CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Direct Observational Therapy for the Treatment of Tuberculosis: A Review of Clinical Evidence and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	November 24, 2020
Report Length:	51 Pages

CADTH

Authors: Kendra Brett, Melissa Severn

Acknowledgements: Diksha Kumar

Cite As: Direct Observational Therapy for the Treatment of Tuberculosis: A Review of Clinical Evidence and Guidelines. Ottawa: CADTH; 2020 Nov. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **Requests@CADTH.ca**

Abbreviations

DOT	direct observational therapy
RCT	randomized controlled trial
SR	systematic review
TB	tuberculosis
VOT	video observational therapy

Context and Policy Issues

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis*.[1] It is transmitted between humans primarily through aerosols that are generated through the forceful expiration of air (e.g., coughing, sneezing).[1] Infection with *M. tuberculosis* does not always result in active TB disease, producing instead an asymptomatic latent TB infection.[1] People with latent TB cannot spread the disease to others, but they can develop active TB disease.[1] Symptoms of active TB disease include a bad cough, fever, and weight loss.[2]

The current treatment for active and latent TB involve long courses of antibiotic treatments, which often include more than one drug.[3,4] Incomplete treatment adherence is a major challenge of TB treatment, and failing to complete the treatment can result in persistent disease or the development of drug-resistant TB.[5] One of the strategies for improving adherence is directly observed or direct observational therapy (DOT).[3-5] Standard DOT is conducted in person and involves directly watching the patient swallow each dose of medication.[3] Compared to self-administered therapy, DOT has been shown to be effective, however, it is very resource intensive for both the patient and the health care service.[5] It is unclear who should provide DOT, and whether this person needs to be a health care professional (e.g., public health nurse) or whether lay people can also provide DOT (e.g., family, community members). It is also unclear whether the location where DOT is administered is important. DOT could involve the patients returning to a health care facility every day (e.g., TB clinic, hospital), but it is also possible that DOT can occur at other locations (e.g., workplace, home). Alternatively, thanks to advances in technology, video observational therapy (VOT) is possible, where patients are observed taking their medication over video (often facilitated through a smart phone).[5] VOT can occur in real time (i.e., synchronous VOT), or patients can record and submit videos (i.e., asynchronous VOT). VOT could help minimize resources for providing DOT, but there are some privacy concerns with VOT due to the technology.

The purpose of the current report is to summarize and critically appraise the relevant evidence regarding the provision of DOT for the treatment of TB. Additionally, evidence-based guidelines with recommendations regarding the use of DOT for the treatment of TB will be reviewed.

This report is a component of a larger CADTH Condition Level Review on TB. A condition level review is an assessment that incorporates all aspects of a condition, from prevention, detection, treatment, and management. For more information on CADTH's Condition Level Review of TB, please visit the project page (https://www.cadth.ca/tuberculosis).

Research Questions

1. What is the clinical evidence regarding the provision of direct observational therapy for the treatment of tuberculosis?
2. What are the evidence-based guidelines regarding the use of direct observational therapy for the treatment of tuberculosis?

Key Findings

Three systematic reviews and six randomized controlled trials were identified regarding the clinical evidence for provision of direct observational therapy (DOT) for the treatment of tuberculosis. The evidence suggested that DOT provided by a family member was as effective as DOT provided by non-family members. Evidence regarding the location for the provision of DOT suggested that alternative locations such as at home, at work, or in the community, can be more or similarly effective as DOT provided in health care facilities. The provision of video observational therapy was found to be equally or more effective than DOT. The body of evidence was limited by its heterogeneity and was largely low to moderate in quality

Six evidence-based guidelines were identified regarding the use of DOT for the treatment of tuberculosis. Two guidelines provide strong and conditional recommendations, based on low-quality evidence, that DOT should be administered by people trained specifically to provide DOT. One guideline provides a conditional recommendation, based on moderate-quality evidence, to administer DOT in a community setting or at home rather than a health care facility. For the general population, and members of vulnerable or hard-to-reach populations, two guidelines recommend video observational therapy as an alternative to DOT, based on weak evidence.

Methods

Literature Search Methods

This report is an update of a literature search strategy developed for a previous CADTH report.[6] For the current report, a limited literature search was conducted on key resources including MEDLINE, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused internet search. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, any types of clinical trials or observational studies, and guidelines. The initial search was limited to English-language documents published between January 1, 2015 and April 28, 2020. For the current report, database searches were rerun on September 30, 2020 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since April 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People receiving pharmaceutical treatment for tuberculosis infection
Intervention	Direct observational therapy (i.e., patient is observed while taking a dose of pharmaceutical treatment to ensure treatment adherence)
Comparator	Q1. Directly observed therapy conducted by an alternative provider (e.g., public health nurse, other health care professionals, tuberculosis community leaders, students, laypeople) Video observed therapy Q2. Not applicable
Outcomes	Q1. Differences in treatment adherence between different methods of direct observational therapy Q2. Recommendations regarding how to administer directly observed therapy, such as who should administer it or the method of administration
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[7] for systematic reviews (SRs), the Downs and Black checklist[8] for randomized controlled trials (RCTs), and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[9] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 536 citations were identified in the literature search. Following screening of titles and abstracts, 502 citations were excluded and 34 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 25 publications were excluded for various reasons, and 15 publications met the inclusion criteria and were included in this report. These comprised three SRs, six RCTs, and six evidence-based guidelines. Appendix 1 presents the PRISMA[10] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Three SRs,[11-13] six RCTs,[14-19] and six evidence-based guidelines[20-25] were identified and included in this report, and are summarized below. Two[12,13] of the three SRs had broader inclusion criteria than the present review. Specifically, one of the SRs[13] included all digital

health technologies that support adherence to TB treatments, and one of the SRs[12] included self-administered therapy as an eligible comparator in addition to other methods of DOT. Only the characteristics and results of the subset of relevant studies will be described in this report.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One SR[13] that compared in-person DOT with VOT was published in 2018 and conducted their literature search in June 2016. This SR identified two non-randomized studies relevant to the current report.[13]

Two SRs with meta-analysis[11,12] compared different approaches for administering DOT. The SR by Zhang et al. (2016)[12] was published in 2016 and searched the literature until to February 2015. Eight RCTs and nine cohort studies were included in the SR, and the eight RCTs and 6 of the cohort studies were included in the meta-analysis.[12] The SR by Wright et al. (2015)[11] was published in 2015 and searched the literature up to July 2014. One RCT and seven non-randomized studies were included in this SR and meta-analysis.[11] Three primary studies identified in the SRs overlapped across both SRs; the degree of overlap is summarized in Appendix 5.

Two RCTs[18,19] were published in 2020, one RCT[17] was published in 2019, one RCT[14] was published in 2016, and two RCTs[15,16] were published in 2015. All of the RCTs were two-arm trials, and due to the nature of the interventions none of the studies were able to blind the patients to the intervention. Five of the RCTs[15-19] randomized the participants to the intervention. The other RCT[14] was a non-inferiority trial that used a cluster-randomized approach and randomized the districts to the intervention.

Six relevant guidelines were identified. One guideline was developed in 2020 by the World Health Organization (WHO). [25] One guideline was developed in 2019 by the British HIV Association (BHIVA).[20] The National Institute for Health and Care Excellence (NICE) developed a guideline in 2017.[24] Three guidelines were developed in 2016, and they were developed by the European Centre for Disease Prevention and Control (ECDC),[21] the Singapore Ministry of Health,[23] and a joint guideline by the American Thoracic Society (ATS), CDC, and Infectious Diseases Society of America (IDSA).[22]

Country of Origin

The SRs were led by authors in Switzerland,[13] China,[12] and Australia,[11] and included primary studies conducted in Australia, USA, India, South Africa, Thailand, Zambia, Tanzania, and Iraq.

Four of the RCTs were led by authors in the country where the study was conducted: China,[18] India,[14] Nigeria[15] and the USA.[16] One RCT was led by authors in England and was conducted in Moldova.[19] One RCT was led by authors in the UK and conducted in England.[17]

The WHO guideline[25] is meant to apply globally. Two guidelines[20,24] are meant to apply to the United Kingdom. The other guidelines are meant to apply to Europe,[21] the United States,[22] and Singapore.[23]

Patient Population

Two of the SRs[11,13] included primary studies with patients with any type of TB. The other SR[12] included primary studies with patients with pulmonary TB and excluded other forms of TB.

The patient population varied across the six RCTs with respect to the age of the patients, and the length of time remaining in the TB treatment. Three RCTs[16,18,19] included adults 18 years of age or older, one RCT[17] included people 16 years or older, and another RCT[15] included people who were 15 years or older. The other RCT[14] included children less than 15 years old.

In three RCTs, the patients were eligible if they had started treatment for TB prior to enrollment in the trial, but the RCTs had different requirements for the minimum time remaining of treatment (i.e., one month (N = 405),[18] two months (N = 226),[17] four months (N = 197)[19]). In these three RCTs, patients with known drug-resistant TB[18] or multi-drug resistant TB[17,19] were excluded. Two RCTs (N = 150,[15] and N = 624[14]) only included those who had yet to start treatment for TB. The other RCT[16] included patients with TB with problematic substance use (i.e., illicit drugs or alcohol; N = 96) but did not specify whether those who had already started TB treatment were eligible for the study.

The target population in the NICE guideline[24] and the Singapore guideline[23] is all patients with TB. The target population in the WHO guideline[25] is patients with drug-resistant TB, whereas the ATS/CDC/IDSA guideline [22] is specific to those with drug-susceptible TB. The target population of the BHIVA guideline[20] is patients with TB who are HIV positive. The ECDC guideline [21] is specific to vulnerable and hard-to-reach populations with TB. For all of the guidelines, the population was broader than the eligible population for this report. Only the components specific to patients who are receiving TB treatment that is directly observed were relevant to this report.

The intended users for all six guidelines are healthcare workers and other key TB stakeholders.[20-25]

Interventions and Comparators

Four studies in this report compared DOT to VOT. In one SR[13] with broader eligibility criteria, the intervention and comparator relevant to this report were VOT and in-person DOT. One RCT compared synchronous VOT (i.e., medication taken under observation on live video using a smartphone app) to standard clinic-based DOT (once every two days).[18] Two RCTs used asynchronous VOT (i.e., patients record and submit a video of themselves taking the medication daily) compared to standard clinic-based DOT (Monday to Friday)[19] or compared to DOT provided in a clinic, community setting, or at the home by a health care worker or lay worker three to five days per week.[17]

Five studies in this report investigated DOT provided in different places or by different providers. In two SRs[11,12] community-based DOT (i.e., DOT provided in the community by community health workers and volunteers) was compared to clinic-based DOT[11,12] or family- or workplace-based DOT.[12] One RCT in children, compared home-based DOT provided by a family member compared to DOT provided by a non-family member (location unspecified).[14] One RCT[15] compared home-based DOT provided by staff or health care workers to hospital-based DOT. In the RCT[16] that specifically recruited people with problematic substance use, DOT provided by former substance users was compared to DOT provided by public health workers.

For all six guidelines, the interventions considered within the guideline were broader than the eligible interventions for this report. The interventions in the guidelines that were relevant to this report include interventions to enhance treatment adherence, such as DOT or VOT.[20-25]

Outcomes

The relevant treatment adherence outcomes in the studies included in this report included different measures of treatment adherence (i.e., did patients adhere to or miss any appointments or doses of medication);[13,14,16,17,19] successful treatment (i.e., cured or completed treatment);[11-15,18,19] treatment failure (e.g., patient continues to test positive for TB, or develops drug-resistant TB);[12,18] or treatment default (e.g., treatment interrupted for 2 or more consecutive months) or lost to treatment follow-up.[11,12,18]

For the WHO guideline[25] the outcomes that were considered in the SRs and when formulating the recommendations were treatment adherence, treatment failure, loss to follow-up, and adverse events. The NICE guideline[24] considered adherence related outcomes, and the ECDC guideline[21] considered treatment completion as the outcome of interest. The outcomes considered in the SRs conducted for the ATS/CDC/IDSA guideline[22] were mortality, treatment success, treatment completion, relapse, adherence, and time to smear conversion. Two guidelines[20,23] did not report which outcomes were considered when developing the recommendations

Summary of Critical Appraisal

The critical appraisal of the included studies is summarized below and additional details regarding the strengths and limitations of the included publications are provided in Appendix 3.

Systematic Reviews

Both SRs with meta-analyses[11,12] had well clear and described eligibility criteria for the review, and also provided detailed descriptions of the included studies in the review (e.g., population, type of DOT, outcomes). The SR by Ngwatu et al. (2018)[13] was lacking details with regard to the population, intervention, and comparators of interest in the review, and did not provide adequate descriptions of the included studies (e.g., minimal details provided about the population and interventions). One SR[11] reported the sources of funding for the primary studies, and the other two SRs[12,13] did not. None of the SRs reported whether they had an a priori protocol, increasing the risk of reporting bias.

All three SRs included both RCTs and non-randomized studies, which is appropriate given the intervention and comparators, and they all had two authors perform the study selection and data extraction in duplicate. Two of the SRs[12,13] had comprehensive search strategies (including searching trial registries, and providing the full search strategy); the other SR[11] provided the complete search strategy but did not search the grey literature or trial registries and it is possible that they may not have identified all relevant literature. A full list of excluded studies and the reasons for exclusion at the full text level was provided in two SRs,[11,13] but was absent in the other SR.[12]

An adequate assessment of the risk of bias in the non-randomized studies was conducted in all three SRs (i.e., assessed for bias due to selection, outcome reporting)[11-13] and both SRs with meta-analyses[11,12] used appropriate tools to assess risk of bias in RCTs. The SR by Wright et al. (2015)[11] also assessed the overall quality of the study based on factors

such as study limitations, inconsistency and indirectness of the evidence. Two of the SRs[12,13] did not discuss the potential impact of the risk of bias of the individuals studies when interpreting the results. The other SR[11] considered the quality of the studies as a limitation to their findings, and discussed the potential impact of the different biases present in the studies. The SR by Zhang et al. (2016)[12] reported that two reviewers independently conducted the assessment of risk of bias, and it was not reported in the other two SRs whether more than one reviewer was involved in the assessment of risk of bias, which could affect the assessment.

Both SRs with meta-analyses[11,12] used random effects analyses for their analyses where the clinical heterogeneity was high, and they discussed the potential impact of the clinical and statistical heterogeneity on the results. In addition, both studies conducted meta-analyses that combined RCTs with non-randomized studies, which may not have been appropriate, but also conducted separate analyses that only contained one type of study design (i.e., RCT or non-randomized study). Neither SR assessed the potential impact of the risk of bias in the individual studies on the results of the meta-analysis, and it is unclear whether the studies assessed as low quality or high risk of bias influenced the results. Both SRs[11,12] acknowledged that they were at risk of publication bias, but only one SR[11] reported that the reason for not conducting a statistical or graphical test for publication bias was due to there being fewer than 10 studies.

The authors of all three SRs declared that they had no conflicts of interest.[11-13] Two SRs[12,13] reported the source of their funding; one SR[13] included an explicit statement that the content of the report was not influenced by the funding agency, but it was not reported whether the funder influenced the report in the other SR.[12] The SR by Wright et al. (2015)[11] did not report whether funding was received and it is unclear whether there was the potential for bias from the funder.

Randomized Controlled Trials

The reporting was generally well done across the RCTs, with a few exceptions. All six RCTs[14-19] had detailed descriptions of the objectives of the study, the outcomes of interest, the interventions, and the baseline characteristics of the population. Five of the RCTs[14,15,17-19] also provided clear descriptions of the patient eligibility criteria, and one RCT[16] did not report all the necessary population inclusion criteria (i.e., unclear whether patients were eligible if they had already started TB treatment). The reporting of the findings was clear for four RCTs,[14,17-19] and in the other two RCTs[15,16] the main findings were not clearly reported making it more difficult to assess the analyses and conclusions. Five RCTs[14-18] reported the actual probability values, whereas the other RCT[19] only reported that the probability was less than a certain amount (e.g., $P < 0.01$) but also reported confidence intervals for their results. Three RCTs[17-19] reported small losses to follow-up in both groups (i.e., fewer than five people per group) that would have been unlikely to affect the outcomes, and the other three RCTs[14-16] reported that there were no patients lost to follow-up.

Due to the nature of the interventions, it was not possible to blind the patients to the intervention in any of the RCTs,[14-19] and it is unknown whether this may have affected the results of the studies. Two of the RCTs[15,17] explicitly stated that the outcome assessors or analysts were blinded to the interventions, thus reducing the potential for measurement bias due to awareness of the intervention. The other four RCTs[14,16,18,19] reported that blinding was not possible or did not report whether outcome assessors were blinded, and it is unknown whether this may have impacted the findings of the studies.

One RCT[15] recruited patients who were newly diagnosed with TB, and followed all of the patients for the same length of time. Another RCT[14] also recruited patients who were newly diagnosed with TB and followed patients until the completion of their treatment, but the length of follow up was not reported and it is unclear whether the patients were followed for the same length of time. Three RCTs[17-19] recruited patients who had started their TB treatment with varying lengths of time remaining in their treatment and did not report the length of follow-up, thus it is unknown if the length of follow-up was the same for all patients and whether this influenced the findings in these studies. The other RCT[16] did not report whether patients had started TB treatment prior to enrollment or the length of follow-up, thus is it unknown if the length of treatment or follow-up may have affected the outcomes.

Five RCTs[15-19] used appropriate methods for randomizing the participants (e.g., computer generated random sequence), and in the other RCT[14] it was unclear if the method used was truly random, as the method for generating the random numbers was not described. Two of the RCTs[17,19] used an appropriate method for allocation concealment (e.g., patients allocated to intervention by computer generated randomization tool upon enrollment). In three of the RCTs[15,16,18] there was a risk of selection bias due to the method of allocation concealment (e.g., sealed opaque envelopes), as it may have been possible that the allocation sequence could have been revealed. The other RCT[14] was a cluster randomized trial that randomized districts to the intervention, therefore the allocated intervention was known prior to recruitment which could have biased the selection of participants.

The statistical analyses were generally well done across the RCTs, however, none of the studies adjusted their analysis for conducting multiples statistical tests. One of the RCTs[14] was a non-inferiority trial, which established their non-inferiority margin (i.e., –5%) a priori based on routinely collected program data on TB treatment success rate in their state. In addition, both the intention-to-treat analysis and the per-protocol analysis were reported, which is the correct approach for a non-inferiority trial. The authors of this non-inferiority trial[14] used the intention-to-treat analysis to form their conclusions for the test of non-inferiority, however, it would have been more appropriate to use the per-protocol analysis. Nonetheless, both analyses in this non-inferiority trial[14] were similar, adding confidence to the conclusion.

Two RCTs[17,19] were adequately powered for the primary outcome but not the secondary outcomes. It was unclear if a statistical power calculation was done in two RCTs.[16,18] One RCT[15] explicitly stated that they did not conduct a statistical power calculation and used a convenience sample size instead. The non-inferiority trial[14] calculated their sample size based off of 80% power, which may be insufficient power for a non-inferiority trial as it may bias the results towards non-inferiority.

The authors declared that they did not have any conflicts of interest in all six RCTs.[14-19] The source of the funding was reported in all the RCTs; three RCTs[14,15,17] also declared that the funders did not have any influence on the designs or reporting of the studies, and it was not reported whether the funders had any influence on the content of the report in the other three RCTs.[16,18,19]

Guidelines

Four of the guidelines[20,22-24] in this report were previously included in CADTH reports on guidelines for the treatment of TB[26] or for TB in people with compromised immunity.[27] The detailed critical appraisal of these guidelines can be found in those reports. In brief, the BHIVA guideline,[20] the NICE guideline,[24] and the ATS/CDC/IDSA guideline[22] used high-

quality systematic methods to search for evidence and develop the recommendations. The Singapore Guideline[23] did not report sufficient methodological details, and it was unclear whether a systematic approach was used to search for and evaluate the evidence.

The WHO guideline[25] had a clear description of the scope of the guideline, the health questions covered, the population to whom the guideline was meant to apply, and the target users of the guideline. The recommendations were specific and unambiguous, and were easy to identify in the document. This guideline followed standardized methodology developed by the WHO for guideline development,[28] and used a systematic approach to search for, select, and evaluated the evidence. The quality of the evidence was evaluated by assessing the risk of bias in the primary studies and grading the quality of the evidence using a standardized process. The process for formulating the recommendations was clear and transparent and there is an explicit link between the evidence and the recommendations. The guideline development group included members from all relevant disciplines, and the role and area of expertise of each member was clear. A qualitative study was undertaken to assess the views and preferences of the target population, but patients were not directly involved in developing the recommendations. The guideline was externally reviewed, and there is a specific procedure in place for updating the guideline. The funding agency was reported but it was not reported whether the funder was involved in the content of the guideline. All members of the guideline development group reported their potential conflicts of interest, and if any conflicts were declared significant they were not involved in the development of the recommendations.

The ECDC guideline[21] had clear descriptions of the objective of the guideline, the population to whom the guideline was meant to apply, and the target users of the guideline. A clear description was provided on the process for selecting the guideline panel. The names, organizations, and countries of the panel members were provided, however the roles and areas of expertise of each panel member was not reported. The health questions covered by the guideline were not specifically stated, although the research questions addressed by the SRs that informed the guideline are available in the protocol registration for each of the four SRs. The guideline did not report on the details of their search, thus it is unclear if systematic methods were used to search for evidence. The SRs that informed the guideline are not published but their protocol registrations include details of the planned search (e.g., databases, search terms, restrictions), although it is not known if there were deviations from the protocol. The eligibility criteria for selecting the evidence was well described in the protocol registrations for the SRs, and the guideline included a detailed description of the Delphi process for synthesis the evidence into recommendations. The evidence tables reported on the strength of the evidence for each primary study in the SRs, as well as the panel's assessment of the evidence (e.g., acceptability, feasibility), but no formal process for grading the evidence was used. The guideline did not report whether input was sought from the target population, nor was it reported how the benefits and risk of the interventions were considered when formulating the recommendations, thus the link between the evidence and recommendations was unclear. In addition, it was not reported whether the guideline was externally reviewed. The recommendations in this guideline are not easily identifiable, and they do not offer clear, unambiguous guidance. The authors declared no conflicts of interest, but the funding body was not reported.

Summary of Findings

Relevant findings are summarized below, and a detailed summary of the findings and authors conclusions are presented in Appendix 4.

Clinical Evidence for Direct Observational Therapy for Tuberculosis

One SR[13] and three RCTs[17-19] were identified regarding the clinical effectiveness of DOT compared to VOT.

Two SRs with meta-anlyses[11,12] and three RCTs[14-16] were identified regarding the clinical evidence of DOT provided in different locations or by different providers. There was some overlap in the primary studies that were included in these two SRs; the pooled estimates from separate reviews thus contain some of the same data. A citation matrix illustrating the degree of overlap is presented in Appendix 5.

Treatment Adherence

Different DOT Providers or Places

In one non-inferiority RCT,[14] in a subgroup of children who had successfully completed treatment, those who received DOT provided by a family member had similar numbers of missed doses of treatment compared to those who received DOT provided by a non-family member.

In one RCT,[16] patients with TB with problematic substance use who were treated with DOT provided by former substance users experienced no statistically significant difference in treatment interruptions, compared to those treated with standard DOT. In this study, those treated with standard DOT had a statistically significantly higher risk of not adhering to their treatment (i.e., refusing to take their medication or not showing up to schedule DOT appointments), and a statistically significantly higher risk failing to complete their treatment, (39% versus 15%) compared to those who received DOT from former substance users.[16]

DOT Compared to VOT

In the SR by Ngwatu et al (2018),[13] one of the relevant non-randomized studies reported no difference in treatment adherence (as measured by appointment compliance) between patients treated with VOT or DOT. The other relevant non-randomized study in this SR did not report on this outcome.

In one RCT[19] that compared patients treated with asynchronous VOT to those treated with DOT found a statistically significant difference in the number of days of non-adherence to medication and the proportion of patients who adhered to at least 80% of treatments over a two-week period (75.1% versus 19.5%), both in favour of treatment with asynchronous VOT.

In one RCT[17] when compared to standard DOT, patients treated with asynchronous VOT had statistically significantly higher odds of completing over 80% of their scheduled treatment observations in the first two months of treatment, a statistically significantly higher proportion of completed treatment observations (77% versus 39%) over the full follow-up period (up to 6 months), and a statistically significantly higher proportion of observed treatment doses per patient (78% versus 36%).

Successful Treatment

Different DOT Providers or Places

In the SR and meta-analysis by Zhang et al. (2016),[12] those treated with community-based DOT had a statistically significantly greater risk of successful treatment (i.e., composite outcome of cured or completed) compared to those treated with clinic-based DOT. When

studied separately, those treated with community-based DOT had a statistically significantly higher likelihood of completing treatment compared to those who used clinic-based DOT, but there was no difference between groups in the likelihood of cured treatments.[12]

In the SR and meta-analysis by Wright et al. (2015)[11] patients treated with community-based DOT had higher odds of treatment success compared to those treated with clinic-based DOT. This result was borderline statistically significant with the lower bound of the confidence interval close to one (i.e,.1.01), and the probability value was close to the cut-off for significance.[11] Similar results were observed in the analysis that combined RCTs with non-randomized studies [with very high (84%) statistical heterogeneity], and the analysis of non-randomized studies alone [lower statistical heterogeneity (19%)].[11]

One SR and meta-analysis found no difference in the likelihood of successful treatment (i.e., composite outcome of cured or completed), or cured or completed treatment when studied independently between those treated with community-based DOT and those treated with family-based DOT.[12]

In one SR and meta-analysis of two cohort studies, those treated with community-based DOT were statistically significantly less likely to experience treatment success (i.e., cured or completed) compared to those treated with workplace-based DOT.[12]

In the non-inferiority trial in children with TB,[14], similar rates of treatment success were observed in both groups (i.e., DOT provided by a family member or by a non-family member), and DOT provided by a family member (the new intervention) was shown to be non-inferior to DOT provided by a non-family member (the existing procedure).

In one RCT[15] of DOT provided by health care workers, a statistically significantly higher proportion of patients treated with hospital-based DOT did not complete their treatment compared to those treated by home-based DOT.

DOT Compared to VOT

One SR[13] reported no difference in the rate of treatment completion in those treated with VOT compared to those treated with DOT in the two relevant non-randomized studies.

One RCT[18] reported no differences in the proportion of patients who experienced a positive TB treatment outcome (i.e., cured or completed treatment) between those treated with synchronous VOT and those treated with DOT.

One RCT[19] reported no difference in treatment success between patients treated with asynchronous VOT and those treated with DOT.

Treatment Failure

Different DOT Providers or Places

In the SR and meta-analysis by Zhang et al. (2016),[12] there was no difference in the risk of treatment failure between those treated with community-based DOT and those treated with clinic-based DOT, or between patients treated with community-based DOT compared to family-based DOT.

DOT Compared to VOT

One RCT[18] reported no differences in the proportion of patients who experienced a negative TB treatment outcome (i.e., death or treatment failure) between those treated with synchronous VOT and those treated with DOT.

Treatment Default or Lost to Treatment Follow-Up

Different DOT Providers or Places

In the SR and meta-analysis by Zhang et al. (2016),[12] those treated with community-based DOT had a lower risk of treatment default compared to those treated with clinic-based DOT; the finding was statistically significant when 10 studies were included in the meta-analysis (RCTs and cohort studies), but the significance was lost when only RCTs were considered in the analysis.

In the SR and meta-analysis by Wright et al. (2015)[11] patients treated with community-based DOT had similar odds of being lost to follow-up during treatment compared to those treated with clinic-based DOT.

DOT Compared to VOT

One RCT[18] reported no differences in the proportion of patients who were lost to follow-up during the treatment between those treated with synchronous VOT and those treated with DOT.

Guidelines Regarding the use of Direct Observational Therapy for Tuberculosis

Six evidence-based guidelines[20-25] included recommendations regarding the use of DOT.

Who should receive DOT

In patients with HIV, the BHIVA guideline[20] recommends that DOT may be included as part of patient centered treatment plans, and recommends the use of DOT in patients with HIV with multi-drug resistant TB; these recommendation were based off the clinical judgement and experience of the guideline development group. This guideline[20] recommends against the use of DOT in patients with HIV with active TB; this is a strong recommendation based on moderate quality evidence.

The NICE guideline[24] recommends DOT as part of enhanced case management for certain at-risk groups (e.g., evidence of nonadherence to treatment, history of homelessness, multi-drug resistant TB) and the children of these at-risk groups; these recommendations were based off low-quality evidence but are made with certainty that for most patients DOT will do more good than harm.

The ATS/CDC/IDSA guideline[22] recommends the use of DOT for routing treatment of all forms of TB; this is a conditional recommendations based on evidence with low-certainty in the findings.

The Singapore guideline[23] recommends DOT for all infectious TB cases; moderate recommendation based on moderate quality evidence. The Singapore guideline[23] also recommends the use of DOT for the treatment of patients with multi-drug resistant TB; weak recommendation based on expert opinion.

Who should administer DOT

The WHO guideline[25] recommends that DOT be administered by trained lay providers or health-care workers rather than family members or unsupervised treatment; this is a conditional recommendation based on evidence with very low certainty in the findings.

The NICE guideline[24] recommends that trained, non-clinically qualified professional can be employed to administer DOT; this recommendation was based off low-quality evidence and made with certainty that DOT will do more good than harm for most patients.

Where should DOT be administered

The WHO guideline[25] recommends community- or home-based DOT over health facility-based DOT or unsupervised treatment; this is a conditional recommendation based of evidence with moderate certainty in the findings.

VOT

The WHO guideline[25] recommends using VOT to replace DOT where the technology is available. This is a conditional recommendation based on evidence with low-certainty in the findings.

In patients with HIV, the BHIVA guideline[20] recommends that VOT may be included as part of patient centered treatment plans; this recommendation was based off the clinical judgement and experience of the guideline development group. However, the BHIVA guideline[20] specifically recommends against the use of VOT in patients with HIV with active TB; this is a strong recommendation based on moderate quality evidence. This guideline recommends the use of VOT in patients with HIV with multi-drug resistant TB; this recommendation was based off the clinical judgement and experience of the guideline development group.

In vulnerable and hard-to-reach populations, the ECDC guideline[21] recommends that VOT can be an alternative to DOT; this recommendation was based on weak evidence.

Limitations

There are various limitations with the evidence in this report on the clinical evidence and guidelines regarding the provision of DOT for the treatment of TB.

A key limitation of this evidence is the heterogeneity of the findings. This report includes comparisons across a variety of interventions, including the type of VOT (i.e., synchronous or asynchronous VOT), who served as the providers of DOT (e.g., family members, former substance users, health care workers, lay people), and the location where DOT was provided (e.g., home, clinic, community). There was also substantial heterogeneity in patients included in this body of evidence; the majority of studies were conducted in adults but the age cut-off varied across studies, with one study conducted in children, and one study conducted in patients with problematic substance use. In addition, the stage of TB treatment varied across studies, with some studies restricting eligibility to patients who had not started TB treatment and other allowing entry to the study based on the minimum number of months remaining in the TB treatment (ranging from one to four months). These differences would have affected the length of time that the patients received the DOT or VOT intervention. It is unclear how the heterogeneity of this body of evidence may affect the certainty of the evidence, and the generalizability of these findings to the clinical context.

This evidence is also limited by the paucity of high-quality clinical evidence. The three SRs included in this report were low to moderate quality, and included a mix of primary studies assessed by the authors as ranging from very-low to moderate quality. The six RCTs included in this review were low quality, with various risks of bias due to unblinded participants, poor allocation concealment, and poor outcome reporting. In addition, the relevant recommendations in the guidelines were based primarily on expert opinion or low-quality evidence, with some moderate-quality evidence. The overall low-quality evidence reduces the certainty of the findings in this report.

The outcomes included in this report were also limited to those relating to treatment adherence, thus it is unknown whether the interventions studied in this report influence other TB related outcomes (e.g., development of drug resistant TB, adverse events).

The generalizability of the findings in this report remain unclear. One RCT[16] was limited to a very specific population (i.e., patients with TB with problematic substance use) and the intervention was targeted for this population (i.e., DOT provided by former substance users), and the findings might not be generalizable to the general population. In addition, none of the studies were conducted in Canada, and while one guideline[25] is meant to apply globally, none of the guidelines are specific to Canada. The 2014 TB standards[3,4] published by Public Health Agency of Canada includes recommendations regarding DOT, however, this guideline has not been updated since 2014 and was not eligible for inclusion in this report. It is unknown if the studies conducted outside of Canada and recommendations from guidelines developed outside of Canada are generalizable to the Canadian clinical practice as there may be geographical differences between countries in access to care for TB, specifically DOT providers.

Conclusions and Implications for Decision or Policy Making

This report was comprised of three SRs,[11-13] and six RCTs[14-19] with clinical evidence regarding the provision of DOT for the treatment of TB. Six evidence-based guidelines[20-25] were summarized regarding the use of DOT for the treatment of TB.

DOT is recommended for the general population with TB,[22,23] for those with multi-drug resistant TB,[23,24] for high-risk groups requiring enhanced case-management,[24] and for patients with HIV with multi-drug resistant TB.[20] One guideline recommended against the use of DOT in patients with HIV with drug-susceptible active TB.[20]

With regard to who should administer DOT, two guidelines recommended that DOT be provided by lay providers or health care workers trained to administer DOT.[24,25] This report found that DOT provided by a family member resulted in similar outcomes compared to DOT provided in the community or by a non-family member. In one SR and meta-analysis, family-based DOT and community-based DOT had similar rates of cured or completed treatment, or the risk of treatment failure.[12] In addition, in children with TB, the provision of DOT by a family member at home was shown to be no worse than the current standard of care (i.e., DOT provided by a non-family member) with regard to the rate of treatment success, and both groups had similar numbers of missed doses of treatment.[14] This suggests that for some patients, DOT provided by a family member may be a practical alternative to the provision of DOT by non-family members (e.g., community or government workers) or in the community. Although one guideline[25] specifically recommended the use of trained DOT providers rather than having family members providing DOT.

In the specific situation of patients with TB with problematic substance use, the choice of DOT provider may affect adherence outcomes, as those treated by a former substance user (trained to provide DOT), were more likely to adhere to their treatment and more likely to complete their complete their treatment, compared to those who were treated with standard DOT.[16]

With regard to where DOT should be administered, one guideline[25] recommends community-based or home-based DOT rather than facility-based DOT. This report includes one study that suggests that when DOT was provided by health care workers, that those who received DOT at home were more likely to complete their treatment compared to those who received hospital-based DOT.[15] Patients who received workplace-based DOT were also more likely to have a successful treatment outcome (i.e., cured or completed) compared to those treated with community-based DOT.[12]

The evidence in this report suggests that community-based DOT may produce similar or improved outcomes when compared to clinic-based DOT. There is some evidence that patients treated with community-based DOT were more likely to experience treatment success (i.e., cured or completed treatment) when compared to clinic-based DOT.[11,12] When these outcomes were examined separately, those who received community-based DOT were more likely to complete their treatment but there was no difference in the likelihood of their TB being cured.[12] In addition, patients treated with community-based DOT or clinic-based DOT experienced similar rates of treatment failure,[12] and had similar chances of being lost to follow-up during treatment.[11,12]

In general, the evidence concerning the impact of the location for the provision of DOT on the success of TB treatment suggests that some locations (e.g., home, workplace, community) may result in similar or improved outcomes, and that these locations should be considered when selecting a DOT location.

With regard to the method of administering DOT, VOT is recommended as an alternative to DOT for the general population with TB,[25] in vulnerable and hard-to-reach populations,[21] and in patients with HIV with multi-drug resistant TB,[20] based on weak evidence. In contrast VOT is not recommended in people with HIV with active TB, based moderate evidence.[20]

The evidence in this report suggests that VOT results in similar or improved outcomes for treatment adherence and treatment success compared to DOT. When compared to standard DOT, asynchronous VOT resulted in better treatment adherence,[17,19] and similar rates of treatment success (i.e. cured or completed treatment).[19] he use of synchronous VOT resulted in no difference in treatment success (i.e., cured or completed treatment), treatment failure (i.e., death or treatment failure), or the proportion of patients lost to follow during treatment, when compared to standard DOT,[18] but it was not reported whether there were differences in treatment adherence. Similar rates of treatment adherence or successful (i.e., completed) treatment were also observed in a non-randomized study identified in a SR,[13] between those treated with VOT versus DOT, however, it was not specified whether VOT was synchronous or asynchronous.

Overall, VOT may be a good alternative to DOT. VOT may be particularly useful in areas where resources for DOT are limited, or in populations where in-person DOT might be difficult. Considerations should be made regarding whether the patients have access to the technology for VOT and whether they are capable of using the technology.

The findings highlighted this report are associated with a moderate degree of uncertainty due to the low- to moderate-quality evidence and the heterogeneity in the included publications. The limitations of the included publications of this report should be considered when interpreting the findings. Similar results were observed across the different forms of DOT, the different DOT providers, and different DOT locations, suggesting that no method of DOT is substantially better than another approach. It may be necessary to consider additional factors when selecting an approach to DOT for patients with TB, such as the cost-effectiveness, resource availability, and barriers to accessing DOT.

References

1. Long R, Schwartzman K. Canadian Tuberculosis Standards, Chapter 2 - Pathogenesis and Transmission of Tuberculosis. 7th Ed ed. Ottawa: Public Health Agency of Canada; 2014: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-14.html. Accessed 2020 Oct 29.
2. Tuberculosis: Symptoms and treatment. Ottawa: Public Health Agency of Canada; 2019: https://www.canada.ca/en/public-health/services/diseases/tuberculosis.html. Accessed 2020 Oct 29.
3. Menzies D, Elwood K. Canadian Tuberculosis Standards, Chapter 5 - Treatment of Tuberculosis Disease. Ottawa: Public Health Agency of Canada; 2014: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-17.html. Accessed 2020 Oct 29.
4. Menzies D, Alvarez GG, Khan K. Canadian Tuberculosis Standards, Chapter 6 - Treatment of Latent Tuberculosis Infection. Ottawa: Public Health Agency of Canada; 2014: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-18.html. Accessed 2020 Oct 29.
5. Reichman LB. Adherence to tuberculosis treatment Waltham (MA): UpToDate; 2019 Sep 26.
6. Direct Observational Therapy for the Treatment of Tuberculosis: Clinical Evidence and Guidelines. *(CADTH rapid response report: summary of abstracts)*. Ottawa: CADTH; 2020 May: https://www.cadth.ca/sites/default/files/pdf/htis/2020/RB1475%20DOT%20for%20TB%20Final.pdf. Accessed 2020 Nov 23.
7. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj.* 2017;358:j4008.
8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.
9. Agree Next Steps C. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2020 Nov 23.
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
11. Wright CM, Westerkamp L, Korver S, Dobler CC. Community-based directly observed therapy (DOT) versus clinic DOT for tuberculosis: a systematic review and meta-analysis of comparative effectiveness. *BMC Infect Dis.* 2015;15:210.
12. Zhang H, Ehiri J, Yang H, Tang S, Li Y. Impact of Community-Based DOT on Tuberculosis Treatment Outcomes: A Systematic Review and Meta-Analysis. *PLoS ONE.* 2016;11(2):e0147744.
13. Ngwatu BK, Nsengiyumva NP, Oxlade O, et al. The impact of digital health technologies on tuberculosis treatment: a systematic review. *Eur Respir J.* 2018;51(1):01.
14. Dave PV, Shah AN, Nimavat PB, et al. Direct Observation of Treatment Provided by a Family Member as Compared to Non-Family Member among Children with New Tuberculosis: A Pragmatic, Non-Inferiority, Cluster-Randomized Trial in Gujarat, India. *PLoS ONE.* 2016;11(2):e0148488.
15. Adewole OO, Oladele T, Osunkoya AH, et al. A randomized controlled study comparing community based with health facility based direct observation of treatment models on patients' satisfaction and TB treatment outcome in Nigeria. *Trans R Soc Trop Med Hyg.* 2015;109(12):783-792.
16. Ricks PM, Hershow RC, Rahimian A, et al. A randomized trial comparing standard outcomes in two treatment models for substance users with tuberculosis. *Int J Tuberc Lung Dis.* 2015;19(3):326-332.
17. Story A, Aldridge RW, Smith CM, et al. Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicentre, analyst-blinded, randomised, controlled superiority trial. *Lancet.* 2019;393(10177):1216-1224.
18. 1Guo P, Qiao W, Sun Y, Liu F, Wang C. Telemedicine Technologies and Tuberculosis Management: A Randomized Controlled Trial. *Telemedicine Journal & E-Health.* 2020;26(9):1150-1156.
19. Ravenscroft L, Kettle S, Persian R, et al. Video-observed therapy and medication adherence for tuberculosis patients: randomised controlled trial in Moldova. *Eur Respir J.* 2020;56(2).
20. Anonymous. British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2019. *HIV Med.* 2019;20 Suppl 6:s2-s83.
21. Guidance on tuberculosis control in vulnerable and hard-to-reach populations. Stockholm: European Centre for Disease Prevention and Control; 2016: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/TB-guidance-interventions-vulnerable-groups.pdf. Accessed 2020 Oct 6.
22. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clin Infect Dis.* 2016;63(7):e147-e195.
23. Prevention, Diagnosis and Management of Tuberculosis. Singapore: Ministry of Health; 2016: https://www.moh.gov.sg/docs/librariesprovider4/guidelines/moh-tb-cpg-full-version-for-website.pdf. Accessed Oct 6, 2020.
24. Turnbull L, Bell C, Child F. Tuberculosis (NICE clinical guideline 33). *Arch.* 2017;102(3):136-142.

25. WHO. WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. 2020: https://www.who.int/publications/i/item/9789240007048 Accessed Oct 6, 2020.

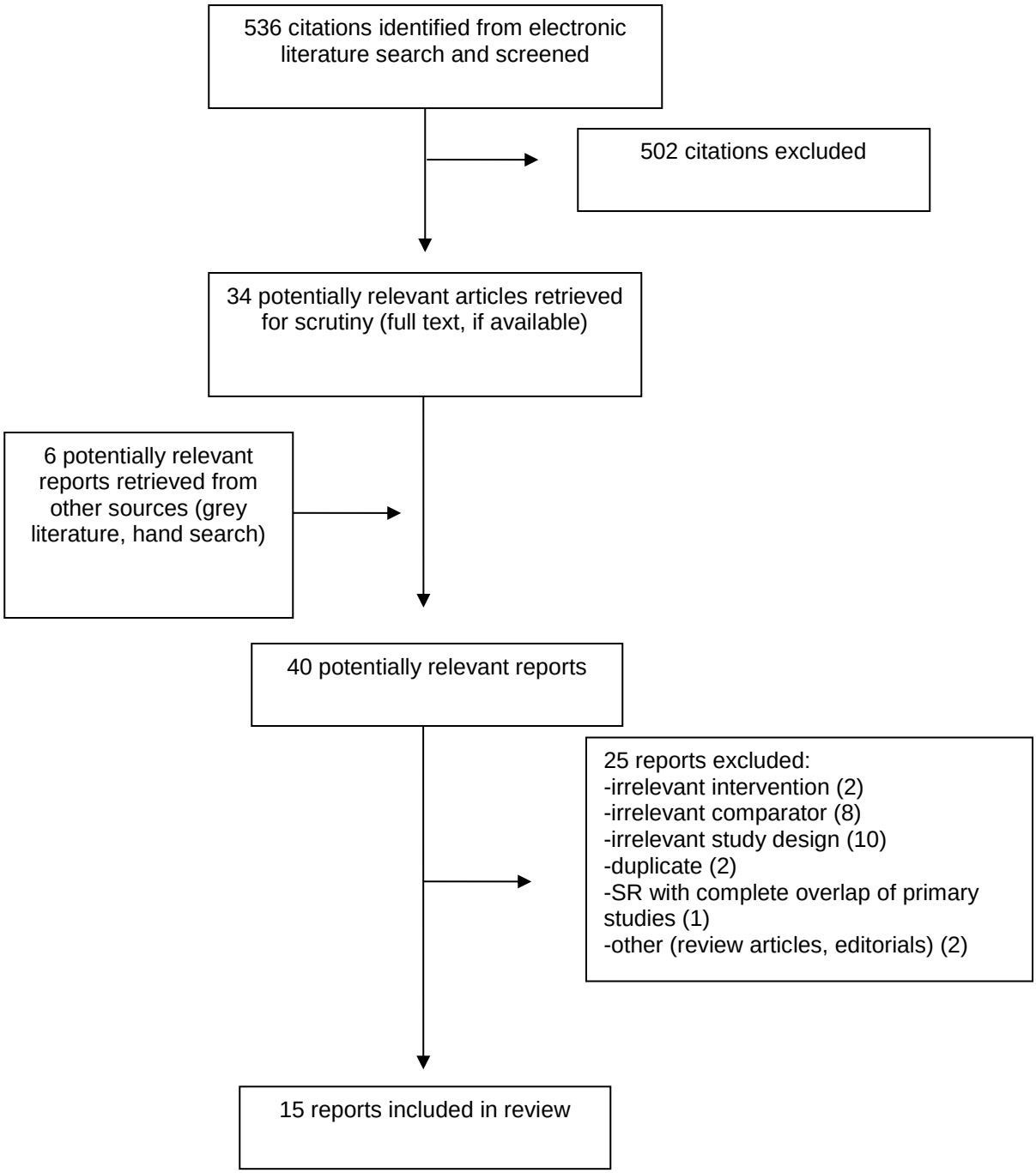
26. Treatment of Tuberculosis: A Review of Guidelines. *(CADTH rapid response report: summary with critical appraisal)*. Ottawa: CADTH; 2020 Mar: https://cadth.ca/treatment-tuberculosis-review-guidelines. Accessed 2020 Oct 30.

27. Tuberculosis in People with Compromised Immunity: A Review of Guidelines. *(CADTH rapid response report: summary with critical appraisal)*. Ottawa: CADTH; 2020 Mar: https://cadth.ca/tuberculosis-people-compromised-immunity-review-guidelines. Accessed 2020 Oct 30.

28. World Health Organization. WHO handbook for guideline development. Geneva: World Health Organization; 2014: http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf. Accessed 2020 Oct 30.

29. Developing NICE guidelines: the manual. London: National Institute for Health and Care Excellence; 2014; updated 2018: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview. Accessed 2020 Oct 30.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Network Meta-Analyses

Study citation, country, funding source	Number and designs of primary studies included	Population characteristics	Intervention and comparator(s)	Relevant clinical outcomes, length of follow-up
Ngwatu et al. (2018)[13] Switzerland **Funding:** European Respiratory Society, via the World Health Organization Stop TB Program	7 studies in total: 2 NRS relevant to this report	**Includes**: Patients with TB **Excludes**: Not reported	**Eligible interventions**: digital health technology interventions to support adherence to TB treatment **Relevant interventions**: VOT **Eligible comparators**: local standard of care (as defined by study authors) **Relevant comparator**: in-person DOT	**Primary outcomes**: Adherence to treatment or appointments **Follow-up**: Not specified
Zhang et al. (2016)[12] China **Funding:** National Science Foundation of China, and Social Science and Technology Innovation Subject in Chongqing	8 RCTs and 9 cohort studies included in SR Of these, 8 RCTs and 6 cohort studies were included in the meta-analysis	**Includes**: Patients with pulmonary TB (included new cases, and those undergoing retreatment) **Excludes**: Patients with extrapulmonary TB	**Eligible interventions**: Community-based DOT provided by lay/community health workers, volunteers, peers, friends (excludes family or workplace individuals) **Eligible comparators**: Clinic-based DOT, family-based DOT, workplace-based DOT, self-administered therapy **Relevant comparator**: Clinic-based DOT, family-based DOT, workplace-based DOT	**Primary outcomes**: Successful treatment (i.e., cured or completed treatment) **Secondary outcomes**: Cured treatment (assessed by sputum smear), completed treatment, treatment failure (assessed by sputum smear), default (i.e., treatment interruption for 2 or more months) **Follow-up**: not specified
Wright et al. (2015)[11] Australia **Funding:** none reported	1 RCT and 7 NRS included in the SR and meta-analysis	**Includes**: Patients with any type of TB (i.e., pulmonary, extra-pulmonary, drug-sensitive, drug-resistant) **Excludes**: none reported	**Eligible interventions**: Community-based DOT delivered by community health workers or community volunteers **Eligible comparator**: Clinic-based DOT	**Primary outcomes**: Proportion of patients successfully treated **Secondary outcomes**: Proportion of patients lost to treatment follow up **Follow-up**: not specified

DOT = direct observational therapy; NRS = non-randomized study; RCT = randomized controlled trial; SR = systematic review; TB = tuberculosis; VOT = video observed therapy

Table 3: Characteristics of Included Randomized Controlled Trials

Citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Relevant Clinical outcomes, length of follow-up
Guo et al. (2020)[18] China **Funding**: Shandong Medicine and Health Science and Technology Development Plan, and Shandong University-affiliated Shandong Provincial Chest Hospital	RCT, 2 arms 1:1 randomization Setting: One hospital, between January and December 2018	**Inclusion criteria**: Adults (>18 years), with bacteriologically confirmed TB, who could be treated out of hospital, with at least 1 month remaining of treatment **Excludes**: Younger than 18, those with drug-resistant TB, unable to use a smartphone due to physical conditions **Number of patients**: VOT = 203 DOT = 202 **Mean age (SD)**: VOT = 40.2 (16.1) DOT = 44.3 (17.7) **TB retreatment (%)** VOT = 15.3% DOT = 18.3%	**Intervention**: synchronous VOT, carried out using a smartphone app, medication taken on live video under observation by administrator **Comparator**: DOT, per regular clinic protocol, required observation by health care worker or lay worker once every 2 days	**Primary outcome**: TB treatment result, identified as follows: - good (cured and treatment completed) - poor (death, failure) -lost to follow up (i.e., treatment interrupted for 2 consecutive months or more) **Follow-up**: not specified
Ravenscroft et al. (2020)[19] England **Funding**: United Nations Development Program, and unlimited internet provided by Moldcell	RCT, 2 arm 1:1 randomization Setting: Capital city of Moldova in Eastern Europe, January 2016 to November 2017	**Inclusion criteria**: Adults (>18 years) with TB, have at least 4 months of treatment remaining, and are in either intensive phase, continuation phase, or phase after finishing intramuscular injection of streptomycin or treatment **Excludes**: multi-drug resistant TB, people who are homeless or suffer from alcoholism or drug misuse **Number of patients**: VOT = 98 DOT = 99 **Mean age (SD)**: VOT = 38.73 (13.95) DOT = 38.27 (14.11)	**Intervention**: asynchronous VOT; patients recorded themselves taking the medication and send in a video daily to the VOT observer. **Comparator**: DOT, following standard procedure, patients visited local TB clinic daily Monday to Friday to be observed taking medicine All patients received food vouchers as adherence incentives	**Primary outcome**: adherence to medication (i.e., number of days over a two-week period [weekdays only] a patient not observed adhering to medication) **Secondary outcomes**: treatment success (measured by sputum smear and X-ray) **Follow-up**: 12 months

Citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Relevant Clinical outcomes, length of follow-up
Story et al. (2019)[17] UK **Funding:** National Institute of Health Research Program Grants for Applied Research scheme	RCT, superiority trial Analyst-blinded Randomization by minimization to ensure balance across sites and stage of treatment Setting: Multi-center at 22 clinics in England, between September 2014 and December 2016	**Inclusion criteria**: People 16 year or older, with active pulmonary or non-pulmonary TB **Excludes**: People with multi-drug resistant TB, those with less than 2 months of treatment remaining, and those who were not suitable for VOT due to lack of access to facilities to charge a smartphone **Number of patients**: N = 226 randomized VOT, n = 112 DOT, n = 114 **Age range (%)**: 16 to 34: VOT, 57% vs. DOT, 54% 35 to 54: VOT, 31% vs. DOT, 40% **Pulmonary TB (%)** VOT,76% vs. DOT, 72%	**Intervention**: Asynchronous VOT. Patients recorded and sent videos of every dose, 7 days per week using a smartphone app **Comparator**: DOT in a clinic, community (e.g., pharmacy or hostel), or home setting. Treatment was observed 3 to 5 days per week by a health-care or lay worker, with other doses self-administered.	**Primary outcome**: Successful completion of 80% or more of scheduled treatment observations in the 2 months post-randomization **Secondary outcomes**: Proportion of scheduled observations successfully completed in 2 months post-enrollment, and throughout treatment **Follow-up**: 2 months, and up to 6 months
Dave et al. (2016)[14] India **Funding**: Government Revised National Tuberculosis Control Program, Gujarat, India.	RCT, non-inferiority trial Decided a priori (based on routinely collected data on treatment success rate) that the margin for determining non-inferiority was –5% (for primary outcome) Cluster-randomized, stratified Intention-to-treat analysis and a per-protocol analysis	**Inclusion criteria**: Children < 15 years, with newly diagnosed TB **Excludes**: Children who required hospitalization **Number of patients**: Family DOT = 359 Non-family DOT = 265 **Age range (%)**: 6 to 10: Family DOT, 34.8% vs, non-family DOT, 32.1% 11 to 14: Family DOT, 34.3% vs, non-family DOT, 37.7% **Smear positive pulmonary TB, %** Family DOT, 16.2% Non-family DOT, 16.2%	**Intervention**: DOT provided by family member at home **Comparator**: DOT provided by non-family member (e.g., government or community provider)	**Primary outcome**: Treatment success (cured and completed treatment) **Secondary outcomes**: Number of missed doses among children who successfully completed treatment **Follow-up**: not reported

Citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Relevant Clinical outcomes, length of follow-up
	Setting: 30 districts in Gujarat from June to September 2012	**Extrapulmonary TB, %** Family DOT, 54.6% Non-family DOT, 54.0%		
Adewole et al. (2015)[15] Nigeria **Funding**: World Health Organization Tropical Diseases Research	RCT, 2-arm Block randomization Setting: 4 TB clinics in Nigeria	**Inclusion criteria**: People 15 years or older, who haven't yet started TB treatment[18] **Excludes**: TB patients younger than 15, or already on treatment **Number of patients**: Home-based DOT, n = 75 Hospital-based DOT, n = 75 **Mean age (SD)**: Home-based DOT, 37.7 (17.0) Hospital-based DOT, 35.2 (14.7)	**Intervention**: Home-based DOT provided by staff or health care workers, daily **Comparator**: Hospital-based DOT, daily Both interventions lasted for the first 2 months of treatment (the "intensive phase"), followed by monthly clinic visits for 4 more months	**Primary outcome**: Treatment completion at the end of 2 months **Follow-up**: 2 months
Ricks et al. (2015)[16] USA **Funding:** National Heart, Lung and Blood Institute of the National Institutes of Health	RCT Setting: 2 TB clinics in low socioeconomic inner-city Chicago neighborhoods between October 1996 and June 2000	**Inclusion criteria**: People 18 or older with active TB, with problematic substance use (illicit drug use and/or daily consumption of 2 or more alcoholic beverages) **Excludes**: none reported **Number of patients**: Enhanced DOT, n = 48 Standard DOT, n = 46 **Mean age (SD)**: 41.4 (9.5)	**Intervention**: DOT provided by former substance users (with several years in recovery), who were trained HIV prevention outreach workers **Comparator**: DOT provided by public health workers In both treatment arms, DOT was provided at a location of the patient's choice	**Primary outcome**: Treatment completion (i.e., whether patient took > 80% of prescribed doses within 6 months or all doses in 1 year) **Secondary outcomes**: Treatment gaps (i.e., number of consecutive missed DOT appointments) **Follow-up**: up to 1 year

DOT = direct observational therapy; RCT = randomized controlled trial; TB = tuberculosis; VOT = video observed therapy.

Table 4: Characteristics of Included Guidelines

Intended users, target population	Relevant intervention and outcomes	Evidence collection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
WHO, 2020[25]					
Intended users: Policy-makers in ministries of health, managers of national tuberculosis programs **Target population:** Patients with suspected or confirmed DR-TB	**Intervention:** Treatment of DR-TB - patient support for treatment adherence (e.g., education, DOT) **Outcomes**: Treatment adherence, treatment failure, loss to follow-up, adverse events	Nine previous WHO guidelines were consolidated, and their SRs were updated (where necessary), and new evidence was integrated into the evidence tables. The evidence for each research question was appraised and used to formulate recommendations. The GRADE "evidence-to-decision" tables were used to guide discussions on the benefits and harms, the quality of evidence, the cost, feasibility, acceptability, equity, values, and preferences.	GRADE approach used to appraise the evidence. Four levels of evidence quality: High: Very confident that the true effect lies close to that of the estimate of the effect. Moderate: Moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different.	Development of the recommendations followed the process outlined in the WHO Handbook for Guideline Development[28] Recommendations were formulated a consensus process. When consensus could not be reached, a voting process was used. Two levels of strength of the recommendation: Strong: the GDG was confident that the desirable effects of adherence would outweigh the undesirable effects. Could be either in favour of or against an intervention. Conditional: the GDG concluded that the desirable effects of adherence would probably outweigh the undesirable effects, but the GDG was not confident about the trade-off. Reasons for lack of confidence included: absence of high-quality evidence; imprecise estimates of benefit or harm; uncertainty or variation in the value of the outcomes for different individuals; and small benefits or benefits that might not be worth the cost.	The external review group reviewed the draft of the final guideline, and remarks were evaluated by the steering group and incorporated into the final version of the guidelines The recommendations and supporting documents were reviewed and endorsed by all GDG members.

Intended users, target population	Relevant intervention and outcomes	Evidence collection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
BHIVA, 2019[20]					
Intended Users: Physicians, health care professionals **Target Population:** Adults living with HIV	**Intervention:** - Treatment of LTBI - Treatment of active TB - DOT - VOT **Outcomes:** Not reported	A systematic search of the literature was conducted for each selection criteria and topic. Nine different searches were conducted, and each PICO criteria was outlined every search. The writing group members identified and evaluated the available literature for each of the nine searches	Modified GRADE approach was used to assess the quality of the body of evidence and the strength of the recommendations for each research question. The strength of the recommendation looked at the quality of the defined outcomes of the intervention but also the difference between desirable and undesirable effects, values and preferences or resource use. The quality of evidence was graded into four categories: A = true effect lies close to the estimate effect supported by high quality evidence B = moderate quality evidence with consistent effects and exclusion of most potential sources of bias. C = low quality evidence with a variety of limitations including the effects and potential bias. D = evidence only based on case studies or expert opinion leading to little confidence in the effect estimate.	Based upon the GRADE instrument the authors aimed to reach a consensus on the strength of recommendation and level of supporting evidence. Quality of the evidence: A = true effect lies close to the estimate effect supported by high quality evidence B = moderate quality evidence with consistent effects and exclusion of most potential sources of bias. C = low quality evidence with a variety of limitations including the effects and potential bias. D = evidence only based on case studies or expert opinion leading to little confidence in the effect estimate. The evidence was graded into: Grade 1(A, B, C and D) = strong recommendation Grade 2 (A, B, C and D) = weaker or conditional recommendation Good practice points = recommendations based on the clinical judgement and experience of the group where there is not, or unlikely to be, sufficient evidence. They are regarded as sound clinical practice, but do not replace evidence-based recommendations.	Before final approval by the writing group, the guidelines were published online for public consultation and an external peer review was commissioned.

Intended users, target population	Relevant intervention and outcomes	Evidence collection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
NICE, 2017[24]					
Intended users: Healthcare professionals and TB multidisciplinary teams. Substance misuse services, prisons and immigration removal centers Local government and commissioners. TB control boards, directors of public health and public health consultants. People with TB and their carers. **Target population:** General population (all ages)	**Intervention:** Adherence to treatment and follow-up - DOT - other strategies **Outcomes:** Adherence related outcomes	Update to a previous 2011 version of the guideline. Multiple SRs were conducted for the entire guideline, using comprehensive search strategies. For each SR, detailed eligibility criteria were reported. GRADE evidence profiles were prepared. Criteria considered included risk of bias, inconsistency.	NICE methodological checklists were used to critically appraise RCTs and cohort studies. GRADE was used to critically appraisal the body of evidence.	Developed in accordance with the NICE manual for developing guidelines[29] Recommendations consider the trade off of benefits and harms, and the quality of the evidence. The results of the meta-analyses were sent to the guideline development group prior to each meeting. At the meetings, the findings were presented in evidence tables, excluded study tables, GRADE profiles, and evidence statements on the findings. Statements summarizing the groups interpretation of the findings was used to form the recommendations. A consensus method was used to formulate the recommendations. Specific 'linking evidence to recommendation' criteria were used to guide the development of the recommendations. The wording used in the recommendations denotes the certainty in the recommendations. The terms used in this guideline are: "Offer' – for the vast majority of patients, an intervention will do more good than harm 'Do not offer' – the intervention will not be of benefit for most patients	The guideline was published online for two formal rounds of public and stakeholder consultation prior to publication. This process involves responding to each comment, and maintaining an audit trail.

Intended users, target population	Relevant intervention and outcomes	Evidence collection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
				'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient." (p. 90)	
ATS/CDC/IDSA, 2016[22]					
Intended Users: National TB programs, or their equivalents in ministries of health, and for other policy-makers working on TB **Target Population:** General population	**Intervention:** Treatment of active TB: - DOT **Outcomes:** Mortality, treatment success, treatment completion, relapse, adherence, time to smear conversion,	For each research question, a systematic review was conducted using systematic methods. Methodologists prepared evidence profiles for each review. Evidence-to-decision tables were prepared based on benefits, harms, patient values and costs.	The certainty of the evidence for each outcome was then assessed using GRADE, based on risk of bias, precision, consistency, magnitude, directness, risk of publication bias, the dose-effect relationship, and confounding.	Development of recommendations followed procedures outlined in a "Guideline Development Checklist" (available online) The guideline panel used the evidence summaries and the evidence-to-decision tables to formulate the recommendations. Recommendations were decided by consensus, and none required voting. Recommendations were rated as either "strong" or "weak/ conditional." "Strong recommendation For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not. For clinicians: Most individuals should receive the intervention.	A final draft of the guideline was peer reviewed by experts in the field, and the document was revised to incorporate the comments.

Intended users, target population	Relevant intervention and outcomes	Evidence collection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
				Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. Weak/Conditional recommendation. For patients: The majority of individuals in this situation would want the suggested course of action, but many would not. For clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences..“ (p. 9, Appendix A)	
ECDC, 2016[21]					
Intended users: National policymakers, entities responsible for health care planning and social support, national TB programs, civil society organizations and non-governmental	**Intervention:** Interventions for enhanced case management (e.g., DOT) **Outcomes:** Treatment completion	Four SRs were performed to synthesis evidence. Evidence tables were created to summarize the evidence.	Strength of evidence for each primary study was assessed [The strength of evidence was assessed and reported as “no evidence,” “weak evidence,” “moderate evidence,” and “strong evidence.”], and a four criteria and a grading system was developed to convey the ad hoc scientific panel opinions. This grading system assessed: acceptability,	An ad hoc scientific panel reviewed and assessed the evidence-base from the systematic literature reviews. Opinions on the evidence from the systematic reviews were collected through a Delphi process. Acceptability of the intervention by the target population, feasibility to implement the intervention, use of resources to implement the	No external review process reported.

Intended users, target population	Relevant intervention and outcomes	Evidence collection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Organizations, those working with vulnerable groups **Target population:** Vulnerable and hard-to-reach populations			feasibility (highly feasible, use of resources, anticipated cost-effectiveness	intervention, anticipated cost-effectiveness	
Singapore Guideline, 2016[23]					
Intended Users: All healthcare practitioners in Singapore **Target Population:** General population	**Intervention:** - DOT **Outcomes:** Not reported	Not reported	Methods for assessing the quality of the evidence was not reported, but the level of evidence scheme was reported: "*Levels of Evidence:* *1++ = High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.* *1+ = Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.* *1- = Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias* *2++ = High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal* *2+ = Well conducted case control or cohort studies with a low risk of confounding or bias*	The recommendations were appraised by scoring the strength of the evidence, and the grade of the recommendation. (No other details provided) *Grades of recommendation:* *A = At least one meta-analysis, systematic review of RCTs, or RCT rated as 1+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results* *B = A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+ + or 1+* *C = A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+ +*	No external review process reported.

Intended users, target population	Relevant intervention and outcomes	Evidence collection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
			and a moderate probability that the relationship is causal *2- = Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal* *3 = Non-analytic studies, e.g. case reports, case series* *4 = Expert opinion"* (p. 2)	*D = Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+* *GPP (good practice point) = Recommended best practice based on the clinical experience of the guideline development group*." (p. 2)	

ATS= American Thoracic Society; BHIVA = British HIV Association; CDC = Centers for Disease Control and Prevention; DOT = direct observational therapy; DR = drug-resistant; ECDC = European Centre for Disease Prevention and Control; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; IDSA = Infectious Disease Society of America; NICE = National Institute for Health and Care Excellence; PICO = population, intervention, comparison and outcomes; RCT = randomized controlled trial; SR = systematic review; TB = tuberculosis; WHO = World Health Organization.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses Using AMSTAR 2[7]

Strengths	Limitations
Ngwatu et al. (2018)[13]	
• Includes both RCTs and NRS • Comprehensive search strategy was used including searching multiple databases, and trial registries, and providing the complete search strategy. • Two authors performed study selection and data extraction in duplicate • A list of excluded studies was provided in the appendix with the reason for exclusion • Observational studies were critically appraised with a modified tool, and the risk of bias due to selection, confounding, and outcome measurement was reported • Authors reported no potential conflicts of interest • Source of funding was reported and it was stated that the funders did not influence the content of the review	• Eligibility criteria for the review was not clear or well defined. Details were lacking for the population, the intervention and the comparator. • Outcomes of interest were not defined. • No mention of an a priori protocol • Did not report how discrepancies in study selection or data extraction were resolved • Description of the included studies lacked details regarding the population, the specifics of the interventions and comparator, which outcomes were reported, and the length of follow up • Did not report the source of funding of the primary studies • Did not report how many people conducted the risk of bias assessments • Authors did not discuss how the risk of bias of the primary studies may have affected the results of the review
Zhang et al. (2016)[12]	
• Well described eligibility criteria for the review (i.e., population, intervention, comparator, outcomes) • Includes both RCTs and NRS • Comprehensive search strategy, including searching multiple databases, grey literature, hand searching, and providing complete search strategy • Used modified tools to assess risk of bias, assessed some of the main risks (e.g., allocation concealment for RCTs, selection for NRS) • Two reviewers performed study selection and data extraction in duplicate, disagreements were resolved through consensus • Two reviewers completed the risk of bias assessment • Primary studies were described in detail • Reported meta-analyses of only RCTs separately • Used random effects meta-analyses when there was high statistical heterogeneity • The authors discussed the potential impacts of the clinical heterogeneity of the studies • Authors reported no potential conflicts of interest	• No mention of an a priori protocol • Did not provide a list of excluded studies • Did not report the source of funding of the primary studies • Unclear if they were justified in combined both NRS and RCTs in meta-analyses • Did not account for the risk of bias of the individual studies when conducting the meta-analysis or when discussing the results of the review • Did not investigate the risk of publication (small study) bias, but acknowledged that it is a risk of this report • Reported the source of funding, but not whether the funding agency influence the review

Strengths	Limitations
Wright et al. (2015)[11]	
• Well described eligibility criteria for the review (i.e., population, intervention, comparator, outcomes) • Includes both RCTs and NRS • Search strategy included searching multiple databases and reference lists of included studies, and providing the complete search strategy • Two reviewers performed study selection and data extraction in duplicate, disagreements were resolved through consensus • A list of excluded studies was provided in the appendix with the reason for exclusion • Detailed description of primary studies, including reporting of the source of funding of the primary studies • Risk of bias was appropriately assessed in the primary studies, as was the overall quality of the studies (i.e., assessed allocation, reporting bias, inconsistency, study type, etc.) • Random effects meta-analysis was conducted to account for heterogeneity of studies, and a secondary meta-analysis conducted using only the NRSs to adjust for the heterogeneity • The authors considered the overall low quality of the studies when interpreting their findings • The authors discussed the clinical and statistical heterogeneity of the findings, and the potential impacts on the results • Authors acknowledged the risk of publication bias, but due to there being fewer than 10 studies could not investigate further • Authors reported no potential conflicts of interest	• No mention of an a priori protocol • Did not search trial registries or grey literature • Two reviewers performed study selection and data extraction in duplicate, disagreements were resolved through consensus • Did not report how many people conducted the risk of bias assessments • Unclear if they were justified in combined both NRS and RCTs in meta-analyses • Did not report the source of the funding

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2 NRS = non-randomized study; RCT = randomized controlled trial;

Table 6: Strengths and Limitations of Randomized Controlled Trials Using the Downs and Black checklist[8]

Strengths	Limitations
Guo et al. (2020)[18]	
• The study aim, main outcomes, eligibility criteria, and treatments were clearly described • Simple outcome data was reported • Actual probability values (P value) were reported • Appropriate statistical tests were used • All patients received the allocated intervention • Patients for both groups were recruited over the same period of time • Computer generated randomization was used • Minimal number of patients lost to follow-up in both groups • The authors reported no competing financial interests	• It was not possible to blind the patients to the intervention they received, which may have influenced the outcomes • Health professionals and researchers were not blinded to the intervention, unclear how this may have influenced the findings • The length of the treatment (and therefore length of follow up) was not reported and may have varied across participants, which may have influenced the results • The method of allocation was not secure and there was a risk that the sequence could have been known (risk of selection bias) • Unclear whether a statistical power calculation was done • Source of funding was reported, but they did not report whether the funders influenced the content of the manuscript • No statistical adjustment for multiple comparisons
Ravenscroft et al. (2020)[19]	
• The study aim, main outcomes, eligibility criteria, and treatments were clearly described • Simple outcome data was reported • Minimal number of patients lost to follow-up in both groups • Appropriate statistical tests were used • All patients received the allocated intervention • Patients for both groups were recruited over the same period of time • Computer generated randomization • Good allocation concealment protocol • Study was adequately powered for the primary outcome • The authors reported no conflicts of interest	• It was not possible to blind the patients to the intervention they received, which may have influenced the outcomes • Did not report actual probability (P) values • Did not report whether individuals assessing the outcomes or conducting the statistical analysis were blinded to the intervention, and unclear whether this influenced findings • Length of treatment may have varied across participants (not reported) which may have influenced the length of follow up in the groups • Source of funding was reported, but they did not report whether the funders influenced the content of the manuscript • No statistical adjustment for multiple comparisons
Story et al. (2019)[17]	
• The study aim, main outcomes, eligibility criteria, and treatments were clearly described • Simple outcome data was reported • Actual probability values (P value) were reported • Minimal number of patients lost to follow-up in both groups • Researcher conducting the analysis was blinded to the intervention groups • Follow-up was the same for all participants for the primary outcome at 2 months	• It was not possible to blind the patients to the intervention they received, which may have influenced the outcomes • For some of the secondary outcomes, the follow-up may have varied across participants (length not reported), which may have influenced the outcomes • No statistical adjustment for multiple comparisons

Strengths	Limitations
• Appropriate statistical tests were used • All patients received the allocated intervention • Computer generated randomization • Good allocation concealment protocol • Study was adequately powered for the primary outcome • The authors reported no conflicts of interest • Source of funding was reported, and it was stated that the funders did not influence the study or the manuscript	
Dave et al. (2016)[14]	
• The study aim, main outcomes, eligibility criteria, and treatments were clearly described • Simple outcome data was reported • Actual probability values (P value) were reported • No patients lost to follow-up • Established the margin for the non-inferiority test a priori (based on routinely collected outcome data), and conducted both an intention-to-treat analysis and a per-protocol analysis for the primary outcome (a good approach for non-inferiority trials) • Similar numbers of patients in both groups did not comply with their assigned intervention; and reasons for non-compliance were provided • The authors reported no conflicts of interest • Source of funding was reported, and it was stated that the authors were solely responsible for the content of the manuscript	• It was not possible to blind the patients to the intervention they received, which may have influenced the outcomes • Health professionals and researchers were not blinded to the intervention, unclear how this may have influenced the findings • Conclusion for main outcome based on intention-to-treat analysis, rather than per-protocol analysis (the preferred approach) • Length of follow-up not reported • Cluster randomization of districts used, and it was unclear whether method of randomization was truly random • As it was a cluster randomized trial, the intervention was known prior to recruitment of all patients • Sample size was calculated based on 80% power, which may be insufficient power for non-inferiority trial, so unclear if trial was adequately powered
Adewole et al. (2015)[15]	
• The study aim, main outcomes, eligibility criteria, and treatments were clearly described • Actual probability values (P value) were reported • No patients lost to follow-up • Researcher assessing the outcomes were blinded to the intervention groups • All patients were followed for the same length of time • Appropriate statistical tests were used • All patients received the allocated intervention • Adequate randomization technique was used • The authors reported no conflicts of interest • Source of funding was reported, and it was stated that the funders did not influence the study or the manuscript	• Some of the findings were not clearly reported • It was not possible to blind the patients to the intervention they received, which may have influenced the outcomes • Procedure for allocating the intervention assignments could have been broken resulting in the assignments being revealed prior to recruitment • No power calculation was conducted, rather a convenience sample size was used

Strengths	Limitations
Ricks et al. (2015)[16]	
• The study aim, main outcomes, and treatments were clearly described • Actual probability values (P value) were reported • No patients were reported as lost to follow-up • Appropriate statistical tests were used • All patients received the allocated intervention • Adequate randomization technique was used • The authors reported no conflicts of interest	• For the eligibility criteria, it was unclear whether the patients were newly diagnosed tuberculosis patients, or whether they could have already started treatment (thus affecting the length of follow up) • Some of the findings were not clearly reported • It was not possible to blind the patients to the intervention they received, which may have influenced the outcomes • Did not report whether individuals assessing the outcomes or conducting the statistical analysis were blinded to the intervention, and unclear whether this influenced findings • Did not report length of follow-up and it was unclear whether all patients were followed for the same length of time • Procedure for allocating the intervention assignments could have resulted in assignments being revealed prior to recruitment • Unclear whether a statistical power calculation was done • Source of funding was reported, but they did not report whether the funders influenced the content of the manuscript

Table 7: Strengths and Limitations of Guidelines Using AGREE II[9]

Item	Guideline					
	WHO, 2020[25]	**BHIVA, 2019[20]**	**NICE, 2017[24]**	**ATS/CDC/IDSA, 2016[22]**	**ECDC, 2016[21]**	**Singapore Guideline, 2016[23]**
Domain 1: Scope and Purpose						
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Partially	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes	Yes	Partially
Domain 2: Stakeholder Involvement						
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Yes	Yes	Partially	Partially

Item	Guideline					
	WHO, 2020[25]	**BHIVA, 2019[20]**	**NICE, 2017[24]**	**ATS/CDC/IDSA, 2016[22]**	**ECDC, 2016[21]**	**Singapore Guideline, 2016[23]**
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Partially	Yes	Yes	No	No	No
6. The target users of the guideline are clearly defined.	Yes	Partially	Yes	Yes	Yes	Yes
Domain 3: Rigour of Development						
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes	Yes	Partially	No
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	Yes	Yes	Yes	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	Yes	Yes	Partially	Partially
10. The methods for formulating the recommendations are clearly described.	Yes	Yes	Yes	Yes	Yes	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Partially	Yes	Yes	No	No
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes	Partially	Partially
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes	Yes	Yes	No	No
14. A procedure for updating the guideline is provided.	Yes	Yes	Yes	No	Yes	Yes
Domain 4: Clarity of Presentation						
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes	No	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	No	Yes
Domain 5: Applicability						
18. The guideline describes facilitators and barriers to its application.	Partially	Yes	No	No	Yes	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Partially	Partially	Partially	No	No

Item	Guideline					
	WHO, 2020[25]	**BHIVA, 2019[20]**	**NICE, 2017[24]**	**ATS/CDC/IDSA, 2016[22]**	**ECDC, 2016[21]**	**Singapore Guideline, 2016[23]**
20. The potential resource implications of applying the recommendations have been considered.	Yes	Partially	Yes	Partially	Partially	No
21. The guideline presents monitoring and/or auditing criteria.	Yes	No	Yes	No	No	Partially
Domain 6: Editorial Independence						
22. The views of the funding body have not influenced the content of the guideline.	Partially	Yes	Partially	Yes	No	No
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes	Yes	No

AGREE II = Appraisal of Guidelines for Research and Evaluation II; ATS= American Thoracic Society; BHIVA = British HIV Association; CDC = Centers for Disease Control and Prevention; DR = drug-resistant; ECDC = European Centre for Disease Prevention and Control; IDSA = Infectious Disease Society of America; NICE = National Institute for Health and Care Excellence; TB = tuberculosis; WHO = World Health Organization.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews and Network Meta-Analyses

Main study findings	Authors' conclusion
Ngwatu et al. (2018)[13]	
Prospective Cohort from the USA VOT, n = 61 DOT, n = 329 **Treatment completion**: VOT (96%) vs. DOT (97%) RR = 0.99, 95% CI, 0.93 to 1.05 **Adherence, appointment compliance**: VOT (95%) vs. DOT (91%) RR = 1.05, 95% CI, 1.04 to 1.06 Retrospective Cohort from Australia VOT, n = 128 DOT, n = 70 **Treatment completion**: VOT (48%) vs. DOT (33%) RR = 1.47, 95% CI, 0.96 to 2.25 Both studies were assessed by the authors to have high risk of bias due to confounding and measurement of the outcome.	"These studies compared VOT to high-functioning DOT programs; there was no difference in adherence, which suggests that comparably high adherence can be obtained using digital technologies for treatment support" (p. 8)[13]
Zhang et al. (2016)[12]	
Community-based DOT vs. clinic-based DOT 6 RCTs, six cohort studies **Successful treatment**: 12 studies, Random effects RR = 1.14, 95% CI, 1.03 to 1.27 6 RCTs, Fixed effects RR = 1.11, 95% CI, 1.02 to 1.19 **Completed treatment**: 7 studies, Fixed effects	"Thus, this systematic review and meta-analysis updated available evidence on the beneficial effect of community-based DOT on TB control, and suggested that community-based DOT had increased successful treatment rate and completed treatment, and reduced rates of death and transfer out compared with clinic based DOT. Workplace-based DOT may have advantage in promoting successful treatment in patients who continue to work during treatment." (p. 14)[12] "Though a plethora of factors are associated with preventive or curative TB treatment, evidence from this meta-analysis shows that community-based DOT, as one key component of community involvement in TB control, can improve TB treatment outcomes´(p. 15)[12]

Main study findings	Authors' conclusion
RR = 1.24, 95% CI, 0.92 to 1.68 5 RCTs, Fixed effects RR = 1.74, 95% CI, 1.05 to 2.90 **Cured treatment:** 10 studies, Random effects RR = 1.11, 95% CI, 0.95 to 1.29 6 RCTs, Fixed effects RR = 1.07, 95% CI, 0.98 to 1.17 **Treatment default**: 10 studies, Random effects RR = 0.75, 95% CI, 0.58 to 0.98 5 RCTs, Fixed effects RR = 0.75, 95% CI, 0.52 to 1.07 **Treatment failure**: 9 studies, Fixed effects RR = 1.37, 95% CI, 0.68 to 2.76 6 RCTs, Fixed effects RR = 1.27, 95% CI, 0.55 to 2.89 <u>Community-based DOT vs. family-based DOT</u> 3 RCTs, one cohort study **Successful treatment**: 4 studies, Fixed effects RR = 0.99, 95% CI, 0.98 to 1.04 3 RCTs, Fixed effects RR = 0.99, 95% CI, 0.94 to 1.03 **Cured treatment:** 3 studies, Fixed effects RR = 1.09, 95% CI, 0.99 to 1.09 2 RCTs, Fixed effects RR = 1.08, 95% CI, 0.97 to 1.20	

Main study findings	Authors' conclusion
Completed treatment: 3 studies, Fixed effects RR = .93, 95% CI, 0.75 to 1.15 2 RCTs, Fixed effects RR = 0.97, 95% CI, 0.79 to 1.20 **Treatment failure**: 3 studies, Fixed effects RR = 0.67, 95% CI, 0.13 to 3.47 2 RCTs, Fixed effects RR = 0.88, 95% CI, 0.12 to 6.40 <u>Community-based DOT vs. workplace-based DOT</u> 2 cohort studies **Successful treatment**: 2 studies, Fixed effects RR = 0.85, 95% CI, 0.79 to 0.90	
Wright et al. (2015)[11]	
<u>Community-based DOT vs. clinic-based DOT</u> **Proportion of patients successfully treated** 1 RCT and 7 NRS, Random effects: OR = 1.54, 95% CI, 1.01 to 2.36 P = 0.046, I^2 = 84% 5 prospective NRS only, Random effects: OR = 1.31, 95% CI, 1.01 to 1.71 P = 0.045, I^2 = 19% **Proportion of patients lost to treatment follow up** 1 RCT and 6 NRS, Random effects: OR = 0.86, 95% CI, 0.48 to 1.55 P = 0.62, I^2 = 83% 5 prospective NRS only, Random effects: OR = 1.14, 95% CI, 0.42 to 3.11 P = 0.8, I^2 = 79%	"This systematic review and meta-analysis of eight studies that compared treatment outcomes of community-based DOT with clinic DOT showed that community-based DOT was associated with higher treatment success than clinic DOT." (p. 5)[11] "Our meta-analysis showed a benefit from community-based DOT compared to clinic DOT for treatment success, but no overall difference between the two DOT strategies for loss to follow-up." (p. 9)[11]

Main study findings	Authors' conclusion
Quality of included studies assessed by SR authors as very-low to low.	

CI = confidence interval; DOT = direct observational therapy; OR = odds ratio; NRS = non-randomized study; RCT = randomized controlled trial; RR = relative risk; VOT = video observed therapy

Table 9: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Guo et al. (2020)[18]	
Synchronous VOT vs. DOT **Good TB treatment outcome (i.e., cured or treatment completed) (%)** VOT, 96.1% vs. DOT, 94.6% P = 0.474 **Poor TB treatment outcome (i.e., death, treatment failure) (%)** VOT, 2% vs. DOT, 2.5% P = 0.994 **Lost to follow-up (%)** VOT, 0.5% vs. DOT, 2.0% P = 0.365	"The compliance of both groups was high, so we also observed treatment completion at high rates. The two observed treatment methods had no statistical differences, and all could accomplish their tasks well." (p. 1154)[18]
Ravenscroft et al. (2020)[19]	
Asynchronous VOT vs. DOT **Days of non-adherence to medication per two week period, mean, n** VOT, 1.29 vs. DOT, 5.24 Difference = 4 days, 95% CI, 3.35 to 4.67 days, P < 0.01 **Adherence to at least 80% of treatment over 2 weeks, %** VOT, 75.1% vs. DOT, 19.5% Difference = 55.6%, 95% CI, 48 to 63%, P < 0.01 **Treatment success** 4 months: VOT, 11.1% vs. DOT, 15.0% 10 months: VOT, 92.1% vs. DOT, 86.0% 12 months: VOT, 93.5% vs. DOT, 90.3%	"In this trial, VOT increased observed medication adherence for tuberculosis patients compared to clinic-based DOT, a difference of 4 days of adherence per 2-week period" (p.16)[19]

Main study findings	Authors' conclusion
Story et al. (2019)[17]	
Asynchronous VOT vs. DOT **Successful completion ≥80% of scheduled treatment observations in 2 months** VOT, 70% vs. DOT, 31% OR = 5.48, 95% CI, 3.10 to 9.68, P < 0.0001 **Proportion of scheduled observations completed in 2 months** VOT, 79% vs. DOT, 45% **Proportion of doses observed per patient, mean (SD)** VOT, 78%(41%) vs. DOT, 36% (31%) Adjust mean difference in proportion: 41%, 95% CI, 29 to 53, P < 0.0001 **Proportion of scheduled observations completed in full follow-up period (up to 6 months)** VOT, 77% vs. DOT, 39%, P < 0.0001	"In this trial, VOT enabled higher levels of treatment observation for patients with tuberculosis, both over the first 2 months of treatment and throughout treatment, than DOT." (p. 1221)[17]
Dave et al. (2016)[14]	
Family DOT vs. Non-family DOT **Primary outcome, treatment success rate, tested for non-inferiority:** Intention-to-treat analysis, Treatment success rate: Family DOT, 95.8%, 95% CI, 94.1% to 97.1% Non-family DOT, 93.2%, 95% CI, 88.9% to 95.9% Difference between groups: 3.0%, 95% CI, –0.7% to 6.7% Since lower limit of the 95% CI (–0.7%) is greater than the a priori margin of –5%, Family DOT was non-inferior to non-family DOT Per-protocol analysis, Treatment success rate: 20 children excluded from analysis due to not receiving allocated intervention. Family DOT, n = 347 Non-family DOT, n = 257 Family DOT, 95.8%, 95% CI, 94.6% to 97.0% Non-family DOT, 92.7%, 95% CI, 89.6% to 95.8%	"Since the lower limit of the 95% confidence interval (–0.7% is greater than –5% (the non-inferiority limit), the new intervention was concluded to be non-inferior to the existing intervention" (p. 7)[14] "We observed a high acceptance rate (97%) for family DOT. Family DOT achieved similar treatment success rates to that of non-family member DOT among children with TB in Gujarat" (p. 10)[14] "These results support those obtained in earlier studies among patients of all age groups which showed that family-member and community DOT strategies can achieve desired success rates." (p. 10)[14] "The high level of treatment adherence recorded in the intervention group indicates good uptake of the intervention among family members" (p. 10)[14]

Main study findings	Authors' conclusion
Difference between groups: 3.1%, 95% CI, –0.6% to 6.9% Since lower limit of the 95% CI (–0.6%) is greater than the a priori margin of –5%, Family DOT was non-inferior to non-family DOT **Secondary outcome, missed doses during treatment, % (of those who successfully completed treatment)** Per-protocol analysis only Family DOT, n = 344 Non-family DOT, n = 247 None: Family DOT, 78.8% vs. Non-family DOT, 73.9% 1 to 3: Family DOT, 13.7% vs. Non-family DOT, 14.3% ≥ 4: Family DOT, 7.6% vs. Non-family DOT, 11.8% P = 0.19	
Adewole et al. (2015)[15]	
Home-based DOT vs. Hospital-based DOT **Did not complete treatment, n (%)** Home-based DOT, 2 (3%) vs. Hospital-based DOT, 15 (20%), P = 0.01	"This study evaluated a novel form of community-based DOT that entails health workers delivering TB treatment to patients in their homes as compared to a health facility based approach. This new approach was associated with better patient compliance to treatment, at 2 month and satisfaction with care received."
Ricks et al. (2015)[16]	
Enhanced DOT (provided by former substance users) vs. standard DOT **Failure to complete treatment** Standard DOT, 39% vs. Enhanced DOT, 15% RR = 2.7, 95% CI, 1.2 to 5.8, P = 0.01 **Mean number of treatment interruptions** Standard DOT,4.5 vs. Enhanced DOT, 1.4, P = 0.059 **Refusal to take medication or not being found at scheduled DOT appointment** Standard DOT vs. Enhanced DOT RR = 2.6, 95% CI, 1.4 to 4.8	"This study represents the first randomized trial in the United States to compare the effect of two different DOT strategies on anti-tuberculosis treatment completion and adherence among substance users. Patients in the standard DOT arm had a 2.7 times greater risk of not completing treatment and a 2.6 times greater risk for missing a DOT appointment than patients in the enhanced arm." (p. 330)[16]

CI = confidence interval; DOT = direct observational therapy; OR = odds ratio; RR = relative risk; TB = tuberculosis; VOT = video observed therapy.

Table 10: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
WHO, 2020[25]	
Recommendation 1: "Community- or home-based DOT is recommended over health facility-based DOT or unsupervised treatment." (p. 62) Evidence from RCTs and observational studies showed that community- or home-based DOT had higher rates of treatment success, cure, treatment completion and 2-month sputum conversion. Community- or home-based DOT also had lower rates of mortality and lower rates of unfavourable outcomes compared with health facility-based DOT. When comparing community-/ home-based DOT or health facility-based DOT with unsupervised treatment, there were no significant differences across the outcomes in RCTs. However, cohort studies showed higher rates of treatment success and adherence, and a lower rate of loss to follow-up with community-/home-based DOT compared with SAT. Observational data from cohort studies also showed lower rates of treatment completion, and slightly higher rates of failure and loss to follow-up in health-facility DOT compared to SAT.	Recommendation 1: conditional recommendation, moderate certainty in the evidence
Recommendation 2: "DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment." (p. 62) Evidence from three RCTs and 12 observational studies showed that DOT by lay providers had higher rates of treatment success and cure, and a slightly lower rate of loss to follow-up compared with unsupervised treatment. Patients receiving DOT from a family member had higher rates of treatment success and lower rates of loss to follow-up compared with patients using unsupervised treatment.	Recommendation 2: conditional recommendation, very low certainty in the evidence
Recommendation 3: "Video-observed treatment (VOT) may replace DOT when the video communication technology is available, and it can be appropriately organized and operated by health-care providers and patients." (p. 62) Evidence from two cohort studies showed that patients who were provided with VOT had no statistically significant difference in treatment completion and mortality compared to patients who had in-person DOT.	Recommendations 3: conditional recommendation, very low certainty in the evidence

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
BHIVA,2019[20]	
Recommendation 1: "We recommend individualized, enhanced patient-centered care plans for all patients, some of which may include directly observed therapy (DOT) and video observed therapy (VOT)." (p. 10) Recommendation 2: "We recommend against the routine use of DOT and VOT in patients with active TB but recommend these in multi DR-TB cases." (p. 10) Evidence from RCTs and observational studies (of predominantly HIV-negative persons with drug-susceptible TB) suggests that DOT is not significantly better than SAT in preventing microbiological failure, relapse or acquired drug resistance.	Recommendation 1: Good practice point Recommendation 2: Strong recommendation/ Grade 1B (against routine use), good practice point (multi DR-TB cases)
NICE, 2017[24]	
Recommendation 1: "Offer directly observed therapy as part of enhanced case management in people who: • do not adhere to treatment (or have not in the past) • have been treated previously for TB • have a history of homelessness, drug or alcohol misuse • are currently in prison, or have been in the past 5 years • have a major psychiatric, memory or cognitive disorder • are in denial of the TB diagnosis • have multidrug-resistant TB • request directly observed therapy after discussion with the clinical team • are too ill to administer the treatment themselves" (p. 57) Evidence for this recommendation was reported in a previous version of guideline. Evidence was a combination of experience and expertise and evidence from the literature. Recommendation 2: "In children whose parents are members of any of the above groups, offer directly observed therapy as part of enhanced case management and include advice and support for parents to assist with treatment completion." (p. 56) Evidence extrapolated from the evidence supporting recommendation 1. Recommendation 3: "TB control boards and local TB services should consider employing trained, non-clinically qualified professionals to work alongside clinical teams to agreed protocols, and to contribute to a variety of activities. Examples of this may include awareness raising and supporting people to	The wording of the recommendations reflects the certainty in the recommendation. Recommendation 1: Offer = for the vast majority of patients, the intervention will do more good than harm Recommendation 2: Offer = for the vast majority of patients, the intervention will do more good than harm

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
attend appointments (including other health and social care appointments). They could also help with collecting samples, contact tracing, case management including directly observed therapy and cohort review, or any other aspect of the service if: • they are trained to deliver the intervention or processes effectively • they are supported, mentored and supervised by a named case manager, such as a TB nurse • they have the skills to monitor, evaluate and report on their work practices and outcomes to maintain a process of ongoing evaluation and service improvement in relation to cohort review" (p. 73) Recommendation based off expert testimony and evidence from case-studies.	Recommendation 3: Consider = the benefit is less certain; the intervention will do more good than harm for most patients Evidence was considered low-quality (from expert testimony and case studies)
ATS/CDC/IDSA, 2016[22]	
"We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis." (p. 150) The systematic review conducted did not find any significant differences between SAT and DOT when assessing several outcomes of interest, including mortality, treatment completion, and relapse. However, DOT was significantly associated with improved treatment success (the sum of patients cured and patients completing treatment) and with increased sputum smear conversion during treatment, as compared to SAT. Also suggests that for a patient-centered approach, the location of the DOT treatment would be selected in consultation with the patient (e.g., office, clinic, home, workplace, school) and provided by trained personnel (not otherwise specified)	Conditional recommendation; low certainty in the evidence
ECDC, 2016[21]	
"VOT can be of benefit as an alternative option for performing DOT" (p. 16) A SR was conducted but no relevant results were identified. A study was identified and added through the Delphi process. This study provided weak evidence that that VOT was feasible and acceptable, with high adherence (high and low resource settings).	Weak evidence. Graded by panel as: likely acceptable, likely feasible, medium impact on resource use, and likely cost-effective
Singapore Guideline, 2016[23]	
Recommendation 1: "DOT should be the standard of care for all infectious tuberculosis cases. Tuberculosis patients who are assessed to have difficulty adhering to treatment or who pose greater public risk of transmission, e.g.	Recommendation 1: Grade C (moderate recommendations), Level 2+ (moderate quality evidence)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
sputum-smear positive or working in institutional settings or settings with susceptible populations, or those at risk of or diagnosed with drug-resistant tuberculosis, are high priority for DOT." (p. 7) Recommendation 2: "Multi DR-TB patients should be treated under strict program conditions by physicians experienced in multi DR-TB management. DOT should be utilized for the entire treatment duration." (p. 8) Evidence not reported Guideline considered DOT providers as healthcare workers or trained Volunteers	Recommendation 2: Grade D (weak recommendation), Level 4 (expert opinion)

ATS= American Thoracic Society; BHIVA = British HIV Association; CDC = Centers for Disease Control and Prevention; DOT = direct observed therapy; DR = drug-resistant; ECDC = European Centre for Disease Prevention and Control; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; IDSA = Infectious Disease Society of America; LTBI = latent tuberculosis infection; NICE = National Institute for Health and Care Excellence; PICO = population, intervention, comparison and outcomes; RCT = randomized controlled trial; SAT = self-administered therapy; TB = tuberculosis; WHO = World Health Organization.

CADTH

Appendix 5: Overlap between Included Systematic Reviews

Table 11: Overlap in Relevant Primary Studies between Included Systematic Reviews

Primary study citation	Systematic review citation	
	Zhang et al. (2016)[12]	Wright et al. (2015)[11]
Wright J, et al. Trop Med Int Health. 2004;9:559-65.	X	
Clarke M, et al. Int J Tuberc Lung Dis. 2015;9:673-9.	X	
Wandwalo E, et al. Int J Tuberc Lung Dis. 2004;8;1248-54.	X	
Lwilla F, et al. Trop Med Int Health. 2003;8:204-10.	X	X
Kamolratanakul P, et al. Trans R Soc Trop Med Hyg. 1999 ;93 :552-7.	X	X
Zvavamwe Z, et al. Int J Nurs Stud. 2009;46:302-9.	X	
Cavalcante SC, et al. Int J Tuberc Lung Dis. 2007;11:544-9.	X	
Adatu F, et al. Int J Tuberc Lung Dis. 7(9 Suppl 1):S63-71.	X	
Newell JN, et al. Lancet. 2006;367:903-9.	X	
Sinanovic E, et al. Int J Tuberc Lung Dis. 2006;10:795-801.	X	
Sinanovic E, et al. Int J Tuberc Lung Dis. 2003;7(9 Suppl 1):S56-62.	X	
Dudley L, et al. Int J Tuberc Lung Dis. 2003;7(9 Suppl 1):S48-55.	X	
Zwarenstein M, et al. Int Journal Tuberc Lung Dis. 2000;4:550-4.	X	
Singh AA, et al. Int J Tuberc Lung Dis. 2004;8:800-2.	X	X
Pungrassami P, et al. Trans R Soc Trop Med Hyg. 2002;96:695-9.	X	
Walley JD, et al. Lancet. 2001;357:664-9.	X	
Becx-Bleumink M, et al. Int J Tuberc Lung Dis. 2001;5:920-5.	X	
Kironde S, and Meintjies M. Int J Tuberc Lung Dis. 2002;6(7):599-608.		X
Miti S, et al. Int J Tuberc Lung Dis. 2003;7(9 Suppl 1):S92-8.		X
Niazi AD, and Al-Delaimi AM. East Mediterr Health J. 2003;9(4):709-17.		X
Nirupa C, et al. Indian J Tuberc. 2005;52:73-7.		X
Tripathy SL, et al. PHA. 2013;3(3):230-4.		X

Appendix 6: Further Information

Non-Randomized Studies

1. Guo X, Yang Y, Takiff HE, et al. A Comprehensive App That Improves Tuberculosis Treatment Management Through Video-Observed Therapy: Usability Study. JMIR Mhealth Uhealth. 2020;8(7):e17658.
2. Bendiksen R, Ovesen T, Asfeldt AM, Halvorsen DS, Gravningen K. Use of video directly observed treatment for tuberculosis in Northern Norway. Tidsskr Nor Laegeforen. 2020;140(1):14.
3. Prasad BM, Chadha SS, Thekkur P, et al. "Is there a difference in treatment outcome of tuberculosis patients: Rural Healthcare Providers versus Community Health Workers?". J. 2020;9(1):259-263.
4. AlSahafi AJ, Shah HBU, AlSayali MM, et al. High non-compliance rate with anti-tuberculosis treatment: a need to shift facility-based directly observed therapy short course (DOTS) to community mobile outreach team supervision in Saudi Arabia. BMC Public Health. 2019;19(1):1168.
5. Garfein RS, Liu L, Cuevas-Mota J, et al. Tuberculosis Treatment Monitoring by Video Directly Observed Therapy in 5 Health Districts, California, USA. Emerg Infect Dis. 2018;24(10):1806-1815.
6. Kibuule D, Verbeeck RK, Nunurai R, et al. Predictors of tuberculosis treatment success under the DOTS program in Namibia. Expert Rev Respir Med. 2018;12(11):979-987.
7. Chuck C, Robinson E, Macaraig M, Alexander M, Burzynski J. Enhancing management of tuberculosis treatment with video directly observed therapy in New York City. Int J Tuberc Lung Dis. 2016;20(5):588-593.
8. Mhimbira F, Hella J, Maroa T, et al. Home-Based and Facility-Based Directly Observed Therapy of Tuberculosis Treatment under Programmatic Conditions in Urban Tanzania. PLoS ONE. 2016;11(8):e0161171.
9. Dobler CC, Korver S, Batbayar O, et al. Success of community-based directly observed anti-tuberculosis treatment in Mongolia. Int J Tuberc Lung Dis. 2015;19(6):657-662.
10. Sitienei J, Kipruto H, Mansour O, et al. Correlates of default from anti-tuberculosis treatment: a case study using Kenya's electronic data system. Int J Tuberc Lung Dis. 2015;19(9):1051-1056.

Additional References

Alternative Comparator

11. Browne SH, Umlauf A, Tucker AJ, et al. Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial. PLoS Med. 2019;16(10):e1002891.