MDR non-rdm to VOT)* …it's like a prison inside..but it's fun *(RDVOT078 VOT-VOT)*	VOT in practice *VOT serving as a reminder / prompt* *VOT and adherence as expectation* *Entrapment*

6.5 Moldova VOT trial qualitative interview key quotes and themes

VOT		
Theme	**Quotes**	**Sub-themes**
Observation Necessity	“I know there are such people who get tired of taking the pills, sometimes they forget to take them and skip the daily doses. They have to take them under observation” “Maybe I wouldn’t have been so disciplined” #MB2012 (randomised VOT)	
	“The individual who wants to get treated should receive treatment even without a tablet. I would have followed the treatment even without a table, it’s for myself, it’s my health” #IB1011 (randomised VOT)	
	“I could have done it even without video, since my health status matters for me” #MG1907 (randomised VOT)	
	“I did not need monitoring. I knew that health is important” “I want to thank the program for its help, it guarded me. There were times when I called after work hours" #AZ0206 (randomised VOT)	

VOT		
Theme	**Quotes**	**Sub-themes**
	“I think this is necessary only for those who don’t follow the treatment, for them to be under special control, those who do not want to be treated” #EZ0808 (randomised VOT)	
	“I think it’s not necessary. Of course, you cannot trust everyone, there are different people” #AO2402 (randomised VOT)	
	“In some way, I agree, since there are many people who throw away their pills, they do not take them if these are given to take home” “I am too young to stay home and take the pills, sometimes I forget to take them. This way I walk daily and it is normal for me” #AS2505 (randomised as VOT, later passed to DOT)	
Motivation Reminder / Habit / Responsibility	“Yes, because I know I have to take them […] I have to record myself. I think this thing motivated me” “this motivated me because i was monitored every day” #MB2012 (randomised VOT)	

VOT		
Theme	**Quotes**	**Sub-themes**
	“VOT is much better, I woke up in the morning and the first thing I would do was to use the tablet and take the pills” “you wake up in the morning, like in the army, you know you should take the pills and you’re free until tomorrow morning” #IB1011 (randomised VOT)	
	“When there is the video, it is was if there is more responsibility. I need to film the video, otherwise they would ask why I had not done it” #AB2804 (randomised VOT)	#clinical activity
	"However, it is good not to miss the moment, it became a reflex” #AZ0206 (randomised VOT)	
	“Every person has the tendency to disregard a certain schedule, and specifically the fact that doctors were present when medicine was administered helped me get treatment and increased my responsibility” #MP0705 (randomised VOT, later passed to DOT)	
Proof / Accountability	“I have to show the fact that I administrate the pills” #MB2012 (randomised VOT)	

VOT		
Theme	**Quotes**	**Sub-themes**
	“So that they are convinced he/she follows the required treatment” #AB2804 (randomised VOT)	
Time / Travel Autonomy	“I was coming to the polyclinic every day to administrate the pills and this used to be much more difficult […] Instead of spending time and coming to the polyclinic every day, I could do something else” “I save a lot of time, I don’t have to come here (in the polyclinic) #MB2012 (randomised VOT)	
	“You should go with the public transport, stay in line at the polyclinic and waste plenty of time” #IB1011 (randomised VOT)	
	“Coming in every day is very difficult” #RR0908 (randomised VOT)	
	“going to the polyclinic every day is inconvenient, it distracts me from house affairs” with VOT “I would have more free time and do other things” #MJ2911 (randomised VOT)	

VOT		
Theme	**Quotes**	**Sub-themes**
	“I am at work and I need to go to the polyclinic every other day or so? I do not know, you need to stay there, and there is a line there” #AB2804 (randomised VOT)	
	“At the polyclinic it is not very good, people have work and other matters to take care of. When you go to the polyclinic you spend around two hours, you stay in line, waste some time, that is the situation” #AB2804 (randomised VOT)	
	“It helps a lot. Especially if patient works. He/she feels comfortable. Every day travelling to the polyclinic is expensive. It takes a lot of time” #IM0301 (randomised VOT)	
	“IT is good that you have the ability to personally choose the time, at the polyclinic the time is limited, meaning 8 hours, while in VOT you have a 12-hour time frame” “The most important thing was that I did not have to go to the polyclinic every day” Saved time? “Yes, including financially, I did not have transport expenses”	

VOT		
Theme	**Quotes**	**Sub-themes**
	#AZ0206 (randomised VOT)	
	“I was shocked. I was really happy of not having to go to the polyclinic” #EZ0808 (randomised VOT)	
	“if I was working, and if it was hard for me to go to the polyclinic. bus since I didn’t need such facilities, that was another reason I refused” “The advantage [of DOT] is that the person leaves home, communicates with people, if the’re not positive they don’t get a depression, for six months there is an imbalance to the day to day life. I think people should move, not only stay at home, otherwise they get inhibited, nobody sees me. #MP0705 (randomised VOT, later passed to DOT)	

VOT		
Theme	**Quotes**	**Sub-themes**
	“I think that it is better to receive treatment at home. It is hard going to the polyclinic everyday if there is bad weather” #VB0801 (randomised VOT, later passed to DOT)	
Trust Open Mouth / Show tongue	“I’m 65 years old and I don’t like when someone thinks I could not take the pills” “I was placing the pill in my mouth and taking it with water” Where you comfortable doing that? “Not so much, that at my age she wouldn’t trust me” #IB1011 (randomised VOT)	
	“Why would it bother me, if that is what is needed” #MG1907 (randomised VOT)	
	“I did not give it much thought. I wanted to get better soon” #MJ2911 (randomised VOT)	
	“It did not bother me, but it was as if you were compelled to get treatment?” #AB2804 (randomised VOT)	
	“I would have felt uncomfortable. This is distrust.”	

VOT		
Theme	**Quotes**	**Sub-themes**
	#VB0801 (randomised VOT, later passed to DOT)	
Asynchronous / Sunchronous	“the fact that someone watches you taking the pills live would be stressful for some people […] It’s not very pleasant when seeing the person” #MB2012 (randomised VOT)	#stressful
	“If you take the pill in front of someone, you feel discomfort, but when you film the video, you simply know that there is someone there, and that is it, it is convenient” MJ2911 (randomised VOT)	#discomfort
	“She should have seen what I was doing, And I would have seen that she received my video. And so I don’t know for sure” #IM0301 (randomised VOT)	
	“It is better this way. I think it makes you uncomfortable, since the stress of illness is hight already, there is no need add to add pressure of someone watching you” #AZ0206 (randomised VOT)	
	“I am more conservative, I do not like this”	

VOT		
Theme	**Quotes**	**Sub-themes**
	#VB0801 (randomised VOT, later passed to DOT)	
Privacy	“I did not even think about it” #MJ2911 (randomised VOT)	
	“I always trust medicine” #IM0301 (randomised VOT)	
	“You know. Every normal person has an instinct of self-preservation and I was concerned” “After all, I want no one to see” EZ0808 (randomised VOT)	
	“Life is long and I don’t trust the databases, even if these stay sealed, I don’t believe it, sometime they might go public” “The internet is big, technologies are thinly developed and rather than information I don’t need surfacing after a while, it is better I am left only with the doctor and the nurse, so that other people don’t know who I am” #MP0705 (randomised VOT, later passed to DOT)	

VOT		
Theme	**Quotes**	**Sub-themes**
	“I would have felt uncomfortable if they leaned that, not even in our home everyone knows. […] I am ashamed” #VB0801 (randomised VOT, later passed to DOT)	
	“On TV they often show information on tuberculosis and I was afraid that they might show me as an example” “I do not trust data privacy […] Maybe if it were possible that people do not show their face” “I am young, what do the older ones have to lose? For me, it is only my family who knows, and if anybody finds out they will point at me, I will not be able to leave my home. Only to go abroad” #AS2505 (randomised VOT, later passed to DOT)	
Dedicated Support	“It is the same as if a mother looks after her child […] it is different when there is someone else looking after you and wanting to help you” #AB2804 (randomised VOT)	
Technology	“It wasn’t difficult for me because I am used to such technics” #MB2012 (randomised VOT)	

VOT		
Theme	**Quotes**	**Sub-themes**
	“My vision is poor, I could press the wrong button and freeze the tablet. That is why I will be going to the polyclinic. It is uncomfortable, but there is no way out of this situation” “It is me who is not interested. I do not like this technology" #VB0801 (randomised VOT, later passed to DOT)	
Device Responsibility	“The liability regarding the monitor, there is a small child in a house who could deteriorate the tablet, then I would be forced to pay or go to court” “I am afraid to risk, due to the device which does not belong to me” #TC1001 (randomised DOT)	
Devices	“I’m a person who fears germs […] the tablets are not disinfected, I don’t know who had it […] Thus, rather than getting treated for a disease and catching another, I better exclude this” #MP0705 (randomised VOT, later passed to DOT)	

DOT		
THEMES	**QUOTES**	**VARIABLES AFFECTED**
Access to Doctor	“You can constantly meet with the doctor who supervises you” #AZ0206	
	“I mean if you have any complications, you can ask for help of a medical worker” #EC0706 (randomised DOT)	
	“The only plus is that they see you every day” #VP0202 (randomised DOT)	
Observation Necessity	“I would still take pills, even if I am at home” #IP2905 (randomised DOT)	
	“I don’t agree. […] I live far away from the polyclinic, it is a little inconvenient. If a person is responsible and mature, he/she can follow treatment without monitoring” #IS1608 (randomised DOT)	
	“It is better to be monitored by the doctor” #TC1001 (randomised DOT)	

DOT		
THEMES	**QUOTES**	**VARIABLES AFFECTED**
	“It is necessary for those who do not control their way of life. For disciplined people, this is not necessary” #CB0401 (randomised DOT)	
	“I feel good and I see no need to come every day to the medical worker” #EC0706 (randomised DOT)	
	“I think is welcome since this disease is contagious, and because some people are not getting treatment they infect others around them” #MP0705 (randomised VOT, later passed to DOT)	
	“I don't consider it necessary” “It is difficult to report to someone for me. I follow the treatment for myself, rather than for someone” #VP0202 (randomised DOT)	

DOT		
THEMES	**QUOTES**	**VARIABLES AFFECTED**
Raining / Snowing / Ice Weather and Environment	"Maybe more [time] when it was raining or snowing" "One day […] it was icy outside and I was feeling bad, feeling afraid to get on the road" "I was concerned about breaking a hand or a leg" #TC1001 (randomised DOT)	
	"On the dat when there was a lot of snow, as there was neither transport means […] then I didn't drink the pills" #VB1701	
	"It would not be necessary to go in any weather to the polyclinic. Especially in rainy and snowy weather" #CB0401 (randomised DOT)	
	"In the winter, I was too in such situations when it was cold and windy. and it was hard to go out" #VP0202 (randomised DOT)	

DOT		
THEMES	**QUOTES**	**VARIABLES AFFECTED**
	“It is slippery now and they could fall, not go through the cold” #AS2505 (randomised VOT, later passed to DOT)	
Proof	“It is good that they could see me taking the pills, so that they would not think that I was staying at home and not drinking the pills, but throwing them” #TC1001 (randomised DOT)	
Clinic opening times Taking home medicines	went to the clinic every day? “Yes, except Saturday and Sundays” #TC1001 (randomised DOT)	
	“Only on Friday, I was taking medicine for the weekend” #VI2703 (randomised DOT)	
	“Yes, one time when I went to the village and took pills for next 4 days” #IS1608	

DOT		
THEMES	**QUOTES**	**VARIABLES AFFECTED**
	“I take them home as well, if I didn’t eat. If I ate, I drink them at the polyclinic” taken home pills up to 5 days #EC0706 (randomised DOT)	
	was treatment interrupted? “No, never” “They give them on hand if days off or holidays coincide” #CB0401 (randomised DOT)	
	“Yes. it happened once. I had to leave for a week. Everyone has such a situation. Because you follow the treatment for a fairly long period” #VP0202 (randomised DOT)	
	“I wrote a request and they were issued to me” #IM0909 (randomised DOT)	
Money for Transport	“Sometimes I would have money issue” #TC1001 (randomised DOT)	

DOT		
THEMES	**QUOTES**	**VARIABLES AFFECTED**
	“I incur big transport expenses” #VB1701 (randomised DOT)	

References

(CDC), Centres for Disease Control and Prevention. 'Adverse events during treatment', CDC, Accessed 04/02/2023.

Abarca Tomás, Bruno, Christopher Pell, Aurora Bueno Cavanillas, José Guillén Solvas, Robert Pool, and María Roura. 2013. 'Tuberculosis in Migrant Populations. A Systematic Review of the Qualitative Literature', *PLOS ONE*, 8: e82440.

Abubakar, I., R. W. Aldridge, D. Devakumar, M. Orcutt, R. Burns, M. L. Barreto, P. Dhavan, F. M. Fouad, N. Groce, Y. Guo, S. Hargreaves, M. Knipper, J. J. Miranda, N. Madise, B. Kumar, D. Mosca, T. McGovern, L. Rubenstein, P. Sammonds, S. M. Sawyer, K. Sheikh, S. Tollman, P. Spiegel, and C. Zimmerman. 2018. 'The UCL-Lancet Commission on Migration and Health: the health of a world on the move', *Lancet*, 392: 2606-54.

Adje, Y. H., K. M. Brooks, J. R. Castillo-Mancilla, D. L. Wyles, P. L. Anderson, and J. J. Kiser. 2022. 'The use of technology-based adherence monitoring in the treatment of hepatitis C virus', *Ther Adv Infect Dis*, 9: 20499361221095664.

Alipanah, N., L. Jarlsberg, C. Miller, N. N. Linh, D. Falzon, E. Jaramillo, and P. Nahid. 2018. 'Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies', *PLoS Med*, 15: e1002595.

Anderson, C., S. R. Anderson, H. Maguire, A. C. Hayward, and A. Story. 2016. 'Tuberculosis in London: the convergence of clinical and social complexity', *Eur Respir J*, 48: 1233-36.

Arakelyan, S., A. S. Karat, A. S. K. Jones, N. Vidal, H. R. Stagg, M. Darvell, R. Horne, M. C. I. Lipman, and K. Kielmann. 2021. 'Relational Dynamics of Treatment Behavior Among Individuals with Tuberculosis in High-Income Countries: A Scoping Review', *Patient Prefer Adherence*, 15: 2137-54.

ASCENT. 'The Unitaid-funded ASCENT project aims to help patients succeed in TB treatment using digital adherence technology', Accessed 16 February 2023.

Atkins, L., J. Francis, R. Islam, D. O'Connor, A. Patey, N. Ivers, R. Foy, E. M. Duncan, H. Colquhoun, J. M. Grimshaw, R. Lawton, and S. Michie. 2017. 'A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems', *Implement Sci*, 12: 77.

Badzi, C. 2020. 'Using Mobile Technology for Monitoring Tuberculosis Treatment Among Women with Tuberculosis in Greater Accra Region, Ghana', Accessed 16 June http://ugspace.ug.edu.gh/handle/123456789/36953.

Bayer, R., and D. Wilkinson. 1995. 'Directly observed therapy for tuberculosis: history of an idea', *Lancet*, 345: 1545-8.

Belknap, Robert, Steve Weis, Andrew Brookens, Kit Yee Au-Yeung, Greg Moon, Lorenzo DiCarlo, and Randall Reves. 2013. 'Feasibility of an Ingestible Sensor-Based System for Monitoring Adherence to Tuberculosis Therapy', *PLOS ONE*, 8: e53373.

Benbaba, Stella, Petros Isaakidis, Mrinalini Das, Sonakshi Jadhav, Tony Reid, and Jennifer Furin. 2016. 'Direct Observation (DO) for Drug-Resistant Tuberculosis: Do We Really DO?', *PLOS ONE*, 10: e0144936.

Bender, B. G., and C. Rand. 2004. 'Medication non-adherence and asthma treatment cost', *Curr Opin Allergy Clin Immunol*, 4: 191-5.

Blaschke, T. F., L. Osterberg, B. Vrijens, and J. Urquhart. 2012. 'Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories', *Annu Rev Pharmacol Toxicol*, 52: 275-301.

Boman, I. L., S. Lundberg, S. Starkhammar, and L. Nygård. 2014. 'Exploring the usability of a videophone mock-up for persons with dementia and their significant others', *BMC Geriatr*, 14: 49.

Borisov, S., E. Danila, A. Maryandyshev, M. Dalcolmo, S. Miliauskas, L. Kuksa, S. Manga, A. Skrahina, S. Diktanas, L. R. Codecasa, A. Aleksa, J. Bruchfeld, A. Koleva, A. Piubello, Z. F. Udwadia, O. W. Akkerman, E. Belilovski, E. Bernal, M. J. Boeree, J. Cadiñanos Loidi, Q. Cai, J. J. Cebrian Gallardo, M. Dara, E. Davidavičienė, L. D. Forsman, J. De Los Rios, J. Denholm, J. Drakšienė, R. Duarte, S. E. Elamin, N. Escobar Salinas, M. Ferrarese, A. Filippov, A. Garcia, J. M. García-García, I. Gaudiesiute, B. Gavazova, R. Gayoso, R. Gomez Rosso, V. Gruslys, G. Gualano, W. Hoefsloot, J. Jonsson, E. Khimova, H. Kunst, R. Laniado-Laborín, Y. Li, C. Magis-Escurra, V. Manfrin, V. Marchese, E. Martínez Robles, A. Matteelli, J. Mazza-Stalder, C. Moschos, M. Muñoz-Torrico, H. Mustafa Hamdan, B. Nakčerienė, L. Nicod, M. Nieto Marcos, D. J. Palmero, F. Palmieri, A. Papavasileiou, M. C. Payen, A. Pontarelli, S. Quirós, A. Rendon, L. Saderi, A. Šmite, I. Solovic, M. B. Souleymane, M. Tadolini, M. van den Boom, M. Vescovo, P. Viggiani, A. Yedilbayev, R. Zablockis, D. Zhurkin, M. Zignol, D. Visca, A. Spanevello, J. A. Caminero, J. W. Alffenaar, S. Tiberi, R. Centis, L. D'Ambrosio, E. Pontali, G. Sotgiu, and G. B. Migliori. 2019. 'Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report', *Eur Respir J*, 54.

Bradbury, M., and D. Lewer. 2021. 'Role of community drug and alcohol services in physical healthcare for people who use illicit opioids: a qualitative study of clinical staff in the UK', *BMJ Open*, 11: e046577.

Braun, Virginia, and Victoria Clarke. 2006. 'Using thematic analysis in psychology', *Qualitative Research in Psychology*, 3: 77-101.

Bricker, J. B., K. E. Mull, J. A. Kientz, R. Vilardaga, L. D. Mercer, K. J. Akioka, and J. L. Heffner. 2014. 'Randomized, controlled pilot trial of a smartphone app for smoking cessation using acceptance and commitment therapy', *Drug Alcohol Depend*, 143: 87-94.

Burnier, M. 2006. 'Medication adherence and persistence as the cornerstone of effective antihypertensive therapy', *Am J Hypertens*, 19: 1190-6.

Cane, J., D. O'Connor, and S. Michie. 2012. 'Validation of the theoretical domains framework for use in behaviour change and implementation research', *Implement Sci*, 7: 37.

Centers for Disease Control and Prevention (CDC). *Chapter 2: Transmission and Pathogenesis of Tuberculosis,* .

Chaulk, C. Patrick, Kristina Moore-Rice, Rosetta Rizzo, and Richard E. Chaisson. 1995. 'Eleven Years of Community-Based Directly Observed Therapy for Tuberculosis', *JAMA*, 274: 945-51.

Chuck, C., E. Robinson, M. Macaraig, M. Alexander, and J. Burzynski. 2016. 'Enhancing management of tuberculosis treatment with video directly observed therapy in New York City', *Int J Tuberc Lung Dis*, 20: 588-93.

Collin, Simon M., Fatima Wurie, Morris C. Muzyamba, Gerard de Vries, Knut Lönnroth, Giovanni Battista Migliori, Ibrahim Abubakar, Sarah R. Anderson, and Dominik Zenner. 2019. 'Effectiveness of interventions for reducing TB incidence in countries with low TB incidence: a systematic review of reviews', *European Respiratory Review*, 28: 180107.

Connolly, L. E., P. H. Edelstein, and L. Ramakrishnan. 2007. 'Why is long-term therapy required to cure tuberculosis?', *PLoS Med*, 4: e120.

Craig, G. M., L. M. Joly, and A. Zumla. 2014. ''Complex' but coping: experience of symptoms of tuberculosis and health care seeking behaviours--a qualitative interview study of urban risk groups, London, UK', *BMC Public Health*, 14: 618.

Craig, G. M., and A. Zumla. 2015. 'The social context of tuberculosis treatment in urban risk groups in the United Kingdom: a qualitative interview study', *Int J Infect Dis*, 32: 105-10.

Crawshaw, A. F., and H. Kirkbride. 2018. 'Public Health England's Migrant Health Guide: an online resource for primary care practitioners', *Public Health*, 158: 198-202.

Cross A , Kumar M , and Soren P. 2015. '99DOTS: monitoring and improving TB medication adherence using mobile phones and augmented packaging OA-414-05. Cape Town, South Africa: Union World Conference on Lung Health'.

Curtis, R., S. R. Friedman, A. Neaigus, B. Jose, M. Goldstein, and D. C. Des Jarlais. 1994. 'Implications of directly observed therapy in tuberculosis control measures among IDUs', *Public Health Rep*, 109: 319-27.

Cutler, David M., and Wendy Everett. 2010. 'Thinking Outside the Pillbox — Medication Adherence as a Priority for Health Care Reform', *New England Journal of Medicine*, 362: 1553-55.

Czaja, S. J., D. Loewenstein, R. Schulz, S. N. Nair, and D. Perdomo. 2013. 'A videophone psychosocial intervention for dementia caregivers', *Am J Geriatr Psychiatry*, 21: 1071-81.

D'Ambrosio, L., M. Dara, M. Tadolini, R. Centis, G. Sotgiu, M. J. van der Werf, M. Gaga, D. Cirillo, A. Spanevello, M. Raviglione, F. Blasi, and G. B. Migliori. 2014. 'Tuberculosis elimination: theory and practice in Europe', *Eur Respir J*, 43: 1410-20.

Dahle, U. R., V. Eldholm, B. A. Winje, T. Mannsaker, and E. Heldal. 2007. 'Impact of immigration on the molecular epidemiology of Mycobacterium tuberculosis in a low-incidence country', *Am J Respir Crit Care Med*, 176: 930-5.

Dara, M., P. de Colombani, R. Petrova-Benedict, R. Centis, J. P. Zellweger, A. Sandgren, E. Heldal, G. Sotgiu, N. Jansen, R. Bahtijarevic, and G. B. Migliori. 2012. 'Minimum package for cross-border TB control and care in the WHO European region: a Wolfheze consensus statement', *Eur Respir J*, 40: 1081-90.

Dayer, L., S. Heldenbrand, P. Anderson, P. O. Gubbins, and B. C. Martin. 2013. 'Smartphone medication adherence apps: potential benefits to patients and providers', *J Am Pharm Assoc (2003)*, 53: 172-81.

de Vries, S. G., A. L. Cremers, C. C. Heuvelings, P. F. Greve, B. J. Visser, S. Belard, S. Janssen, R. Spijker, B. Shaw, R. A. Hill, A. Zumla, M. J. van der Werf, A. Sandgren, and M. P. Grobusch. 2017. 'Barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative literature', *Lancet Infect Dis*, 17: e128-e43.

Delamothe, T. 2008. 'Founding principles', *Bmj*, 336: 1216-8.

DeMaio, J., L. Schwartz, P. Cooley, and A. Tice. 2001. 'The application of telemedicine technology to a directly observed therapy program for tuberculosis: a pilot project', *Clin Infect Dis*, 33: 2082-4.

Demiris, G., D. Parker Oliver, E. Wittenberg-Lyles, K. Washington, A. Doorenbos, T. Rue, and D. Berry. 2012. 'A noninferiority trial of a problem-solving intervention for hospice caregivers: in person versus videophone', *J Palliat Med*, 15: 653-60.

Denkinger, C. M., J. Grenier, A. K. Stratis, A. Akkihal, N. Pant-Pai, and M. Pai. 2013. 'Mobile health to improve tuberculosis care and control: a call worth making', *Int J Tuberc Lung Dis*, 17: 719-27.

Douglas, T. S. 2012. 'Biomedical engineering at UCT - challenges and opportunities', *S Afr Med J*, 102: 456.

Droznin, M., A. Johnson, and A. M. Johnson. 2017. 'Multidrug resistant tuberculosis in prisons located in former Soviet countries: A systematic review', *PLOS ONE*, 12: e0174373.

Dubler NN, Bayer R, Landesman S, and White A. 1992. "Tuberculosis in the 1990s: ethical, legal and public policy issues in screening, treatment and the protection of those in congregate facilities: a report from the Working Group on TB and HIV

" In, 1-42. New York: United Hospital Fund New York.

ECDC;, and WHOEurope;. 2019. "ECDC/WHO Europe: Tuberculosis surveillance and monitoring 2019." In.

"An expanded DOTS framework for effective tuberculosis Control: stop TB communicable diseases." In.: World Health Organization (2002).

Falzon, D., H. Timimi, P. Kurosinski, G. B. Migliori, W. Van Gemert, C. Denkinger, C. Isaacs, A. Story, R. S. Garfein, L. G. do Valle Bastos, M. A. Yassin, V. Rusovich, A. Skrahina, L. Van Hoi, T. Broger, I. Abubakar, A. Hayward, B. V. Thomas, Z. Temesgen, S. Quraishi, D. von Delft, E. Jaramillo, K. Weyer, and M. C. Raviglione. 2016. 'Digital health for the End TB Strategy: developing priority products and making them work', *Eur Respir J*, 48: 29-45.

Farmer, Tracy, Kerry Robinson, Susan J Elliott, and John Eyles. 2006. 'Developing and implementing a triangulation protocol for qualitative health research', *Qualitative health research*, 16: 377-94.

Fitzpatrick, Suzanne, Glen Bramley, and Sarah Johnsen. 2012. 'Pathways into Multiple Exclusion Homelessness in Seven UK Cities', *Urban Studies*, 50: 148-68.

Fottrell, E. 2015. 'Commentary: The emperor's new phone', *Bmj*, 350: h2051.

Frieden, Thomas R., and John A. Sbarbaro. 2007. 'Promoting adherence to treatment for tuberculosis: the importance of direct observation', *Bulletin of the World Health Organization*, 85: 407-09.

Garfein, R. S., K. Collins, F. Munoz, K. Moser, P. Cerecer-Callu, F. Raab, P. Rios, A. Flick, M. L. Zuniga, J. Cuevas-Mota, K. Liang, G. Rangel, J. L. Burgos, T. C. Rodwell, and K. Patrick. 2015. 'Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study', *Int J Tuberc Lung Dis*, 19: 1057-64.

Garfein, R. S., K. Collins, F. Muñoz, K. Moser, P. Cerecer-Callu, F. Raab, P. Rios, A. Flick, M. L. Zúñiga, J. Cuevas-Mota, K. Liang, G. Rangel, J. L. Burgos, T. C. Rodwell, and K. Patrick. 2015. 'Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study', *Int J Tuberc Lung Dis*, 19: 1057-64.

Garfein, Richard S., and Riddhi P. Doshi. 2019. 'Synchronous and asynchronous video observed therapy (VOT) for tuberculosis treatment adherence monitoring and support', *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*: 100098.

Gerrish, K., A. Naisby, and M. Ismail. 2013. 'Experiences of the diagnosis and management of tuberculosis: a focused ethnography of Somali patients and healthcare professionals in the UK', *J Adv Nurs*, 69: 2285-94.

Gibson, N., A. Cave, D. Doering, L. Ortiz, and P. Harms. 2005. 'Socio-cultural factors influencing prevention and treatment of tuberculosis in immigrant and Aboriginal communities in Canada', *Soc Sci Med*, 61: 931-42.

Grace, Jocelyn, and Richard Chenhall. 2007. 'A Rapid Anthropological Assessment of Tuberculosis in a Remote Aboriginal Community in Northern Australia', *Human Organization*, 65: 387-99.

Hall, C. S., E. Fottrell, S. Wilkinson, and P. Byass. 2014. 'Assessing the impact of mHealth interventions in low- and middle-income countries--what has been shown to work?', *Glob Health Action*, 7: 25606.

Hazell B, and Robson R. 2015. "Pharmaceutical waste reduction in the NHS " In.: NHS England.

Heuvelings, C. C., S. G. de Vries, P. F. Greve, B. J. Visser, S. Belard, S. Janssen, A. L. Cremers, R. Spijker, B. Shaw, R. A. Hill, A. Zumla, A. Sandgren, M. J. van der Werf, and M. P. Grobusch. 2017. 'Effectiveness of interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review', *Lancet Infect Dis*, 17: e144-e58.

Hirpa, S., G. Medhin, B. Girma, M. Melese, A. Mekonen, P. Suarez, and G. Ameni. 2013. 'Determinants of multidrug-resistant tuberculosis in patients who underwent first-line treatment in Addis Ababa: a case control study', *BMC Public Health*, 13: 782.

Hoffman, J. A., J. R. Cunningham, A. J. Suleh, A. Sundsmo, D. Dekker, F. Vago, K. Munly, E. K. Igonya, and J. Hunt-Glassman. 2010. 'Mobile direct observation treatment for tuberculosis patients: a technical feasibility pilot using mobile phones in Nairobi, Kenya', *Am J Prev Med*, 39: 78-80.

Horne, R. . 2001. *Compliance, adherence and concordance. In Pharmacy Practice.* (London: Taylor & Francis).

Horne, R., S. C. Chapman, R. Parham, N. Freemantle, A. Forbes, and V. Cooper. 2013. 'Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework', *PLOS ONE*, 8: e80633.

Horne, R., R. Parham, R. Driscoll, and A. Robinson. 2009. 'Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease', *Inflamm Bowel Dis*, 15: 837-44.

Horne, R., J. Weinman, N. Barber, R. A. Elliott, and M. Morgan. 2005. "Concordance, Adherence and Compliance in Medicine Taking: A conceptual map and research priorities. ." In. London: National Institute for Health Research (NIHR) Service Delivery and Organisation (SDO) Programme.

Horne, Rob, Vanessa Cooper, Vari Wileman, and Amy Chan. 2019. 'Supporting Adherence to Medicines for Long-Term Conditions: A Perceptions and Practicalities Approach Based on an Extended Common-Sense Model', *European Psychologist*, 24: 82-96.

Horsburgh, C. R., Jr., C. E. Barry, 3rd, and C. Lange. 2015. 'Treatment of Tuberculosis', *N Engl J Med*, 373: 2149-60.

Hou, W. L., F. J. Song, N. X. Zhang, X. X. Dong, S. Y. Cao, X. X. Yin, J. N. Liu, and Z. X. Lu. 2012. 'Implementation and community involvement in DOTS strategy: a systematic review of studies in China [Review article]', *The International Journal of Tuberculosis and Lung Disease*, 16: 1433-40.

'Initial therapy for tuberculosis in the era of multidrug resistance. Recommendations of the Advisory Council for the Elimination of Tuberculosis'. 1993. *MMWR Recomm Rep*, 42: 1-8.

Iseman, M. D., D. L. Cohn, and J. A. Sbarbaro. 1993. 'Directly observed treatment of tuberculosis. We can't afford not to try it', *N Engl J Med*, 328: 576-8.

Jackson, Christina, Lina Eliasson, and John Weinman. 2014. "Applying COM-B to medication adherence." In.

Jones, A. S. K., N. Bidad, R. Horne, H. R. Stagg, F. B. Wurie, K. Kielmann, A. S. Karat, H. Kunst, C. N. J. Campbell, M. Darvell, A. L. Clarke, and M. C. I. Lipman. 2021. 'Determinants of non-adherence to anti-TB treatment in high income, low TB incidence settings: a scoping review', *Int J Tuberc Lung Dis*, 25: 483-90.

Kaona, F. A., M. Tuba, S. Siziya, and L. Sikaona. 2004. 'An assessment of factors contributing to treatment adherence and knowledge of TB transmission among patients on TB treatment', *BMC Public Health*, 4: 68.

Karumbi, J., and P. Garner. 2015. 'Directly observed therapy for treating tuberculosis', *Cochrane Database Syst Rev*: Cd003343.

Kawatsu, L., K. Uchimura, A. Ohkado, and S. Kato. 2018. 'A combination of quantitative and qualitative methods in investigating risk factors for lost to follow-up for tuberculosis treatment in Japan - Are physicians and nurses at a particular risk?', *PLOS ONE*, 13: e0198075.

Kielmann K, Vidal N, Karat AS, Stagg HR, Lipman M,. 2019. "Supporting adherence to treatment for tuberculosis (TB): a relational view." In *Int J Tuberc Lung Dis*.

Kielmann, K., N. Vidal, V. Riekstina, M. Krutikov, M. J. van der Werf, E. Biraua, P. Duric, and D. A. J. Moore. 2018. '"Treatment is of primary importance, and social assistance is secondary": A qualitative study on the organisation of tuberculosis (TB) care and patients' experience of starting and staying on TB treatment in Riga, Latvia', *PLOS ONE*, 13: e0203937.

Kik, S. V., S. P. Olthof, J. T. de Vries, D. Menzies, N. Kincler, J. van Loenhout-Rooyakkers, C. Burdo, and S. Verver. 2009. 'Direct and indirect costs of tuberculosis among immigrant patients in the Netherlands', *BMC Public Health*, 9: 283.

Kochi, A. 1991. 'The global tuberculosis situation and the new control strategy of the World Health Organization', *Tubercle*, 72: 1-6.

Komarnisky, Sara, Paul Hackett, Sylvia Abonyi, Courtney Heffernan, and Richard Long. 2016. '"Years ago": reconciliation and First Nations narratives of tuberculosis in the Canadian Prairie Provinces', *Critical Public Health*, 26: 381-93.

Konradsen, H., T. Lillebaek, T. Wilcke, and K. Lomborg. 2014. 'Being publicly diagnosed: a grounded theory study of Danish patients with tuberculosis', *Int J Qual Stud Health Well-being*, 9: 23644.

Kosmala-Anderson, J. P., L. M. Wallace, A. Turner, and C. Bourne. 2014. 'Self-reported effects of attending the Health Foundation's Co-Creating Health self-management programme for patients with type 2 diabetes mellitus in London, England', *Arch Med Sci*, 10: 773-81.

Krueger, K., D. Ruby, P. Cooley, B. Montoya, A. Exarchos, B. M. Djojonegoro, and K. Field. 2010. 'Videophone utilization as an alternative to directly observed therapy for tuberculosis', *Int J Tuberc Lung Dis*, 14: 779-81.

Kulane, A., B. M. Ahlberg, and I. Berggren. 2010. '"It is more than the issue of taking tablets": the interplay between migration policies and TB control in Sweden', *Health Policy*, 97: 26-31.

Kupferschmidt, Kai. 2011. "Why Tuberculosis Is So Hard to Cure." In *Science*.

Laila, M., V. Rialle, L. Nicolas, C. Duguay, and A. Franco. 2008. 'Videophones for the delivery of home healthcare in oncology', *Stud Health Technol Inform*, 136: 39-44.

Lee, S. B., and J. Valerius. 2020. 'mHealth Interventions to Promote Anti-Retroviral Adherence in HIV: Narrative Review', *JMIR Mhealth Uhealth*, 8: e14739.

Lei, Xun, Ke Huang, Qin Liu, Yong-Feng Jie, and Sheng-Lan Tang. 2016. 'Are tuberculosis patients adherent to prescribed treatments in China? Results of a prospective cohort study', *Infectious Diseases of Poverty*, 5: 38.

Leventhal, Howard, Michael Diefenbach, and Elaine A. Leventhal. 1992. 'Illness cognition: Using common sense to understand treatment adherence and affect cognition interactions', *Cognitive Therapy and Research*, 16: 143-63.

Leventhal, Howard, Elaine A. Leventhal, and Richard J. Contrada. 1998. 'Self-regulation, health, and behavior: A perceptual-cognitive approach', *Psychology & Health*, 13: 717-33.

Liu, X., J. J. Lewis, H. Zhang, W. Lu, S. Zhang, G. Zheng, L. Bai, J. Li, X. Li, H. Chen, M. Liu, R. Chen, J. Chi, J. Lu, S. Huan, S. Cheng, L. Wang, S. Jiang, D. P. Chin, and K. L. Fielding. 2015. 'Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial', *PLoS Med*, 12: e1001876.

Liu, X., J. Thompson, H. Dong, S. Sweeney, X. Li, Y. Yuan, X. Wang, W. He, B. Thomas, C. Xu, D. Hu, A. Vassall, S. Huan, H. Zhang, S. Jiang, K. Fielding, and Y. Zhao. 2023. 'Digital adherence technologies to improve tuberculosis treatment outcomes in China: a cluster-randomised superiority trial', *Lancet Glob Health*, 11: e693-e703.

Luchenski, S., N. Maguire, R. W. Aldridge, A. Hayward, A. Story, P. Perri, J. Withers, S. Clint, S. Fitzpatrick, and N. Hewett. 2018. 'What works in inclusion health: overview of effective interventions for marginalised and excluded populations', *Lancet*, 391: 266-80.

Lutge, E. E., C. S. Wiysonge, S. E. Knight, D. Sinclair, and J. Volmink. 2015. 'Incentives and enablers to improve adherence in tuberculosis', *Cochrane Database Syst Rev*: Cd007952.

M'Imunya J, M., T. Kredo, and J. Volmink. 2012. 'Patient education and counselling for promoting adherence to treatment for tuberculosis', *Cochrane Database Syst Rev*, 2012: Cd006591.

Macdonald, M. E., N. Rigillo, and P. Brassard. 2010. 'Urban aboriginal understandings and experiences of tuberculosis in Montreal, Quebec, Canada', *Qual Health Res*, 20: 506-23.

Manby, L., C. Aicken, M. Delgrange, and J. V. Bailey. 2022. 'Effectiveness of eHealth Interventions for HIV Prevention and Management in Sub-Saharan Africa: Systematic Review and Meta-analyses', *AIDS Behav*, 26: 457-69.

Mann, D. M., V. Kudesia, S. Reddy, M. Weng, D. Imler, and L. Quintiliani. 2013. 'Development of DASH Mobile: a mHealth lifestyle change intervention for the management of hypertension', *Stud Health Technol Inform*, 192: 973.

Marra, C. A., F. Marra, V. C. Cox, A. Palepu, and J. M. Fitzgerald. 2004. 'Factors influencing quality of life in patients with active tuberculosis', *Health Qual Life Outcomes*, 2: 58.

Michie, S., M. Johnston, C. Abraham, R. Lawton, D. Parker, and A. Walker. 2005. 'Making psychological theory useful for implementing evidence based practice: a consensus approach', *Qual Saf Health Care*, 14: 26-33.

Michie, Susan, Maartje M. van Stralen, and Robert West. 2011. 'The behaviour change wheel: A new method for characterising and designing behaviour change interventions', *Implementation Science*, 6: 42.

Mitchison, D. A. 1998. 'How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis', *Int J Tuberc Lung Dis*, 2: 10-5.

Mochizuki-Kawai, H., M. Tanaka, T. Suzuki, Y. Yamakawa, S. Mochizuki, M. Arai, and M. Kawamura. 2008. 'Elderly adults improve verbal fluency by videophone conversations: a pilot study', *J Telemed Telecare*, 14: 215-8.

Moffatt, J., M. Mayan, and R. Long. 2013. 'Sanitoriums and the Canadian colonial legacy: the untold experiences of tuberculosis treatment', *Qual Health Res*, 23: 1591-9.

Mohsen, W., P. Chan, M. Whelan, A. Glass, M. Mouton, E. Young, Q. Tran, S. Arora, S. Davison, T. Lama, C. Cobrador, and M. Levy. 2019. 'Hepatitis C treatment for difficult to access populations: can telementoring (as distinct from telemedicine) help?', *Intern Med J*, 49: 351-57.

Moonan, P. K., T. N. Quitugua, J. M. Pogoda, G. Woo, G. Drewyer, B. Sahbazian, D. Dunbar, K. C. Jost, Jr., C. Wallace, and S. E. Weis. 2011. 'Does directly observed therapy (DOT) reduce drug resistant tuberculosis?', *BMC Public Health*, 11: 19.

Muller, A. M., C. S. Osorio, D. R. Silva, G. Sbruzzi, P. de Tarso, and R. Dalcin. 2018. 'Interventions to improve adherence to tuberculosis treatment: systematic review and meta-analysis', *Int J Tuberc Lung Dis*, 22: 731-40.

Munro, S. A., S. A. Lewin, H. J. Smith, M. E. Engel, A. Fretheim, and J. Volmink. 2007. 'Patient adherence to tuberculosis treatment: a systematic review of qualitative research', *PLoS Med*, 4: e238.

Munro, Salla, Simon Lewin, Tanya Swart, and Jimmy Volmink. 2007. 'A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?', *BMC Public Health*, 7: 104.

Murray, E., C. May, and F. Mair. 2010. 'Development and formative evaluation of the e-Health Implementation Toolkit (e-HIT)', *BMC Med Inform Decis Mak*, 10: 61.

Murray, E., S. Treweek, C. Pope, A. MacFarlane, L. Ballini, C. Dowrick, T. Finch, A. Kennedy, F. Mair, C. O'Donnell, B. N. Ong, T. Rapley, A. Rogers, and C. May. 2010. 'Normalisation process theory: a framework for developing, evaluating and implementing complex interventions', *BMC Med*, 8: 63.

Nguyen, T. A., M. T. Pham, T. L. Nguyen, V. N. Nguyen, D. C. Pham, B. H. Nguyen, and G. J. Fox. 2017. 'Video Directly Observed Therapy to support adherence with treatment for tuberculosis in Vietnam: A prospective cohort study', *Int J Infect Dis*, 65: 85-89.

Ngwatu, B. K., N. P. Nsengiyumva, O. Oxlade, B. Mappin-Kasirer, N. L. Nguyen, E. Jaramillo, D. Falzon, and K. Schwartzman. 2018. 'The impact of digital health technologies on tuberculosis treatment: a systematic review', *Eur Respir J*, 51.

NICE;. 2009. "Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE guidelines [CG76]." In.

———. 2016. "National Institute for Health and Clinical Excellence. Tuberculosis NICE guideline [NG33]: Jan 2016." In. London: NICE.

Nieuwlaat, R., N. Wilczynski, T. Navarro, N. Hobson, R. Jeffery, A. Keepanasseril, T. Agoritsas, N. Mistry, A. Iorio, S. Jack, B. Sivaramalingam, E. Iserman, R. A. Mustafa, D. Jedraszewski, C. Cotoi, and R. B. Haynes. 2014. 'Interventions for enhancing medication adherence', *Cochrane Database Syst Rev*, 2014: Cd000011.

Nnoaham, K. E., R. Pool, G. Bothamley, and A. D. Grant. 2006. 'Perceptions and experiences of tuberculosis among African patients attending a tuberculosis clinic in London', *Int J Tuberc Lung Dis*, 10: 1013-7.

O'Cathain, A., E. Murphy, and J. Nicholl. 2010. 'Three techniques for integrating data in mixed methods studies', *Bmj*, 341: c4587.

O'Connor, Siobhan, Peter Hanlon, Catherine A. O'Donnell, Sonia Garcia, Julie Glanville, and Frances S. Mair. 2016. 'Understanding factors affecting patient and public engagement and

recruitment to digital health interventions: a systematic review of qualitative studies', *BMC Medical Informatics and Decision Making*, 16: 120.

Ormerod, L. P., and R. J. Prescott. 1991. 'Inter-relations between relapses, drug regimens and compliance with treatment in tuberculosis', *Respir Med*, 85: 239-42.

Pablos-Mendez, A., C. A. Knirsch, R. G. Barr, B. H. Lerner, and T. R. Frieden. 1997. 'Nonadherence in tuberculosis treatment: predictors and consequences in New York City', *Am J Med*, 102: 164-70.

Pai, M. , R. Subbaraman, and A. Daftary. 2017. 'Monitoring and improving adherence to tuberculosis medications. '.

Parker Oliver, D., G. Demiris, E. Wittenberg-Lyles, D. Porock, J. Collier, and A. Arthur. 2010. 'Caregiver participation in hospice interdisciplinary team meetings via videophone technology: A pilot study to improve pain management', *Am J Hosp Palliat Care*, 27: 465-73.

Pasipanodya, Jotam G., and Tawanda Gumbo. 2013. 'A Meta-Analysis of Self-Administered vs Directly Observed Therapy Effect on Microbiologic Failure, Relapse, and Acquired Drug Resistance in Tuberculosis Patients', *Clinical Infectious Diseases*, 57: 21-31.

Patricia Moscibrodzki; Steven Parkinson; Raphael Ferry; Nnamdi Nwaneri; and William Thies. 2021. "Mapping the Technology Landscape of National TB Programs. ." In.: The Global Fund to Fight AIDS, Tuberculosis and Malaria.

PHE;. 2019. "Public Health England: Tuberculosis in England 2018." In.

Pujol-Cruells, A., and C. Vilaplana. 2019. 'Specific Interventions for Implementing a Patient-Centered Approach to TB Care in Low-Incidence Cities', *Front Med (Lausanne)*, 6: 273.

Ravenscroft, L., S. Kettle, R. Persian, S. Ruda, L. Severin, S. Doltu, B. Schenck, and G. Loewenstein. 2020. 'Video-observed therapy and medication adherence for tuberculosis patients: randomised controlled trial in Moldova', *Eur Respir J*, 56.

Raviglione, M. C., H. L. Rieder, K. Styblo, A. G. Khomenko, K. Esteves, and A. Kochi. 1994. 'Tuberculosis trends in eastern Europe and the former USSR', *Tuber Lung Dis*, 75: 400-16.

Sagbakken, M., G. A. Bjune, and J. C. Frich. 2012. 'Humiliation or care? A qualitative study of patients' and health professionals' experiences with tuberculosis treatment in Norway', *Scand J Caring Sci*, 26: 313-23.

Schluger, N., C. Ciotoli, D. Cohen, H. Johnson, and W. N. Rom. 1995. 'Comprehensive tuberculosis control for patients at high risk for noncompliance', *Am J Respir Crit Care Med*, 151: 1486-90.

Searle, A., J. Park, and J. Littleton. 2007. 'Alliance and compliance in tuberculosis treatment of older Pakeha people in Auckland, New Zealand', *Int J Tuberc Lung Dis*, 11: 72-7.

Shields, M. D., A. LQahtani F, M. P. Rivey, and J. C. McElnay. 2018. 'Mobile direct observation of therapy (MDOT) - A rapid systematic review and pilot study in children with asthma', *PLOS ONE*, 13: e0190031.

Shiratani, K. N. 2019. 'Psychological changes and associated factors among patients with tuberculosis who received directly observed treatment short-course in metropolitan areas of Japan: quantitative and qualitative perspectives', *BMC Public Health*, 19: 1642.

Singer, Merrill, and Scott Clair. 2003. 'Syndemics and Public Health: Reconceptualizing Disease in Bio-Social Context', *Medical Anthropology Quarterly*, 17: 423-41.

Sinkou, H., H. Hurevich, V. Rusovich, L. Zhylevich, D. Falzon, P. de Colombani, A. Dadu, M. Dara, A. Story, and A. Skrahina. 2017. 'Video-observed treatment for tuberculosis patients in Belarus: findings from the first programmatic experience', *Eur Respir J*, 49.

Skrajner, M. J., C. J. Camp, J. L. Haberman, T. G. Heckman, A. Kochman, and C. Frentiu. 2009. 'Use of Videophone Technology to Address Medication Adherence Issues in Persons with HIV', *HIV AIDS (Auckl)*, 1: 23-30.

Sokol, M. C., K. A. McGuigan, R. R. Verbrugge, and R. S. Epstein. 2005. 'Impact of medication adherence on hospitalization risk and healthcare cost', *Med Care*, 43: 521-30.

Stagg, H. R., J. J. Lewis, X. Liu, S. Huan, S. Jiang, D. P. Chin, and K. L. Fielding. 2020. 'Temporal Factors and Missed Doses of Tuberculosis Treatment. A Causal Associations Approach to Analyses of Digital Adherence Data', *Ann Am Thorac Soc*, 17: 438-49.

Steinberg, D. M., E. L. Levine, S. Askew, P. Foley, and G. G. Bennett. 2013. 'Daily text messaging for weight control among racial and ethnic minority women: randomized controlled pilot study', *J Med Internet Res*, 15: e244.

Stern, A., R. Valaitis, R. Weir, and A. R. Jadad. 2012. 'Use of home telehealth in palliative cancer care: a case study', *J Telemed Telecare*, 18: 297-300.

Story, A., R. W. Aldridge, C. M. Smith, E. Garber, J. Hall, G. Ferenando, L. Possas, S. Hemming, F. Wurie, S. Luchenski, I. Abubakar, T. D. McHugh, P. J. White, J. M. Watson, M. Lipman, R. Garfein, and A. C. Hayward. 2019. 'Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicentre, analyst-blinded, randomised, controlled superiority trial', *Lancet*, 393: 1216-24.

Story, A., E. Garber, R. W. Aldridge, C. M. Smith, J. Hall, G. Ferenando, L. Possas, S. Hemming, F. Wurie, S. Luchenski, I. Abubakar, T. D. McHugh, P. J. White, J. M. Watson, M. Lipman, R. Garfein, and A. C. Hayward. 2020. 'Programme Grants for Applied Research.' in, *Management and control of tuberculosis control in socially complex groups: a research programme including three RCTs* (NIHR Journals Library

Story, A., R. S. Garfein, A. Hayward, V. Rusovich, A. Dadu, V. Soltan, A. Oprunenco, K. Collins, R. Sarin, S. Quraishi, M. Sharma, G. B. Migliori, M. Varadarajan, and D. Falzon. 2016a. 'Monitoring Therapy Compliance of Tuberculosis Patients by using Video-Enabled Electronic Devices', *Emerging infectious diseases*, 22: 538-40.

Story, A., S. Murad, W. Roberts, M. Verheyen, and A. C. Hayward. 2007. 'Tuberculosis in London: the importance of homelessness, problem drug use and prison', *Thorax*, 62: 667-71.

Story, Alistair, Richard S. Garfein, Andrew Hayward, Valiantsin Rusovich, Andrei Dadu, Viorel Soltan, Alexandru Oprunenco, Kelly Collins, Rohit Sarin, Subhi Quraishi, Mukta Sharma, Giovanni Battista Migliori, Maithili Varadarajan, and Dennis Falzon. 2016b. 'Monitoring Therapy Compliance of Tuberculosis Patients by using Video-Enabled Electronic Devices', *Emerging infectious diseases*, 22: 538-40.

Subbaraman, Ramnath, Laura de Mondesert, Angella Musiimenta, Madhukar Pai, Kenneth H. Mayer, Beena E. Thomas, and Jessica Haberer. 2018. 'Digital adherence technologies for the

management of tuberculosis therapy: mapping the landscape and research priorities', *BMJ Global Health*, 3: e001018.

Sudre, P., G. Ten Dam, and A. Kochi. 1992. 'Tuberculosis: A global overview of the situation today', *Bulletin of the World Health Organization*, 70: 149-59.

Sukrakanchana-Trikham, P., X. Puéchal, J. Rigal, and H. L. Rieder. 1992. '10-year assessment of treatment outcome among Cambodian refugees with sputum smear-positive tuberculosis in Khao-l-Dang, Thailand', *Tubercle and Lung Disease*, 73: 384-87.

Suwankeeree, W., and W. Picheansathian. 2014. 'Strategies to promote adherence to treatment by pulmonary tuberculosis patients: a systematic review', *Int J Evid Based Healthc*, 12: 3-16.

The m-health alliance and STOP TB partnership. 2012. "THE ROLE OF mHEALTH IN THE FIGHT AGAINST TUBERCULOSIS." In.

Tola, H. H., A. Tol, D. Shojaeizadeh, and G. Garmaroudi. 2015. 'Tuberculosis Treatment Non-Adherence and Lost to Follow Up among TB Patients with or without HIV in Developing Countries: A Systematic Review', *Iran J Public Health*, 44: 1-11.

UCL Institute for Global Health. 27-28 Jan 2015. 'mHealth: how can mobile technology improve health in low and middle income countries? '.

van de Berg, S., N. Jansen-Aaldring, G. de Vries, and S. van den Hof. 2018. 'Patient support for tuberculosis patients in low-incidence countries: A systematic review', *PLOS ONE*, 13: e0205433.

van den Hof, Susan, Camilo Antillon Najlis, Emily Bloss, and Masja Straetemans. 2010. 'A systematic review on the role of gender in tuberculosis control', *Report prepared for Tuberculosis Control Programme (TB CAP) September*.

van der Oest, C., R. Chenhall, D. Hood, and P. Kelly. 2005. 'Talking about TB: multicultural diversity and tuberculosis services in Waikato, New Zealand', *N Z Med J*, 118: U1496.

van Hest, N. A., R. W. Aldridge, G. de Vries, A. Sandgren, B. Hauer, A. Hayward, W. Arrazola de Onate, W. Haas, L. R. Codecasa, J. A. Cayla, A. Story, D. Antoine, A. Gori, L. Quabeck, J. Jonsson, M. Wanlin, A. Orcau, A. Rodes, M. Dedicoat, F. Antoun, H. van Deutekom, S. Keizer, and I. Abubakar. 2014. 'Tuberculosis control in big cities and urban risk groups in the European Union: a consensus statement', *Euro Surveill*, 19.

van Hoorn, R., E. Jaramillo, D. Collins, A. Gebhard, and S. van den Hof. 2016. 'The Effects of Psycho-Emotional and Socio-Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes - A Systematic Review and Meta-Analysis', *PLOS ONE*, 11: e0154095.

Verhoeven, F., K. Tanja-Dijkstra, N. Nijland, G. Eysenbach, and L. van Gemert-Pijnen. 2010. 'Asynchronous and synchronous teleconsultation for diabetes care: a systematic literature review', *J Diabetes Sci Technol*, 4: 666-84.

Visca, Dina, Simon Tiberi, Emanuele Pontali, Antonio Spanevello, and Giovanni Battista Migliori. 2020. 'Tuberculosis in the time of COVID-19: quality of life and digital innovation', *European Respiratory Journal*, 56: 2001998.

Vrijens, B., S. De Geest, D. A. Hughes, K. Przemyslaw, J. Demonceau, T. Ruppar, F. Dobbels, E. Fargher, V. Morrison, P. Lewek, M. Matyjaszczyk, C. Mshelia, W. Clyne, J. K. Aronson, and J. Urquhart. 2012. 'A new taxonomy for describing and defining adherence to medications', *Br J Clin Pharmacol*, 73: 691-705.

Wade, V. A., J. Karnon, J. A. Eliott, and J. E. Hiller. 2012. 'Home videophones improve direct observation in tuberculosis treatment: a mixed methods evaluation', *PLOS ONE*, 7: e50155.

Wannheden, C., K. Westling, C. Savage, C. Sandahl, and J. Ellenius. 2013. 'HIV and tuberculosis coinfection: a qualitative study of treatment challenges faced by care providers', *Int J Tuberc Lung Dis*, 17: 1029-35.

Weis, S. E., P. C. Slocum, F. X. Blais, B. King, M. Nunn, G. B. Matney, E. Gomez, and B. H. Foresman. 1994. 'The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis', *N Engl J Med*, 330: 1179-84.

Weiss, Linda, Kate McCoy, Michael Kluger, and Ruth Finkelstein. 2004. 'Access to and use of health care: perceptions and experiences among people who use heroin and cocaine', *Addiction Research & Theory*, 12: 155-65.

Westaway, M. S., P. W. Conradie, and L. Remmers. 1991. 'Supervised out-patient treatment of tuberculosis: evaluation of a South African rural programme', *Tubercle*, 72: 140-44.

Westerman, S. J., and D. R. Davies. 2000. 'Acquisition and Application of New Technology Skills: The Influence of Age', *Occupational Medicine*, 50: 478-82.

WHO. 1991. "World Health, Organization; Forty-Fourth World Health Assembly." In *Agenda item*.

———. 2018. "World Health Organisation. Handbook for the use of digital technologies to support tuberculosis medication adherence." In.

———. 2019. "WHO consolidated guidelines on drug-resistant tuberculosis treatment." In.

———. 2020. "Target product profiles for tuberculosis preventive treatment." In.

———. 2021. "Global Tuberculosis Report 2021." In.: World Health Organisation.

———. 2022. "WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment." In.

"WHO Regional Office for Europe. Review of the National Tuberculosis Programme in the Republic of Moldova, 4–15 February 2013." In.

WHO;. 2003. "World Health Organisation. Adherence to long-term therapies: evidence for action." In. Geneva.

———. 2015a. "World Health Organisation. Digital health for the End TB Strategy - an agenda for action." In.

———. 2015b. "World Health Organisation. Global strategy and targets for tuberculosis prevention, care and control after 2015

" In.:

.

———. 2017. "World Health Organisation. Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update)." In.: WHO.

———. 2019. "Global tuberculosis report 2018." In.: World Health Organisation.

Wieland, M. L., J. A. Weis, B. P. Yawn, S. M. Sullivan, K. L. Millington, C. M. Smith, S. Bertram, J. A. Nigon, and I. G. Sia. 2012. 'Perceptions of tuberculosis among immigrants and refugees at an adult education center: a community-based participatory research approach', *J Immigr Minor Health*, 14: 14-22.

Wilkinson, D. 1994. 'High-compliance tuberculosis treatment programme in a rural community', *The Lancet*, 343: 647-48.

Woodward, A., N. Howard, and I. Wolffers. 2014. 'Health and access to care for undocumented migrants living in the European Union: a scoping review', *Health Policy Plan*, 29: 818-30.

Wynne, Ashley, Solina Richter, Lilian Banura, and Walter Kipp. 2014. 'Challenges in tuberculosis care in Western Uganda: Health care worker and patient perspectives', *International Journal of Africa Nursing Sciences*, 1: 6-10.

Yamada, S., J. Caballero, D. S. Matsunaga, G. Agustin, and M. Magana. 1999. 'Attitudes regarding tuberculosis in immigrants from the Philippines to the United States', *Fam Med*, 31: 477-82.

Zuñiga, J. A., S. E. Muñoz, M. Z. Johnson, and A. Garcia. 2014. 'Tuberculosis treatment for Mexican Americans living on the U.S.-Mexico border', *J Nurs Scholarsh*, 46: 253-62.